Diagnostic and treatment strategies for the management of acute stroke with special reference to clot retrieval

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Statement

I write to introduce this body of work as forming a submission of Doctor of Medical Science as evidenced by 155 high quality peer-reviewed publications. Forty-one papers are presented in full and a full list of 114 publications are given by titles and publication details. The sections below relate to individual aspects of cerebrovascular diseases outlined briefly to place the submitted publications in context.
Abstract

This body of work comprises contributions to human cerebrovascular disease as performed over a period of 12 years (from year 2005 to 2017) as a specialist at major university teaching hospital in Melbourne in collaboration with the most prominent colleagues recognized internationally in this field.

The body of work is divided into 2 parts. The first part comprises of 41 peer-reviewed papers submitted in full in hard copy representing the most pivotal and highly cited papers in major specialist journals where I have been either senior and corresponding author, lead author or a major contributor. This body of work is divided into essentially 6 sections based on prognosis, diagnostic factors, pharmacogenetics, aging, relation to epilepsy and other diseases and my own specialty of therapeutics including endovascular clot retrieval. The second part submitted for completion includes the total 114 peer-reviewed papers representing my contribution, less pivotal to the central themes, to the medical literature. It includes for particular interest my collaboration with engineers in the development of endovascular devices for the performance of therapeutic manoeuvres. Each section is preceded by a brief introductory overview to facilitate assessment.
University of Melbourne
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Declaration of thesis based on compilation of published papers

General Declaration

In accordance with University of Melbourne Doctorate regulations the following declarations are made:

I hereby declare that this thesis comprises only my original works towards the Doctor of Medical Science and it contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 155 original papers published in peer reviewed journals. The ideas and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Neurology under the supervision of Professor Stephen Davis.

The inclusion of co-authors reflects the work from collaboration between researchers and acknowledges input into team-based research.

Signed:……………………………………………………………………………………..Date:………………
Acknowledgements

The work in this thesis would not have been possible without the collaboration, support and help from the colleagues in the Department of Neurology and Radiology at the Royal Melbourne Hospital. I would also like to express my profound thanks to my research collaborators who include, but not limited to, colleagues from the Department of Electrical and Electronic Engineering (University of Melbourne) and colleagues from overseas who are a part of an ongoing research network. I would like to express my gratitude to all the neurology registrars and neurology research students within my department from whom I have learnt that the best way to gain scientific insight is to teach.

In the following I would like to thank in particular:

Professor Stephen Davis has been a tireless mentor since my early days in training in Neurology and has continued to provide guidance and insightful ideas towards research.

Professor Joachim Berkefeld supervised my training in interventional neuroradiology during my two-year fellowship in Frankfurt. He has imparted to me the valuable skills of endovascular intervention and has set me on my path to pursue excellence in stroke treatment.

Professor Terry O'Brien has strongly supported my research career from the time I have work in Melbourne in 2005. For his continuing support, I am deeply grateful.

Last and absolutely by no means the least, is my sincere gratitude to Professor Frank Vajda. He has greatly assisted me in the structure and style of this thesis and my most heartfelt thanks to him.
Overview of cerebrovascular diseases

General

Cerebrovascular diseases encompass a range of pathological conditions caused by dysfunction of the vascular system of the neurological system. The clinical manifestations and consequences are determined by the nature of the vascular dysfunction (e.g. vascular occlusion or vascular rupture) and its deleterious effects on the part of the neurological system to which it supplies. It is the aim of this thesis to present my research efforts in the diagnostics and treatment of cerebrovascular diseases with the focus on two subgroups, namely, ischaemic stroke and subarachnoid haemorrhage.

Subgroups of cerebrovascular disease

Ischaemic stroke

Ischaemic stroke imposes a considerable health burden on a global scale[1]. It is estimated that every one in six people will develop stroke in their lifetime[2]. This translates to 5 million patients with first ever ischemic stroke and 3 million patients with first ever hemorrhagic stroke per annum in the year 2015[3]. Stroke is now the second most common cause of death worldwide following ischaemic heart disease in patients above 60[4]. The health costs in the developed world such as United States of America is estimated at $ 65.5 billion per annum which included sequelae consisting of inpatient care, rehabilitation and long-time care post stroke in patients’ lifetime[5].

The pathophysiology of stroke is driven by arterial occlusion causing precipitous decrease in arterial perfusion and oxygen delivery deprivation to brain parenchyma, leading to rapid neuronal death[6]. The underlying aetiology to arterial occlusion is diverse and includes pathologies affecting the endothelium such as atherosclerosis and cardioembolism[7].

The acute treatment of stroke is based on the insight that critically underperfused brain parenchyma, a result of arterial occlusion, develop rapid and irreversible neuronal death
within a certain time period. Within this time period, the affected parenchyma is electrophysiologically silent but biologically viable (termed the penumbra), offering an opportunity for therapeutic intervention and the attenuation of progressive neuronal cell death[8]. It is this knowledge which has led to several studies proving the clinical efficacy of recanalization of occluded arteries by thrombolytics. Thrombolytics are a group of biological agents, the prototype being tissue plasminogen activators, which actuate the dissolution of thrombus (thrombolysis) by the conversion of plasmin from plasminogen[9]. The breakthrough in revascularization comes from the 6 pivotal trials comparing endovascular treatment with the previous standard therapy intravenous thrombolytics[10-15]. The results demonstrate the superiority of endovascular treatment over standard therapy in the setting of large artery occlusion and it is estimated that approximately 15% of acute stroke patients fall into this criteria[16]. As a result of these findings, the current major efforts are directed towards the optimization of equitable delivery of endovascular treatment in different health systems[17].

Of no less importance than acute recanalization is the prevention of ischaemic stroke. Arterial occlusion is the common final pathway of a diverse range of arterial pathologies. Efforts in elucidating the physiology of atherosclerosis have led to landmark studies demonstrating the benefits of vascular risk factor modification. These investigative efforts include anti-platelets, anti-hypertensives, cessation of smoking and cholesterol lowering agents. Of note, the use of anti-platelets, especially aspirin, is associated with 11% relative risk reduction in stroke recurrence[18]. Anti-hypertensives, such as angiotensin converting enzyme inhibitors, decrease relative stroke risk by 30%[19]. On the other hand, the investigation of cardioembolic mechanisms has led to the establishment of anti-thrombotics, in particular, warfarin, a vitamin K antagonist, for stroke prevention in the setting of atrial fibrillation[20]. Of great interest is the emergence of a new generation of oral anti-thrombotics, including direct antithrombin inhibitors and anti-Xa inhibitors, which demonstrate in recent studies better tolerance and safety than warfarin[21-23].
Subarachnoid haemorrhage and aneurysms

Subarachnoid haemorrhage is less common than ischaemic stroke. It is estimated in the developed world to have an annual incidence of between 8 to 10 per 100,000 population depending on the country of origin[24]. It is noted that the incidence vary across different ethnicities with the highest incidence observed in the countries Finland and Japan[25, 26], reflecting possible genetic influences[27]. In spite of its relative infrequency, subarachnoid haemorrhage assumes a considerable share of health costs on account of its higher mortality and morbidity[28]. About one third of survivors becoming dependent on all activities of daily living, resulting in costs in the developed world of at least 11% of the total attributable to nursing home care[29].

The underlying aetiology is predominantly aneurysmal rupture, accounting 85% of cases[30]. The remaining causes include arterio-venous malformation, trauma, arterial dissection and illicit drug use[31]. One of the principal aims of management is based on the knowledge of the natural history of aneurysmal rupture. It is known that aneurysms once ruptured, have a higher risk of re-rupture, leading to a higher mortality rate of 80% [32]. It follows that management of subarachnoid haemorrhage require the urgent identification of the culprit aneurysm and its exclusion from the circulation either by an open surgical approach or endovascular embolization. Studies have shown at least equivalence of efficacy of the 2 treatment approaches and in certain circumstances, superiority of one over the other[33, 34].
Section 1 Diagnosis and Prognosis

Cerebrovascular disease represents one of the commonest cause of mortality and morbidity. The diagnosis detailed in this section indicate the development of these methods ranging initially from direct puncture carotid artery catheter-based angiogram to more subtle and less invasive approaches such as multi-modal CT imaging (in addition to non-contrast CT, CT angiogram and CT perfusion studies), Doppler carotid ultrasound and transcranial ultrasound, advanced MRI techniques and digital subtraction angiography (via the less risky route, namely, common femoral arterial puncture). The prognosis of cerebrovascular disease has been greatly altered over the past 25 years as a direct result of improved diagnostic facilities and also as a result of therapeutic approached which will be detailed in the next section.

List of my publications submitted in full


Y. Zhang, L. Churilov, A. Meretoja, S. Davis, B. Yan*. Elevated urea level is associated with poor clinical outcome and increased mortality post intravenous tissue plasminogen activator in stroke patients. *Journal of Neurological Sciences* 2013;332:110-115


B. Yan, M. Parsons, S. McKay, D. Campbell, B. Infeld, R. Czajko, S.M. Davis. When to measure lipid profile after stroke? : A prospective serial study Cerebrovascular Disease 2005;19:234-238
Is there association between hyperdense middle cerebral artery sign on CT scan and time from stroke onset within the first 24-hours?

James Haridy1, Leonid Churilov2, Peter Mitchell3, Richard Dowling3 and Bernard Yan3,4*

Abstract

Background: The hyperdense artery sign (HAS) on CT brain scan is an assumed radiological marker of acute intra-arterial thrombotic occlusion. However, the relationship between HAS between time of stroke onset has not been adequately investigated, leading to uncertainty regarding its validity as a marker of acute ischaemia. We attempted to determine if the presence of the hyperdense artery sign is associated with time from stroke onset.

Methods: Retrospective cross-sectional study conducted in a tertiary referral centre. Consecutive patients with acute ischaemic stroke and confirmed middle cerebral arterial occlusion on initial CT angiogram from 2007–2011 were included. Visual estimation and manual measurement of Hounsfield units of affected and corresponding non-affected artery on non-contrast CT was completed and mean density was calculated from four separate readings. Primary outcome measures were Time from stroke onset and HAS on both visual estimation and the ratio of mean value in Hounsfield Units (HU) of affected to non-affected artery.

Results: One hundred and fifty-four subjects with confirmed arterial occlusion on CT Angiogram were included in the study. There were no significant differences in age distribution or vascular risk factor presence between subjects with or without HAS. Subjects with HAS were less likely to be male (50.9 % vs 70.8 %, \( p = 0.02 \)) HAS was found in 106 (68.8 %) of all subjects. Median NIHSS score at presentation was significantly higher in the HAS group (17 vs 12, \( p = 0.02 \)). No statistically significant association between HAS and stroke onset time or density ratio between affected and non-affected artery was detected overall within either the first 24-h or on subgroup analysis of those in the first 4.5-h. A small subgroup of three patients with stroke onset greater than 24-h all had absent HAS.

Conclusions: No evidence of a correlation between time of stroke onset and presence of a HAS within the first 24-h post acute ischaemic stroke was identified. The HAS was associated with a higher NIHSS score at presentation.

Keywords: Ischaemic Stroke, Hyperdense artery sign, Susceptibility vessel sign, Stroke imaging, Neuroimaging, Acute stroke

Background

Despite the development of newer imaging modalities, non-contrast computed tomography (NCCT), given its wide accessibility, remains the principal imaging technique in suspected acute stroke. The hyperdense artery sign (HAS) was first described in 1983 as a radiological marker of intra-arterial thrombotic occlusion and, although not definitively unproven, was possibly an early sign of acute ischaemic stroke [7]. Although HAS is widely described in the middle cerebral artery, termed Hyperdense Middle Cerebral Artery Sign (HMCAS), it is also reported in internal carotid artery, posterior cerebral artery, basilar artery and to a lesser extent, anterior cerebral artery [2, 5, 6, 8–10, 15, 20].

HAS is defined as region of hyperdensity in comparison to the artery on the contralateral side, as seen on NCCT (Figure 1). This has been reported to be present on NCCT in 75 % of acute ischaemic stroke within the first 90 min of symptom onset [14, 24, 25]. The overall
prevalence of HMCAS in acute ischaemic stroke varies in published studies between 5-75 % with the largest systematic review indicating a prevalence of around 25 % [28]. The vast majority of studies to date define a hyper-dense artery as one that is denser than its contralateral counterpart when assessed by one or more neuroradiologists [3, 10, 15, 16, 20, 28].

Recent evidence suggests that clot density on NCCT reflects the composition of the clot [17]. Normally flowing blood column is characterized by a Hounsfield value of approximately 40 units, where an acute clot within a vascular structure averages closer to 61–80 units [17, 19]. As the acute thrombus progresses, its composition changes from RBC-rich ‘red thrombus’ to a predominately fibrin-based ‘white thrombus’. It has been postulated that the extrusion of serum in an acute thrombus, and subsequent increased haemoglobin concentration, is the cause of the increase in density on NCCT [19]. Kirchhof et al. showed that white thrombi had a CT attenuation of 24 +/- 8 HU compared to red thrombi at 76 +/- 9 HU, with a linear relationship between haematocrit level and CT attenuation [13]. Presumably it also reflects the acuity of the thrombus, although further research is required to determine the specific relationship between time from symptom onset and the presence of the HAS. A non-significant relationship has been noted on previous studies, although this has not been examined as a primary outcome [15, 20]. Despite this, prior studies involving intra-arterial thrombolysis have used the HAS and it’s subsequent disappearance as both a selection criteria and outcome measure to define successful recanalization in the first 24-h.

The potential benefits of further imaging guidance to identify onset time is pertinent in the time critical setting of potential thrombolysis within the first 4.5-h following stroke. Although advanced imaging systems examining penumbra and perfusion show promise they are still not available in all centres. In this study, we aimed to establish the relationship between stroke onset time and the HAS.

Methods
Participants
All patients presenting with an ischaemic stroke between 2007–2011 to the Royal Melbourne Hospital stroke care unit who had both NCCT (4.5 mm slices) and CTA on admission were retrospectively identified from the stroke database. Patients imaging was reviewed to identify those who had confirmed vessel occlusion on CTA that corresponded clinically with presenting symptoms. Those who either had haemorrhagic strokes or no confirmed arterial occlusion on CTA were excluded from the study as were those with strokes not affecting the Middle Cerebral Artery (MCA). Demographic and stroke risk factors including hypertension, diabetes, age, smoking history, history of atrial fibrillation, hypercholesterolaemia were extracted from the stroke database. Ethics approval was granted via the human research ethics committee prior to commencement.

Procedures
All NCCTs were reviewed by a blinded assessor (JH) to identify the Hyperdense Middle Cerebral Artery (HMCA) defined as an MCA denser than its contralateral counterpart including the ‘dot’ sign of the MCA in the sylvian fissure. All hyperdense signs carried the additional criteria of disappearance of the increased density on bone window settings. Four random 1 mm² spot measurements in Hounsfield Units (HU) were taken from the highest density area on visual estimation of the affected artery and the mean of these values used, with similar measurements taken from the corresponding non-affected artery on the contralateral side.

Following identification of the HAS, the corresponding CTA was then reviewed. Cases were excluded where a corresponding arterial occlusion was not identified on CTA at the site of the HAS. A randomized subset of two-third of all NCCTs and corresponding CTAs were reviewed independently by a second blinded neuroradiologist (one of BY, PJM or RJD). The interobserver agreement for the HAS and occlusion was assessed using Cohen’s kappa statistics.

Time of stroke onset data was collected and stored in the stroke registry. Where a wake-up stroke occurred, time of stroke onset was measured as midnight.

Data analysis
Statistical analyses were performed using Stata IC v12 software. Data are presented as means and standard deviations or medians and interquartile range for continuous variables and as counts and percentages for categorical variables. Univariate comparisons of various factors of interest between HAS and non-HAS groups were made using Wicoxon-Mann–Whitney ranksum test or Fisher’s exact test depending on the nature of the underlying distribution. The differences in time from onset of stroke symptoms in patients with and without HAS were assessed using Wicoxon-Mann–Whitney ranksum test, while the magnitude of association between time from onset of stroke symptoms and the ratio of artery density between affected/non-affected arteries was assessed using Spearman correlation coefficient. For all statistical analyses, the significance level was set at a p < 0.05.

Results
A total of 154 subjects with acute ischaemic stroke and corresponding MCA arterial occlusion on CTA were included in the in the study. Of these, 106 (68.8 %) had a HAS and 7 (4.5 %) were wake-up strokes. There were no significant differences in age distribution or vascular...
risk factor presence between subjects with or without HAS. There was a significantly higher proportion of males in the group with an absent HAS (70.8 % vs 50.9 %, \( p = 0.02 \)). Median admission NIHSS scores in the HAS group (17 points, interquartile range 10 – 21) were significantly greater than in the non-HAS group (12 points, interquartile range 7 – 18, \( p = 0.02 \)). Mean discharge Modified Rankin Score was significantly higher in the HAS group (3.9 vs 3.2, \( p = 0.01 \)). The baseline and summary characteristics of the subjects are listed in Table 1.

Interrater agreement on review of 102 scans (66 % of total) by a second neuroradiologist of a randomised subset of subjects for visual estimation of the HAS was moderate, with a kappa value 0.60.

Within the first 24-h, the median time from onset of stroke symptoms in patients with HAS was 134 min (interquartile range 89 – 263 min) and without HAS 126 min (interquartile range 85 – 345 min), resulting in the absence of the evidence of statistically significant association between the HAS on visual estimation and time from stroke within the first 24-h (\( p = 0.70 \)). Ratio of artery density between affected/non-affected arteries similarly was not significantly associated with time from stroke onset within the first 24-h (Spearman’s Rho = –0.8; \( p = 0.42 \)).

On subgroup analysis comparing 118 subjects presenting within the first 4.5-h post stroke onset with 36 subjects presenting 4.5-24 h post onset, there was no significant association between presence or absence of the HAS on visual estimation (Fisher’s exact \( p = 0.83 \)).

Figure 2 displays a scatterplot of the ratio to time from stroke onset. An additional three subjects were excluded due to presenting greater than 24-h post stroke onset. All of these subjects had an absent HAS. There were no significant differences in age distribution, sex ratio or presence of vascular risk factors between the groups less than/greater than 24-h post stroke onset.

**Discussion**

Accurate determination of stroke onset time has gained increasing importance with the advent of time-dependent thrombolysis. The benefits on thrombolysis in the first 4.5 h has increased the necessity of objective means to assist in determining stroke onset, especially in patients who are unable to communicate or remember the onset of stroke symptoms (such as wake-up strokes). Newer imaging techniques such as diffusion-weighted MRI and CT-perfusion have yet to show clear guidance as to specific stroke onset time, and are available only in larger centres.

Our study further attempted to define the relationship between the HAS and stroke onset time. Previous studies have consistently found the HAS to be an early sign of ischaemia [6, 8, 10, 15, 20]. The association between time of stroke onset, imaging time and presence of HAS, however has not been studied as a primary outcome.

The HMCAS has consistently shown to be associated with earlier presentation [22], poor clinical outcome and

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### Table 1 Summary statistics for patients with and without hyperdense artery sign

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with HAS</th>
<th>Patients without HAS</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, n(%)</td>
<td>106 (68.8)</td>
<td>48 (31.2)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>69.7</td>
<td>68.4</td>
<td>0.62</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>54 (50.9)</td>
<td>34 (70.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vascular Risk Factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>62 (58.5)</td>
<td>29 (60.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>23 (21.7)</td>
<td>12 (25.0)</td>
<td>0.65</td>
</tr>
<tr>
<td>Cholesterol, mean</td>
<td>4.49 mmol/L</td>
<td>4.60 mmol/L</td>
<td>0.72</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>40 (37.7)</td>
<td>16 (33.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>24 (22.6)</td>
<td>11 (22.9)</td>
<td>0.97</td>
</tr>
<tr>
<td>Ischaemic Heart Disease</td>
<td>21 (19.8)</td>
<td>16 (33.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>12 (11.3)</td>
<td>5 (10.4)</td>
<td>0.87</td>
</tr>
<tr>
<td>NIHSS Score admission, median (range)</td>
<td>17 (0–39)</td>
<td>12 (0–27)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke onset to NCCT, median (range)</td>
<td>134 (52–1092)</td>
<td>126 (34–997)</td>
<td>0.76</td>
</tr>
<tr>
<td>Ratio affected:non-affected artery, median (range)</td>
<td>1.44 (1.09–2.00)</td>
<td>1.02 (0.84–1.47)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean artery density affected artery (HU)</td>
<td>59.0</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>11 (10.4)</td>
<td>2 (4.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>MRS at discharge, mean (range)</td>
<td>3.9 (0–6)</td>
<td>3.2 (0–6)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
prognosis [11, 18, 24, 27], severe neurological deficits and larger stroke territory [18, 24, 27]. Initial NIHSS/MRS scores and outcome at three-months are significantly worse in patients presenting with HMCAS [8, 11, 16, 18, 24, 27, 28]. Our study similarly displayed a significantly higher NIHSS score at admission with a present HAS as well as poorer clinical outcome as evidenced by higher discharge Modified Rankin Score. There was a trend towards greater mortality with a HAS in our study however this was not statistically significant.

Although clot density on NCCT has been reported to decrease in a linear fashion in comparison to time, this has not been specifically studied in relation to time from symptom onset as a primary outcome [4]. In a large study of the SITS register by Kharitonova et al., representing 1905 subjects with a HMCAS at presentation, 48 % had a disappearing HMCAS at 22–36 h after thrombolysis [12]. Those with a disappearing HMCAS on follow-up scan were significantly younger, less likely to have initial CT signs and had milder strokes as measured by initial NIHSS score. Early improvement in NIHSS was a significant predictor for disappearing HMCAS [12]. It is uncertain from the literature as to whether a disappearing HMCAS represents recanalization vs change in clot composition and likewise a persisting HMCAS may not always equate with continued occlusion [12, 22, 26]. Our finding of a higher NIHSS with the HAS, consistent with other studies, may be associated with larger or more prolonged arterial occlusion. The natural history of the HMCAS and rate of disappearance has not been specifically examined to date.

We found that a present HAS (by visual estimation) may be associated with time only on a small subset of patients 24-h post stroke onset. Our findings also show that the HAS is not associated with earlier presentation,
although notably further studies examining subjects presenting greater than 24-h would be beneficial. Previous studies have reported a prevalence of hyperdense MCA sign at 75 % in the first 3-h and in 15 % from hours 12–24. Studies with hyperdense PCA and basilar signs have yielded similar results [15].

Similarly, there was no association between ratio of affected: non-affected mean artery density and time from stroke onset within the first 24-h. Prior studies have reported significantly reduced false positive rates when using measurement of absolute attenuation of affected and normal vessels, using a ratio of > 1.2 [14]. Our finding of a significantly reduced ratio in the subgroup of patients greater 24-h post stroke, although modest, may assist as a guide to determining stroke onset.

We also analysed a subgroup of patients presenting within the first 4.5-h post stroke onset, given accurate determination of stroke onset time in this period is clinically applicable to eligibility for thrombolysis. This subgroup did not display a statistically significant association with either presence of the HAS or arterial density ratio in comparison to those presenting 4.5-24 h post stroke onset.

More recently the HAS has been used as an element of functional outcome predictor scores (the DRAGON criteria) and a prognostic marker for thrombolysis [1, 23]. The HAS is a common inclusion in the development of functional outcome predictors scores for patients who receive thrombolysis [1, 23]. The lack of time-dependency of the HAS that was shown in our study should be considered in the use of these measures.

There were a number of limitations to our study. The vast majority of scans in our study were taken on 4.5 mm thick slice NCCT, with thin-slice NCCT only recently initiated on a regular basis in our institution. Recent evidence suggests that thin-slice NCCT allows more reliable and sensitive detection of arterial occlusion and has significantly higher inter-rater reliability [21]. Further studies using thin-slice NCCT may yield further information regarding the usefulness of HAS in predicting time from stroke onset.

Conclusion
We showed that the likelihood of HAS in acute ischaemic stroke is not associated with time from onset of stroke within the first 4.5 or 24-h. Ratio of absolute artery density between affected and non-affected artery similarly is not associated with time from stroke onset. The HAS was associated with a higher NIHSS score at presentation.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
JH assisted in study design, performed data collection and drafted the manuscript. LC performed the statistical analysis and assisted in study design. PM and RD participated in reviewing CT scans and reviewed the study design. BY conceived of study, coordinated study design and reviewed CT scans. All authors read and approved the final manuscript.

Acknowledgments
Ethics approval granted from Human Research Ethics Committee, Royal Melbourne Hospital.

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References


Arterial Obstruction on Computed Tomographic or Magnetic Resonance Angiography and Response to Intravenous Thrombolitics in Ischemic Stroke

Grant Mair, MBChB; Rüdiger von Kummer, Prof Dr med; Alessandro Adami, MD; Philip M. White, MD; Matthew E. Adams, MBChB; Bernard Yan, MD; Andrew M. Demchuk, MD; Andrew J. Farrall, MD; Robin J. Sellar, MBBS; Eleni Sakka, MSc; Jeb Palmer; David Perry, BSc; Richard I. Lindley, MD; Peter A.G. Sandercock, DM; Joanna M. Wardlaw, MD; for the IST-3 Collaborative Group

Background and Purpose—Computed tomographic angiography and magnetic resonance angiography are used increasingly to assess arterial patency in patients with ischemic stroke. We determined which baseline angiography features predict response to intravenous thrombolitics in ischemic stroke using randomized controlled trial data.

Methods—We analyzed angiograms from the IST-3 (Third International Stroke Trial), an international, multicenter, prospective, randomized controlled trial of intravenous alteplase. Readers, masked to clinical, treatment, and outcome data, assessed prerandomization computed tomographic angiography and magnetic resonance angiography for presence, extent, location, and completeness of obstruction and collaterals. We compared angiography findings to 6-month functional outcome (Oxford Handicap Scale) and tested for interactions with alteplase effect using ordinal regression in adjusted analyses. We also meta-analyzed all available angiography data from other randomized controlled trials of intravenous thrombolitics.

Results—In IST-3, 300 patients had prerandomization angiography (computed tomographic angiography=271 and magnetic resonance angiography=29). On multivariable analysis, more extensive angiographic obstruction and poor collaterals independently predicted poor outcome ($P<0.01$). We identified no significant interaction between angiography findings and alteplase effect on Oxford Handicap Scale ($P \geq 0.075$) in IST-3. In meta-analysis (5 trials of alteplase or desmoteplase, including IST-3, $n=591$), there was a significantly increased benefit of thrombolitics on outcome (odds ratio>1 indicates benefit) in patients with (odds ratio, 2.07; 95% confidence interval, 1.18–3.64; $P=0.011$) versus without (odds ratio, 0.88; 95% confidence interval, 0.58–1.35; $P=0.566$) arterial obstruction ($P$ for interaction 0.017).

Conclusions—Intravenous thrombolitics provide benefit to stroke patients with computed tomographic angiography or magnetic resonance angiography evidence of arterial obstruction, but the sample was underpowered to demonstrate significant treatment benefit or harm among patients with apparently patent arteries.

Clinical Trial Registration—URL: http://www.isrctn.com. Unique identifier: ISRCTN25756518.

Key Words: arteries ▪ brain infarction ▪ cerebral angiography ▪ meta-analysis ▪ stroke
supply, influences the response to intravenous thrombolytics. A retrospective stroke registry observed a trend for more favorable clinical outcome after intravenous alteplase in patients with intracranial arterial occlusion versus those with no/minimal obstruction in whom it was unclear if intravenous alteplase was beneficial or not.

Few randomized controlled trials (RCTs) of intravenous thrombolytics included CTA or MRA to determine whether angiographic obstruction–occlusion or collateral supply modifies the treatment response. A pooled analysis of DIAS (Desmoteplase in Acute Ischemic Stroke), DIAS-2, and DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) demonstrated that patients with complete arterial occlusion or severe obstruction had better outcomes after desmoteplase than placebo, but in patients with minimal obstruction or normal arteries, there was no significant difference between desmoteplase versus placebo. In EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial), patients with middle cerebral artery (MCA) rather than internal carotid artery (ICA) obstruction demonstrated better outcome after intravenous alteplase, but they did not test for an alteplase–arterial patency interaction.

The IST-3 (Third International Stroke Trial) was a large (n=3035) RCT that tested whether intravenous alteplase given within 6 hours of ischemic stroke improved functional outcome at 6 months compared with control. In IST-3, some centers routinely performed CTA or MRA prerandomization. As prespecified, we investigated whether arterial obstruction or collateral status on prerandomization CTA and MRA influenced outcome after alteplase versus control. In addition, we meta-analyzed all RCTs of intravenous thrombolytics in ischemic stroke with baseline angiography data.

Methods

Third International Stroke Trial

IST-3 was an international, multicenter, PROBE trial (prospective, randomized, open-label, blinded end point) of intravenous alteplase in acute ischemic stroke. Ethical approval was granted by the Multicentre Research Ethics Committees, Scotland (MREC/99/0/78) and by local ethics committees. Enrollment, randomization, data collection and analysis, and adherence to CONSORT (Consolidated Standards of Reporting Trials) recommendations have been published. Briefly, adults with acute stroke of any severity, in whom CT or MR imaging had excluded intracranial hemorrhage and structural stroke mimics, who did not meet the prevailing license criteria for alteplase but had no clear contraindication to treatment, were eligible for the trial if treatment could be started within 6 hours of known stroke onset. Informed consent was obtained for all patients. Baseline stroke severity before randomization was assessed with the National Institutes of Health Stroke Scale (NIHSS). After entry of baseline data, patients were randomly allocated to immediate intravenous alteplase (0.9 mg/Kg) or control. Functional outcome was assessed at 6 months with the Oxford Handicap Scale (OHS), which is similar to the modified Rankin Scale.

Angiographic Imaging in IST-3

IST-3 centers that routinely performed CTA or MRA in stroke submitted these images for assessment. Here, we include only IST-3 patients with angiography performed prerandomization. Images were anonymized and uploaded to a web-based rating platform, the Systematic Image Review System V2. Systematic Image Review System V2 provides secure anonymized image viewing via a browser (http://www.neuroimage.co.uk) and simultaneously records the scan interpretation using a validated proforma (http://www.sbirc.ed.ac.uk/research/imageryanalysis.html).

All angiographic imaging in IST-3 was assessed centrally by a panel of 10 experts in stroke imaging (7 neuroradiologists and 3 neurologists/stroke physicians). Readers were masked to all clinical, treatment, and functional outcome data and to imaging from different time points (concurrent plain imaging was viewed with angiography). IST-3 angiography was analyzed independently from the plain CT and MR imaging scans of the main IST-3 trial.

Scan readers recorded the presence, location, and severity of all arterial obstructions, largest affected artery first plus ≥2 additional segments (Table I in the online-only Data Supplement). Locations were ICA, MCA, anterior cerebral artery, posterior cerebral artery, vertebral artery, or basilar artery. We grouped arterial segments as proximal (ICA, main stem MCA, vertebral artery, and basilar artery) or distal (Sylvian branch of MCA, anterior cerebral artery, and posterior cerebral artery).

Readers coded the focus of arterial obstruction using a modified Thrombolysis in Cerebral Infarction (TICI) and the IST-3 angiography scores. Both are scalar and range from occlusion (0), through decreasing grades of obstruction, to normal (3 for TICI and 4 for IST-3). For this analysis, we categorized the TICI score 0 to 2b and the TICI score 0 to 2a as obstruction and IST-3 score 3 to 4 and the TICI score 2b to 3 as patent.

Readers also coded the clot burden score in patients with anterior circulation obstruction (subtracts the sum of the number of arterial segments affected from 10, where score 0=all segments affected and 10=no segments affected) and the collateral vessel supply in patients with ICA or MCA obstruction (categorized as good where the entire MCA distal to obstruction reconstituted with contrast, moderate where there was some MCA branch reconstitution, or poor if only distal superficial branches reconstituted).

We tested previously interobserver reliability for the IST-3 panel’s CTA assessments (but because of the small number of cases, not MRA) on 15 representative scans, finding substantial agreement for arterial obstruction on TICI, IST-3 angiography, and clot burden scores (Krippendorff ρ=0.60, 0.66, and 0.63, respectively) and moderate agreement for collateral score (0.56).

Statistical Analysis: IST-3 Angiography Data

For univariate analysis of normally distributed data, we compared ratios and means with t tests; for nonparametric data, we used Mann–Whitney U tests to compare medians and Spearman ρ to assess for correlation. We used multifactor ANOVA to look for interactions between combinations of angiographic findings and OHS. To test for associations between angiography findings, alteplase versus control and outcome, we used multivariable ordinal regression to calculate common odds ratios (ORs) with OHS at 6 months as the dependent variable. We first tested the impact of different angiography characteristics on outcome individually, controlled for patient age, NIHSS, time from stroke onset to scan, and alteplase treatment allocation (here, OR <1 indicates worse outcome with alteplase). We then compared alteplase treatment effect on outcome (here, OR <1 favors control) for dichotomies (more normal versus less normal) of each angiography characteristic individually, controlled for patient age, NIHSS, and time from stroke onset to scan and tested for treatment interactions by comparing ORs between dichotomies. For this latter analysis only, we dichotomized clot burden and collateral scores as better (8–9 and good) versus worse (0–7 and moderate–poor, respectively).

Meta-Analysis

We identified all RCTs comparing intravenous thrombolytics with control among patients with baseline angiography after ischemic stroke from the Cochrane Collaboration systematic review on “Thrombolysis for Acute Ischaemic Stroke” and contacted investigators for additional data where necessary. We used the random effects method to perform 2 separate meta-analyses to obtain summary ORs.
Angiography Findings: IST-3
In IST-3, 146 of 300 (48.7%) patients had intracranial arterial obstruction on angiography (Table 2). ICA (47/146=32.2%) or MCA mainstem (57/146=39.0%) obstruction was most common. For those with arterial obstruction, >1 arterial segment was affected in approximately half, 2 segments in 54 of 146 (37.0%), and 3 segments in 15 of 146 (10.3%).

From 288 patients with an IST-3 Angiography score, 104 (36.1%) scored 0 to 2b, whereas 184 (63.9%) scored 3 to 4 (Table 2 for concurrent TICI scores). The median clot burden score was 8 (2 segments affected). Similar proportions had good (48/135=35.6%), moderate (37/135=27.4%), or poor (50/135=37.0%) collateral scores.

Angiography, Stroke Severity, and Functional Outcome: IST-3
On univariate analysis, all categories of angiographic abnormality were associated with significantly worse baseline stroke severity and poorer 6-month outcome (P<0.0001 for most; Table III in the online-only Data Supplement). A 3-way ANOVA found no interaction between any combination of the effects of TICI, clot burden, and collateral scores on OHS (P=0.814; P=0.564; Table IV in the online-only Data Supplement). In multivariable ordinal regression analysis, controlled for age, NIHSS, time from stroke onset to scan and alteplase treatment allocation; having a greater number of obstructed arterial segments (OR, 0.41; 95% confidence interval [CI], 0.22–0.76; P=0.005), a worse clot burden score (OR, 0.78; 95% CI, 0.62–0.97; P=0.026), or poorer collaterals (OR, 0.53; 95% CI, 0.32–0.85; P=0.009) were all independent predictors of worse 6-month outcome, but not proximal versus distal (or ICA versus MCA) arterial obstruction, or the residual arterial caliber at the point of obstruction on IST-3 angiography or TICI scores (Table 3).

Angiography and IV Thrombolytics: Meta-Analysis of All Trials
We included 2 trials of intravenous alteplase (288 patients from IST-3 and 87 from EPITHET) and 3 trials of intravenous desmoteplase (216 patients from DIAS, DIAS-2, and DEDAS). Meta-analysis showed that patients with arterial obstruction were significantly more likely to have better functional outcome with intravenous thrombolytics versus control

| Table 1. Comparison of Baseline Data and Main Outcomes in IST-3 (Third International Stroke Trial) Patients With Angiography Allocated to Alteplase and Control (n=300) |
|---|---|---|---|---|---|---|
| | Alteplase, n=147 | Control, n=153 | P Value for Difference |
| Age, y, median (IQR) | 81 (73–86) | 80 (69–85) | 0.274 |
| Male sex (%) | 63 (42.9) | 69 (45.1) | 0.697 |
| Time from stroke onset to baseline scan, min, mean (SD) | 184 (82) | 175 (78) | 0.344 |
| Time from stroke onset to randomization, min, mean (SD) | 243 (82) | 238 (79) | 0.584 |
| Baseline NIHSS, median (IQR) | 10 (5–17) | 9 (5–16) | 0.603 |
| Clinical stroke syndrome27 (%) | | | 0.590 |
| TACI | 49 (33.3) | 50 (32.7) | |
| PACI | 64 (43.5) | 68 (44.4) | |
| LACI | 11 (7.5) | 14 (9.2) | |
| POCI | 23 (15.6) | 20 (13.1) | |
| ASPECTS,26 median (IQR) | 10 (8–10) | 10 (8–10) | 0.914 |
| 6-mo OHS, median (IQR) | 3 (1–5) | 3 (1–5) | 0.726 |
| 6-mo mortality (%) | 32 (21.8) | 35 (22.9) | 0.819 |

ASPECTS indicates Alberta Stroke Program Early CT Score; IQR, interquartile range; LACI, lacunar infarct; NIHSS, National Institutes of Health Stroke Scale; OHS, Oxford Handicap Scale; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; and TACI, total anterior circulation infarct.
Stroke February 2017

Table 2. Angiography Findings for the 300 Patients Randomized in IST-3 With CTA or MRA

<table>
<thead>
<tr>
<th>Angiographic obstruction, n=300*</th>
<th>Alteplase, n=147</th>
<th>Control, n=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>No</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>No. of obstructed arterial segments, n=146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Largest arterial segment obstructed, n=146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>MCA mainstem</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>MCA Sylvian branch</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Basilar</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Vertebral</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>ACA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PCA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Location of angiographic obstruction, n=142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal vessel only</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Proximal vessel only</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Proximal and distal</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>IST-3 angiography score, n=288</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>2b</td>
<td>7</td>
<td>9</td>
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<td>2a</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>0</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>TICI score, n=288</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>2b</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>2a</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>0</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Clot burden score, n=123</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
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</tr>
<tr>
<td>2</td>
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<td>2</td>
</tr>
</tbody>
</table>

Table 2. Continued

<table>
<thead>
<tr>
<th></th>
<th>Alteplase, n=147</th>
<th>Control, n=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Collateral score, n=135</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Moderate</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Poor</td>
<td>22</td>
<td>28</td>
</tr>
</tbody>
</table>

Clot burden and collateral scores were calculated only with anterior circulation obstruction. Obstruction was obscured or too peripheral for calculation of an IST-3 angiography, TICI or clot burden score in 12 cases. Not all patients with normal IST-3 angiography scores had normal TICI scores and vice versa. ACA indicates anterior cerebral artery; CTA, computed tomographic angiography; ICA, internal carotid artery; IST-3, Third International Stroke Trial; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; and TICI, Thrombolysis in Cerebral Infarction.

*Readers were asked is there an abnormal/occluded artery on CTA/MRA?

(Continued)

Tables continued

Discussion

This analysis of CTA and MRA data from 5 RCTs of intravenous thrombolytics (alteplase and desmoteplase), including IST-3, comprising 591 patients treated within 6 hours of stroke, indicates that patients with angiographic obstruction/occlusion benefit significantly more from intravenous thrombolytics than patients without arterial obstruction. Therefore, where endovascular therapy is not available, intravenous thrombolytics remain an important treatment. The significant interaction between angiography appearance and intravenous thrombolytics does not mean that patients with normal baseline angiography gain no benefit from intravenous thrombolytics; the meta-analysis was neutral in this group, showing neither benefit or harm, but the sample is too small to exclude modest benefit or harm. It is important to remember that patients with normal angiograms may have arterial obstruction(s) too small to see on CTA/MRA, and intravenous thrombolytics may be beneficial in these patients.

In IST-3, we also demonstrate that having a greater number of obstructed arterial segments or poor collateral supply was associated with poor 6-month functional outcome, independent of stroke severity and alteplase treatment, that is, alteplase was less likely to improve outcome in these patients. Those with a greater number of obstructed segments may, therefore, have the most to gain from endovascular therapy, which several RCTs have recently shown to be superior to
intravenous alteplase alone among patients with angiography-confirmed proximal intracranial arterial obstruction. Consistent with our results, post hoc analysis of one of these endovascular treatment trials demonstrated that patients with poor collateral supply had poorer outcomes than those with good collaterals.

We could not confirm in the meta-analysis that patients with MCA versus ICA obstruction responded differently to thrombolytics, but the sample available for this comparison was very small. In general, we were unable to identify available comparable trial data for most of the other angiography characteristics assessed in IST-3. To better understand thrombolysis–angiography interactions, future RCTs of acute stroke therapy with CTA or MRA should examine location, extent, completeness of arterial obstruction, and adequacy of collaterals, to refine how these findings could help treatment decisions.

**Strengths and Limitations**

Strengths of IST-3 include our use of robust, validated methods for scan management, of scoring angiograms, with blind reading and moderate to substantial interobserver agreement. Limitations of IST-3, discussed previously, include the potential introduction of bias through its open design. Angiographic imaging was not a requirement of IST-3, but some centers performed baseline CTA or MRA for ischemic stroke routinely; therefore, the angiography analysis was preplanned to maximize knowledge gained from an RCT. The results of angiography were not used to determine trial eligibility, and at the time of IST-3 enrollment, there were virtually no data on how angiography results should be used in this context. Therefore, clinical uncertainty as to whether treatment with alteplase would be beneficial existed even for patients with large artery obstruction. Angiography was however performed in only 10% of IST-3 centers, potentially reflecting selection bias and restricting generalizability of the findings to all current stroke centers. Nevertheless, IST-3 angiography represents real-world practice, where nearly 50% had angiographic obstruction and with 300 patients, is the largest angiography data set from an RCT of intravenous alteplase in ischemic stroke. Despite this, the wide CIs indicate that our sample is underpowered to estimate the effect of angiography findings on alteplase response. We used dichotomies of better versus worse angiography scoring to simplify scalar data in IST-3. We acknowledge that different dichotomies of the same scalar data could provide different results, but we felt that our technique nevertheless provided a meaningful and useable summary. For the meta-analysis, slight inconsistencies in angiogram rating in future trials should be resolved.

### Table 3. Multivariable Ordinal Regression Analyses Testing for Independent Associations Between Angiographic Findings in IST-3 and 6-Month Functional Outcome on the OHS

<table>
<thead>
<tr>
<th>Imaging Characteristic</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased number of obstructed arterial segments, n=146</td>
<td>0.41</td>
<td>0.22–0.76</td>
<td>0.005</td>
</tr>
<tr>
<td>Obstructed proximal vs distal artery, n=142</td>
<td>0.45</td>
<td>0.20–1.02</td>
<td>0.055</td>
</tr>
<tr>
<td>Obstructed ICA vs MCA, n=135</td>
<td>0.85</td>
<td>0.40–1.81</td>
<td>0.679</td>
</tr>
<tr>
<td>Worse IST-3 angiography score, n=288</td>
<td>0.90</td>
<td>0.78–1.04</td>
<td>0.145</td>
</tr>
<tr>
<td>Worse TICI score, n=288</td>
<td>0.85</td>
<td>0.71–1.01</td>
<td>0.062</td>
</tr>
<tr>
<td>Worse Clot Burden Score, n=123</td>
<td>0.78</td>
<td>0.62–0.97</td>
<td>0.026</td>
</tr>
<tr>
<td>Poor Collateral Score, n=135</td>
<td>0.53</td>
<td>0.32–0.85</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Odds ratio <1 indicates a worse outcome. Six-month OHS was the dependent variable for each separate model. Results are adjusted for patient age, time from stroke onset to scan, stroke severity (National Institutes of Health Stroke Scale), and alteplase treatment allocation. ICA indicates internal carotid artery; IST-3, Third International Stroke Trial; MCA, middle cerebral artery; OHS, Oxford Handicap Scale; and TICI, Thrombolysis in Cerebral Infarction.

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**Figure 1.** IST-3 (Third International Stroke Trial), ordinal regression analyses, of the effect of alteplase treatment on outcome (Oxford Handicap Scale [OHS] as the dependent variable) in patients with more vs less normal results by different angiography features. Results represent odds ratio of better (right of vertical line) or worse (left of line) 6-month outcome with alteplase. Adjusted for age, time from stroke onset to scan, and stroke severity (National Institutes of Health Stroke Scale). ICA indicates internal carotid artery; MCA, middle cerebral artery; and TICI, Thrombolysis in Cerebral Infarction.
be encouraged because this will facilitate between-trial comparisons and meta-analysis.²⁸

Patients recruited in IST-3 after CTA or MRA were randomized and treated, on average, 10 minutes later than were those with only plain scans. The steep time dependency of alteplase effects on outcome means that even this small delay could reduce the potential benefit of treatment,²⁹ particularly on a population level if angiography is performed nondiscriminately in all ischemic stroke patients. Efforts should be directed at minimizing delays attributable to obtaining angiography in stroke.

**Figure 2.** IST-3 (Third International Stroke Trial), bar charts comparing Oxford Handicap Scale (OHS) distribution for alteplase and control groups in those with (A) and without (B) arterial obstruction.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Angiography Grading</th>
<th>Thrombolysis</th>
<th>Control</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Test for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST-3 (n=288)</td>
<td>IST-3 Score 3-4</td>
<td>87</td>
<td>97</td>
<td>0.72 (0.42-1.25)</td>
<td>p=0.075</td>
</tr>
<tr>
<td></td>
<td>0-2b</td>
<td>53</td>
<td>51</td>
<td>1.86 (0.76-4.53)</td>
<td>p=0.148</td>
</tr>
<tr>
<td>EPITHET (n=87)</td>
<td>TIMI 3</td>
<td>21</td>
<td>12</td>
<td>1.57 (0.40-6.12)</td>
<td>p=0.575</td>
</tr>
<tr>
<td></td>
<td>0-2</td>
<td>25</td>
<td>29</td>
<td>1.35 (0.51-3.57)</td>
<td>p=0.360</td>
</tr>
<tr>
<td>Alteplase Trials (n=375)</td>
<td>Normal</td>
<td>108</td>
<td>109</td>
<td>0.82 (0.46-1.45)</td>
<td>p=0.128</td>
</tr>
<tr>
<td></td>
<td>Obstructed</td>
<td>78</td>
<td>80</td>
<td>1.61 (0.63-3.10)</td>
<td>p=0.128</td>
</tr>
<tr>
<td>Desmoteplase Trials (n=216)</td>
<td>TIMI 2-3</td>
<td>143</td>
<td>73</td>
<td>1.11 (0.61-2.41)</td>
<td>p=0.050</td>
</tr>
<tr>
<td></td>
<td>0-1</td>
<td>72</td>
<td>32</td>
<td>4.14 (1.40-12.2)</td>
<td>p=0.017</td>
</tr>
<tr>
<td>Combined Result (n=591)</td>
<td>Normal</td>
<td>329</td>
<td>262</td>
<td>0.88 (0.58-1.35)</td>
<td>p=0.128</td>
</tr>
<tr>
<td></td>
<td>Obstructed</td>
<td>72</td>
<td>32</td>
<td>2.07 (1.18-3.64)</td>
<td>p=0.017</td>
</tr>
</tbody>
</table>

Figure 3. Meta-analysis of IST-3 (Third International Stroke Trial), EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial; alteplase), and the DIAS (Desmoteplase in Acute Ischemic Stroke, DIAS-2, and DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke; desmoteplase) trials comparing the effect of intravenous thrombolytics on functional outcome between patients with arterial patency vs obstruction. Raw treatment data were unavailable for the Desmoteplase trials. Results represent odds ratio of better (right of vertical line) or worse (left of line) outcome after thrombolysis. Open circles represent arterial patency (test for heterogeneity, $I^2=16\%$). Closed circles represent arterial obstruction ($I^2=16\%$). TIMI indicates Thrombolysis in Myocardial Infarction.
Conclusions
Intravenous thrombolytic therapy is significantly more effective in improving functional outcome in patients presenting with ischemic stroke who have arterial obstruction than in those with apparently patent arteries on CTA or MRA. Intravenous thrombolysis, therefore, remain an important treatment option. The data are too sparse to determine, in this analysis, whether patients without apparent arterial obstruction benefit from intravenous thrombolysis, bearing in mind that these patients may have thrombus too small to detect on CTA or MRA.

Acknowledgments
This article acknowledges Dr Veronica Murray, IST-3 (Third International Stroke Trial) National Co-ordinator for Sweden, expert stroke neurologist, friend, and colleague, whose energy, enthusiasm, and huge contribution ensured the success of IST-3 and who died suddenly in late 2014. The IST-3 collaborative group thanks all study participants. We gratefully acknowledge the trial steering committee and national coordinators (Appendix I in the online-only Data Supplement). IST-3 centers providing baseline angiograms are listed in Appendix III in the online-only Data Supplement. We are grateful to the EPITHET trial (Echoplanar Imaging Thrombolytic Evaluation Trial) investigators, especially Stephen M. Davis, Geoffrey A. Donnan, and Mark W. Parsons, for providing raw data for meta-analysis.

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References


Thrombus composition in acute ischemic stroke: A histopathological study of thrombus extracted by endovascular retrieval

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KEYWORDS
Stroke; Thrombus retrieval; Thrombus; Thrombolysis; Ischaemia

Summary
Background and purpose: The composition of occlusive thrombus in acute ischemic stroke may affect treatment success. Neuroimaging characteristics may correlate with thrombus composition. In this study we aimed to investigate the relationship between the hyperdense artery sign (HAS) on imaging and thrombus composition.
Materials and methods: Acute ischemic stroke patients who underwent endovascular thrombus retrieval from 2010–2012 were prospectively recruited. One blinded pathologist prepared the histology sections of retrieved thrombi whereby staining with haematoxylin and eosin and CD34 immunostain were performed. Histology sections were categorised into 4 phases of thrombus formation: red blood cell (RBC) dominant, RBC proportion equal to fibrin, fibrin dominant and organised fibrin. Computed tomography (CT) brain scans were assessed for HAS. Fisher’s exact test was performed to identify an association between HAS and thrombus composition.

Abbreviations: ANOVA, Analysis of variance; CT, Computed tomography; H&E, Haematoxylin and eosin; HAS, Hyperdense artery sign; ICA, Internal carotid artery; IQR, Interquartile range; IV, Intravenous; MCA, Middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; RBC, Red blood cell; SD, Standard deviation; TIA, Transient ischemic attack; tPA, Tissue plasminogen activator.
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Thrombus composition in acute ischemic stroke

Introduction

The most effective treatment for acute ischemic stroke is reperfusion therapy [1,2]. Current guidelines recommend IV tPA as the primary reperfusion therapy, based on randomised controlled studies, demonstrating improved clinical outcomes [1,3,4]. However, IV tPA is associated with high recanalisation failure rates. In particular, recanalisation of an occluded ICA occurs at only 4.4% and recanalisation of the basilar artery occurs at only 4% [5].

It has been postulated that IV tPA is more effective on thrombus in the early phases of formation and organisation, suggesting that thrombus composition may be the mechanism of recanalisation failure. [6–12]. Previous research has demonstrated time dependant histological phases of thrombus formation with the formation of a “white thrombus”, composed mainly of fibrin and platelets, being the first phase [13–16]. In comparison, thrombi of late phase formation, involving the formation of a “red thrombus”, are composed mainly of fibrin and RBC [15,16]. It is possible that the decreased efficacy of IV tPA on late phase thrombus is attributable to the organisation of fibrin within the “red thrombus”. A surrogate marker for organised fibrin is the presence of endothelial cell proliferation which can be detected with CD34 immunostain [17–19]. This novel technique enables the identification of potentially resistant thrombi in the late phases of formation.

Clinical evidence has shown that treatment efficacy for stroke is time-dependant, given that patients demonstrate better clinical outcomes when treatment is administered at the earliest opportunity [1,20–22]. Knowledge of occlusive thrombus composition prior to treatment may enable clinicians to predict the patient’s response to IV tPA and aid in more rapid selection of the most appropriate revascularisation strategy. There is emerging interest in utilising radiologic imaging characteristics as predictors of thrombus composition [23].

Advances in thrombus retrieval technology offers an opportunity to directly examine the occlusive thrombi retrieved from acute ischemic stroke patients [24]. This opens the possibility of correlating thrombus composition with pre-treatment neuroimaging. In this study, we investigated the relationship between radiologic imaging characteristics and thrombus composition. We hypothesised that the presence of HAS, determined by visual asymmetrical increased density of a cerebral artery on plain CT, is associated with the early phases of thrombus formation.

Materials and methods

This study was approved by the Human Research Ethics Committee. Forty acute ischemic stroke patients who underwent thrombus retrieval at our hospital between November 2010 and December 2012 were included in this study. Subjects presented with an acute ischemic stroke, defined by onset < 6 hours, and underwent routine plain CT upon arrival. IV tPA (Alteplase) (Boehringer Ingelheim; Ingelheim, Germany) treatment (0.9 mg per kilogram of body weight) was administered to eligible patients prior to thrombus retrieval being performed. Thrombus retrieval was conducted in the angiography suite by neurointerventionists with the Solitaire™ FR Revascularization Device (Covidien; Mansfield, M.A, USA). Thrombus fragments extracted during the retrieval procedure were immediately fixed in phosphate-buffered formalin (10%). The tissue specimens were then sent to pathology for histopathological analysis. Subjects were excluded from this study if there was no thrombus specimen available for histopathological analysis.

Histopathological analysis

Tissue processing and paraffin embedding of the formalin fixed tissue specimens was performed. The paraffin embedded tissue was sectioned in 10-micrometre thick sections and stained using H&E. The tissue sections were further stained with the immunostain CD34, a marker of endothelial cells. One blinded pathologist performed histological examination of the thrombus specimens. The specimens were qualitatively categorised into one of four phases of thrombus formation—RBC dominant, RBC proportion equal to fibrin, fibrin dominant or organised fibrin pathology. Fibrin organisation was determined by the presence of endothelial cell ingrowth within CD34 immunostained sections. Thrombus pathology was further categorised into early phase (RBC dominant and RBC proportion equal to fibrin) and late phase (fibrin dominant and organised fibrin) pathology.

Plain CT analysis

One neuroradiologist, being blinded to the histopathology results, reviewed the plain CT sequences acquired upon the patients’ presentation to hospital for the presence or absence of HAS. The presence of HAS was recorded by the neuroradiologist by visual inspection and was defined as

Results: Forty patients were included. The mean age was 65.6 ± 12.9 years and 67.5% were male. Atrial fibrillation was detected in 19 (47.5%) patients, diabetes mellitus in 6 (15.0%), hypercholesterolaemia in 11 (27.5%), hypertension in 20 (50.0%) and previous stroke or transient ischemic attack in 8 (20.0%) patients. Of the retrieved thrombi, 11 (27.5%) were RBC dominant, 11 (27.5%) RBC proportion was equal to fibrin, 7 (17.5%) fibrin dominant and 11 (27.5%) organised fibrin pathology. HAS was present in 29 (72.5%) patients and was significantly associated with thrombus early phase pathology (P < 0.05).

Conclusion: HAS was significantly associated with early phase thrombus composition. This may enable the prediction of thrombus composition and allow for targeted selection of therapeutic modality.

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an asymmetrical increased density within the region of an intracranial artery. Hounsfield Unit density measurements of the thrombi were also recorded.

Data collection

Radiographic, angiographic, clinical and demographic data were prospectively collected and stored in a central database as a part of ongoing studies at our centre. These data included age at presentation, gender, occlusion location, IV tPA administration, vascular risk factors (atrial fibrillation, ischemic heart disease, hypertension, diabetes mellitus, hypercholesterolaemia, previous stroke or TIA), baseline NIHSS score, thrombus pathology, CT to treatment time, procedure duration, onset to recanalisation time, HAS by visual inspection, Hounsfield Unit density and mechanism of stroke. The mechanism of stroke was classified as either cardioembolic or non-cardioembolic, where the diagnosis of cardioembolic stroke was defined by the TOAST classification system [25].

Statistical analysis

Pathological, radiographic and clinical data were analysed using descriptive statistical analyses. The presence or absence of HAS, along with the qualitative categorisation of thrombus pathology and diagnosis of cardioembolic stroke were treated as categorical variables. A $\chi^2$ and Fisher’s exact test were performed to explore the relationship between HAS and thrombus composition as well as to explore the relationship between thrombus composition and cardioembolic stroke. An ANOVA was used to explore the association between thrombus composition and onset to recanalisation time as well the association between thrombus composition and procedure duration. Statistical analysis was conducted using IBM® SPSS® Statistics software (Version 19; SPSS, Inc., Chicago, I.L, USA).

Results

Forty acute ischemic stroke patients fulfilled the selection criteria and were included in this study. Of the study population, 27 (67.5%) patients were male and the mean age at presentation was 65.6 (SD ±12.9) years. The Solitaire™ FR revascularization device was used in 40 (100%) cases and 28 (70.0%) patients received IV tPA prior to undergoing thrombus retrieval. Seventeen (42.5%) patients had an ICA occlusion, 22 (55.0%) had a MCA occlusion and 4 (10.0%) had an occlusion in the basilar artery. Patient demographic and clinical characteristics are further summarised in Table 1.

On histopathological examination, 11 (27.5%) of the extracted thrombi were classified as RBC dominant. These H&E stained sections were observed to have dominant proportion of RBC with a minimal amount of fibrin infiltration present (Fig. 1A). Eleven (27.5%) thrombi were classified as RBC proportion equal to fibrin pathology, with H&E stained sections displaying equal proportions of both RBC and fibrin (Fig. 1B). Seven (17.5%) thrombi were classified as fibrin dominant, with H&E stained sections being observed to have mostly fibrin infiltration (Fig. 1C) and 11 (27.5%) thrombi were classified as organised fibrin. These sections demonstrated the presence of endothelial cell ingrowth as indicated by CD34 immunostain and were therefore classified as organised fibrin pathology (Fig. 1D).

Assessment of pre-treatment plain CT sequences showed 29 (72.5%) HAS by visual inspection (Fig. 2). Of the cases with HAS, a higher frequency of early phase pathology (65.5%) than late phase pathology (34.5%) was found, (Table 2), with sub-categorisation of thrombus pathology resulting in RBC proportion equal to fibrin having the highest frequency (37.9%), followed by RBC dominant (27.6%), organised fibrin (20.7%) and fibrin dominant pathology (13.8%). A significant association ($P<0.05$) was found between the presence of HAS by visual inspection and early phase thrombus pathology (Fig. 3). Upon pathology sub-categorisation, a significant association ($P<0.05$) was found between visual inspection of HAS and RBC proportion equal to fibrin pathology. No significant associations were found between the remaining pathology categories and visual inspection of HAS.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean ± SD</strong></td>
<td>65.6 ± 12.9</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>20 (50.0)</td>
</tr>
<tr>
<td><strong>Previous Stroke/TIA, n (%)</strong></td>
<td>8 (20.0)</td>
</tr>
<tr>
<td><strong>IV tPA</strong></td>
<td></td>
</tr>
<tr>
<td>Administered, n (%)</td>
<td>28 (70.0)</td>
</tr>
<tr>
<td><strong>Occlusion location</strong></td>
<td></td>
</tr>
<tr>
<td>ICA, n (%)</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>MCA, n (%)</td>
<td>22 (55.0)</td>
</tr>
<tr>
<td>Basilar artery, n (%)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Cardioembolic stroke, n (%)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td><strong>NIHSS</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline, median (IQR)</td>
<td>17 (6.0)</td>
</tr>
<tr>
<td><strong>Presence of HAS</strong></td>
<td></td>
</tr>
<tr>
<td>Visual Inspection, n (%)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td>Hounsfield unit density, mean ± SD</td>
<td>43.1 ± 8.7</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td></td>
</tr>
<tr>
<td>RBC dominant, n (%)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>RBC = Fibrin, n (%)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>Fibrin dominant, n (%)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Organised fibrin, n (%)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td><strong>SD:</strong> standard deviation; TIA: transient ischemic attack; IV tPA: intravenous tissue plaminogen activator; ICA: internal carotid artery; MCA: middle cerebral artery; NIHSS: National Institute of Health Stroke Scale; IQR: interquartile range; HAS: hyperdense artery sign; RBC: red blood cell.</td>
<td></td>
</tr>
<tr>
<td>$^a$ n = 35.</td>
<td></td>
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</tbody>
</table>
Figure 1 Stained histology sections of retrieved thrombi demonstrating the four pathology categories of (A) RBC dominance in a H&E stained section, (B) RBC equal to fibrin in a H&E stained section, (C) fibrin dominance in a H&E stained section, and (D) fibrin organisation in a CD34 immunostained section.

Figure 2 Pre-treatment plain CT brain scan demonstrating (A) the presence of HAS (arrow) as indicated by an asymmetrical increased hyperdensity in the left ICA and (B) the absence of HAS with no asymmetrical increased hyperdensity present.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Frequency of HAS present and absent in early and late phase thrombus pathology.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early phase pathology</td>
</tr>
<tr>
<td>HAS present</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>Frequency (%)</td>
</tr>
<tr>
<td>HAS absent</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>Frequency (%)</td>
</tr>
</tbody>
</table>

HAS: hyperdense artery sign.
Cardioembolic occlusions were found to have the highest frequency of RBC proportion equal to fibrin pathology (33.3%), followed by organised fibrin pathology (28.6%), RBC dominant pathology (23.8%) and fibrin dominant pathology (14.3%), (Table 3). Further categorisation into late phase and early phase thrombus pathology showed that early phase pathology was more frequent (57.1%) in cardioembolic stroke than late phase pathology (42.9%). There was no significant association found between cardioembolic stroke and the individual thrombus pathologies, late phase or early phase pathology.

The mean time between stroke onset and recanalisation time was longer in late phase pathology thrombi (515.7 ± 468.6 mins) than early phase thrombi (322.9 ± 76.2 mins) ($P=0.1$). Pathology sub-categorisation revealed thrombi of organised fibrin pathology to have the greatest

---

**Table 3** Frequency of cardioembolic occlusion and mean recanalisation and procedure duration times for the four thrombus pathologies.

<table>
<thead>
<tr>
<th>Thrombus composition</th>
<th>Cardioembolic occlusion (%)</th>
<th>Onset to recanalisation time (mins) (mean ± SD range)</th>
<th>Procedure duration (mins) (mean ± SD range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC &gt; fibrin</td>
<td>23.8</td>
<td>340.2 ± 73.8</td>
<td>62.1 ± 23.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>249–480</td>
<td>22–109</td>
</tr>
<tr>
<td>RBC = fibrin</td>
<td>33.3</td>
<td>307.1 ± 78.4</td>
<td>70.3 ± 39.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>178–487</td>
<td>17–142</td>
</tr>
<tr>
<td>Fibrin &gt; RBC</td>
<td>14.3</td>
<td>387.9 ± 112.6</td>
<td>68.3 ± 42.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>260–603</td>
<td>29–149</td>
</tr>
<tr>
<td>Organised fibrin</td>
<td>28.6</td>
<td>597.1 ± 589.0</td>
<td>88.2 ± 19.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>204–1851</td>
<td>58–126</td>
</tr>
</tbody>
</table>

RBC: red blood cell; SD: standard deviation.

$^a$ n = 10.
mean onset to recanalisation time (597.1 ± 589.0 mins), followed by fibrin dominant (387.9 ± 112.6 mins), red blood cell dominant (340.2 ± 73.8 mins) and finally red blood cell equal to fibrin pathology (307.1 ± 78.4 mins), (Table 3). Similarly, mean procedure duration was longer in late phase pathology thrombi (80.4 ± 31.1 mins) than early phase (66.2 ± 31.7 mins) with sub-categorisation revealing organised fibrin to have the longest procedure duration (88.2 ± 19.7 mins) followed by RBC proportion equal to fibrin (70.3 ± 39.1 mins), fibrin dominant (68.3 ± 42.6 mins) and RBC dominant pathology (62.1 ± 23.4 mins) (Table 3). No significant associations were found between thrombus pathology and mean onset to recanalisation time or mean procedure duration.

Discussion

It has been proven that time to treatment is a critical determinant of thrombolysis efficacy. Patients achieve better clinical outcomes when treatment is administered at the earliest opportunity [1,20–22]. Failure of vessels to reanalyse is thought to be due to thrombus composition, with early phase thrombi responding better to IV tPA [6–12]. The results of our study showed a significant association between visual inspection of HAS and early phase thrombus pathology. This is consistent with a previous study [26]. Our finding provides evidence that analysis of pre-treatment plain CT scans is vital to the treatment selection for individual patients. Inspection of pre-treatment plain CT scans enables the presence or absence of HAS to be detected, allowing for thrombus composition to be determined. This may assist clinicians in deciding on the most appropriate therapeutic modality for individual patients, whether it is thrombolytic agents or more invasive techniques such as endovascular thrombus retrieval. The knowledge that pre-treatment plain CT scans can be utilised to predict thrombus composition and hence, response to treatment, is invaluable to clinical outcomes of acute ischemic stroke patients.

Histopathological analysis of retrieved thrombi in our study identified four distinct categories of thrombus composition: RBC dominant, RBC proportion equal to fibrin, fibrin dominant and organised fibrin. Our novel approach of utilising CD34 immunostain to determine organised fibrin pathology proved successful with 11 (27.5%) thrombus specimens being positive for endothelial cell ingrowth. While previous research has mostly identified thrombus composition as being either “red thrombus”, “white thrombus” or mixed, our novel technique of utilising CD34 for the detection of endothelial cells enabled clear differentiation of a fourth thrombus composition category—organised fibrin [11,26,27]. A limited number of previous studies have also identified the heterogeneity displayed between individual thrombus specimens, questioning the conventional diagnosis of thrombi as either “red” or “white” [13,27,28]. Our ability in this study to detect these late phase organised fibrin thrombi with CD34 will enable more thorough pathological analysis to be conducted on these thrombi in future studies and may provide further insight into their possible resistance to thrombolytic treatment.

Statistical analysis of thrombus composition categories with cardioembolic stroke data did not demonstrate significant associations. Previous research has been inconclusive and even contradictory as to the association between thrombus composition and cardioembolic stroke. Early research suggested that cardioembolic stroke may produce thrombi rich in fibrin composition, however, more recent evidence revealed that thrombi of non-cardioembolic stroke were composed of three times more fibrin than thrombi of cardioembolic stroke [29–31]. Furthermore, additional studies have not been able to discern any significant relationship between thrombus composition and cardioembolic stroke [13,32].

One previous study which explored the association between thrombus composition and an early vessel sign on pre-treatment plain CT indicated correlation [26]. However, the study only included cases of MCA occlusion and less than half of their study population had pre-treatment plain CT scans available for analysis. Our study was not limited by thrombus location with MCA, ICA and basilar territories included. This provided a study population that was more representative of the broad spectrum of cases that would present to hospitals. In addition, we were able to analyse pre-treatment plain CT scans for 100% of cases that were included in our study. Furthermore, in the previous study thrombus pathology was categorised into only three groups: RBC dominant, fibrin dominant and mixed. The utilisation of CD34 immunostain in our study enabled a more detailed categorisation of thrombus pathology, with a later, fourth phase category of organised fibrin being identified.

A recent study by Yilmaz et al. investigated whether thrombus attenuation on pre-treatment CT scans was a predictor of the angiographic outcome of mechanical thrombectomy [33]. The results of the study did not find a strong association between CT attenuation and angiographic results of mechanical thrombectomy. While this finding is to be noted, the investigated outcomes of Yilmaz et al. differ to this current histopathological study of retrieved thrombi.

While statistical significance was attained in our study, the small sample size proved a limiting factor. In addition, of all the thrombi retrieved, a proportion were fragmented or macerated due to the nature of the thrombus retrieval procedure. Furthermore, the administration of IV tPA may have altered thrombus composition [29]. This, in turn, could have affected imaging findings due to the possibility of differing results between pathology categorisation and visual inspection of HAS on corresponding pre-treatment plain CT scans. Finally, the possibility that the endothelial cells detected by CD34 immunostain in thrombus specimens were contaminating cells present due to the extraction of the thrombus retrieval device is apparent. However, this occurrence is unlikely due to the endothelial cells detected in our specimens by CD34 being embedded within the thrombus tissue, indicating the natural process of endothelial cell ingrowth. In comparison, if the endothelial cells detected were due to contamination, they would likely be found at the periphery of the thrombus tissue.

Conclusion

We conclude that thrombi composed of early phase pathology are associated with HAS on pre-treatment plain CT scans. The implications of this finding is that the presence or absence of HAS on pre-treatment plain CT scans may
enable clinicians to predict the composition of the occlusive thrombi and the effectiveness of treatment options.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References


Relative Filling Time Delay Based on CT Perfusion Source Imaging: A Simple Method to Predict Outcome in Acute Ischemic Stroke

W. Cao, B.C.V. Campbell, Q. Dong, S.M. Davis, and B. Yan

ABSTRACT

BACKGROUND AND PURPOSE: Collateral vessel status is strongly associated with clinical outcome in ischemic stroke but can be challenging to assess. The aim of this study was to develop a tomography perfusion source imaging–based assessment of collateral vessel status.

MATERIALS AND METHODS: Consecutive patients with ischemic stroke who received intravenous thrombolysis or intra-arterial reperfusion therapy after CTP were retrospectively analyzed. In those with middle cerebral artery or internal carotid artery occlusion, CT perfusion source imaging was used to identify the relative filling time delay between the normal MCA Sylvian branches and those in the affected hemisphere. Receiver operating characteristic analysis and logistic regression were used to assess the association of the relative filling time delay with the 24-hour Alberta Stroke Program Early CT Score based on noncontrast CT and the 90-day modified Rankin Scale score.

RESULTS: There were 217 patients treated in 2009–2011 who had CTP data, of whom 60 had MCA or ICA occlusion and 55 had 90-day mRS data. The intraclass correlation coefficient for relative filling time delay was 0.95. Relative filling time delay was correlated with 24-hour ASPECTS (Spearman $\rho = 0.674; P < .001$) and 90-day mRS score ($\rho = 0.516, P < .01$). Increased relative filling time delay was associated with poor radiologic outcome (ASPECTS, 0–7) (area under the curve = 0.79, $P < .001$) and poor functional outcome (mRS score, 3–6) (area under the curve = 0.77, $P = .001$). In multivariate logistic regression, the association of longer relative filling time delay with poor outcome remained significant, independent of age, sex, and baseline National Institutes of Health Stroke Scale score.

CONCLUSIONS: Relative filling time delay is a useful independent predictor of clinical outcome after ischemic stroke.

ABBREVIATIONS: CTP-SI = CT perfusion source imaging; rFTD = relative filling time delay

Leptomeningeal collateral flow has an important role in maintaining blood flow to brain regions distal to an arterial occlusion.1–5 Imaging assessment of leptomeningeal collaterals in humans does not depict the small interarteriolar connections directly but, instead, relies on an indirect assessment of the extent and rate of backfilling of pial arteries receiving blood flow through these collateral vessels.1,4,6,7 Many leptomeningeal collateral flow studies, most of which were CT angiography studies, used various grading methods to assess the vessel filling status in the Sylvian fissure by observers.3,8–11 Traditional assessment of leptomeningeal collateral flow by using static CTA images lacks temporal resolution. Although newer scanners offer whole-brain perfusion acquisitions that can be reconstructed to provide dynamic CTA by using advanced software,1,2 this technology is not yet widely available.

CT perfusion expands the role of CT in the evaluation of acute stroke by providing physiologic insights into cerebral hemodynamics and, in so doing, complements the strength of CTA by determining the consequences of vessel occlusions and stenosis.9,12,13 Although 1 study used CTP source data to confirm that contrast opacification was indeed retrograde collateral flow, no prior studies have graded collateral status by rating CTP source imaging (CTP-SI). We investigated a simple, time-resolved scale of collateral-derived contrast opacification in the Sylvian fissure as a predictor of radiologic and functional outcome. We hypothesized that delayed filling of the middle cerebral artery in the Sylvian fissure due to poor collateral flow would be associated with worse radiologic and functional outcome after ischemic stroke.
MATERIALS AND METHODS

Patients

We identified patients with acute ischemic stroke presenting to our institution between January 2009 and December 2011 within 4.5 hours of stroke-symptom onset who underwent multimodal CT imaging before reperfusion therapy from our prospectively recorded stroke data base. The subgroup with MCA or internal carotid artery occlusion was selected for this analysis. Patients with MCA occlusion of the M1 or both M2 segments proximal to the Sylvian fissure were included. Baseline National Institutes of Health Stroke Scale scores and 90-day modified Rankin Scale scores were obtained from the data base. The study was approved by the Melbourne Health Human Research Ethics Committee.

Imaging

Noncontrast CT, CT perfusion, and CT angiography were performed before therapy. Two separate CTP slabs, each 24-mm thick, were acquired consecutively (16-section Somatom CT; Siemens, Erlangen, Germany; 80 kV(peak), 209 mAs) and positioned to maximize supratentorial coverage. Iodinated contrast (40-mL iohexol 350 mg I/mL, Omnipaque 350; GE Healthcare, Milwaukee, Wisconsin) was injected at 8 mL/s, and 40 images were acquired every second (total acquisition time, 44 seconds). Each slab was formatted as two 12-mm sections. Follow-up NCCT was performed at a minimum of 24 hours after onset.

Imaging Analysis

NCCT, CTP, and CTA were reviewed by using standard PACS software, allowing reviewers to freely window and view the images. CTA images were reviewed by 1 stroke neurologist, to identify patients with complete (Thrombolysis in Myocardial Infarction, 0) occlusion of the MCA or ICA. In patients with MCA or ICA occlusion, review of cervical CTA did not detect any cases with moderate-to-severe stenosis (≥50%), which might have confounded relative filling time delay (rFTD) interpretation. Unprocessed CTP-SI DICOM images were used to identify the relative filling time delay between the normal MCA Sylvian branches and those in the affected hemisphere. It was calculated as the time difference between the first appearance of contrast in each Sylvian fissure (Fig 1). rFTD was then independently assessed by a neurointerventionalist (W.C.) and a stroke neurologist (B.C.V.C.), blinded to clinical outcomes. The agreement in rFTD assessment between observers (with a tolerance of ±1-second difference) was calculated. Cases with 1-second difference between the 2 raters were averaged, and those with ≥2-second difference were reviewed by an interventional neuroradiologist (B.Y.) to determine consensus. The Alberta Stroke Program Early CT Score of 24-hour NCCT was independently assessed by the neurointerventional and stroke neurologist blinded to all other information before consensus was reached.

Statistical Analysis

Statistical analyses were performed by using the Statistical Package for the Social Sciences, Version 19 (IBM, Armonk, New York), and STATA, Version 12 (StataCorp, College Station, Texas). P < .05 was considered to indicate statistical significance. Interobserver agreement (with tolerance of ±1-second difference) for the assessment of rFTD between the 2 observers was tested by using Cohen κ and intraclass correlation. Patients were dichotomized by using the 90-day mRS score into good (mRS score, 0–2) versus poor (mRS score, 3–6) outcome, and mortality (mRS score, 6) was analyzed separately. The 24-hour ASPECTS was dichotomized into good (ASPECTS, 8–10) versus poor (ASPECTS, 0–7) radiologic outcomes. Differences in patient characteristics between outcomes were tested by the Fisher exact test for categoric and the Mann-Whitney U test for continuous values. Comparisons of rFTD and baseline NIHSS scores between groups were performed by using the Mann-Whitney U test. The Spearman nonparametric rank correlation was performed to assess the correlation between rFTD and baseline NIHSS scores, 90-day mRS scores, and 24-hour ASPECTS. Multivariate binary logistic regression (including variables with P values < .05) was used to assess the association of rFTD with 24-hour ASPECTS and 90-day mRS scores. Receiver operating characteristic analysis was performed to determine the optimal threshold. Positive predictive value, sensitivity, and specificity at the optimal threshold were calculated.

RESULTS

Between January 2009 to December 2011, two hundred seventeen patients with acute ischemic stroke presented to our institution within 4.5 hours of stroke-symptom onset, were imaged with CTP, and then received intravenous tPA or intra-arterial therapy. Of those, 60 patients with acute occlusion identified in the ICA or MCA were included in this study. The mean patient age was 70 ± 10 years with 27/60 (45%) being women. Hypertension was found in 58.3% (35/60); diabetes mellitus, in 28.3% (17/60); hyperlipidemia, in 55% (33/60); atrial fibrillation, in 38.3% (23/60); and current or past smoking, in 18.3% (11/60) of the patients. The baseline median pretreatment NIHSS score was 16 (interquartile range, 3–27). Mean onset-to-therapy time was 141 ± 48 minutes. There were 41 patients (68.3%) treated with intravenous recombinant tissue plasminogen activator, and 19 patients (31.7%) received intra-arterial therapy, including 5 (8.3%) with rtPA/urokinase and 14 (23.3%) with mechanical thrombectomy. The site of
arterial occlusion on CTA was in the proximal (M1) MCA in 44 (73.3%) patients, the distal MCA (M2) in 8 (13.3%) patients, and the ICA in 8 (13.3%) patients. The 90-day mRS score was available in 55 patients. There was no significant difference in baseline characteristics in these patients compared with the entire population.

Good functional outcome (mRS score, 0–2) was seen in 23 patients (41.8%), and death occurred in 21.8% (12/55).

The variables in 60 patients with 24-hour ASPECTS and 55 patients with 90-day mRS scores were significantly associated with worse functional and mortality outcomes. Female sex was associated with worse functional outcome. Higher baseline NIHSS scores were strongly associated with worse radiologic outcome (P = .003).

In receiver operating characteristic analysis, increased rFTD was associated with 24-hour ASPECTS of ≤7 (area under curve = 0.79; 95% CI, 0.68–0.9; P < .001), 90-day mRS scores (3–6) (area under the curve = 0.77; 95% CI, 0.65–0.93; P = .001), and 90-day mortality (area under the curve = 0.79; 95% CI, 0.65–0.93; P = .002). The optimal threshold determined by the Youden index was 4.25 seconds for both functional and radiologic outcomes.

In multivariate logistic regression, rFTD was associated with functional and radiologic outcomes after adjustment for age, sex, and baseline NIHSS scores (Table 2).

Table 1: Comparison of patient characteristics in those with good-versus-poor outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive (n = 43)</th>
<th>Dead (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median) [yr]</td>
<td>69 (41–85)</td>
<td>73.3 (54–88)</td>
<td>.014</td>
</tr>
<tr>
<td>Female (%)</td>
<td>26</td>
<td>56.2</td>
<td>.026</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>52.1</td>
<td>62.5</td>
<td>.444</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>26</td>
<td>28.1</td>
<td>.867</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>60.8</td>
<td>46.8</td>
<td>.305</td>
</tr>
<tr>
<td>Current or past smoker (%)</td>
<td>26</td>
<td>9.3</td>
<td>.343</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>34.3</td>
<td>34.7</td>
<td>.975</td>
</tr>
<tr>
<td>Baseline NIHSS (median)</td>
<td>13 (6–20)</td>
<td>19 (6–27)</td>
<td>.001</td>
</tr>
<tr>
<td>OTT (median) (min)</td>
<td>120 (61–255)</td>
<td>140 (75–265)</td>
<td>.366</td>
</tr>
<tr>
<td>IV-tPA (%)</td>
<td>60.9</td>
<td>71.9</td>
<td>.561</td>
</tr>
<tr>
<td>IA-tPA/UK (%)</td>
<td>13</td>
<td>6.2</td>
<td>.639</td>
</tr>
<tr>
<td>Clot retrieval (%)</td>
<td>26.1</td>
<td>21.9</td>
<td>.717</td>
</tr>
<tr>
<td>rFTD (median) (sec)</td>
<td>3.5 (0–7.5)</td>
<td>5.75 (0–10)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Table 1. As expected, increased age and higher baseline NIHSS scores were significantly associated with worse functional and mortality outcomes. Female sex was associated with worse functional outcome. Higher baseline NIHSS scores were strongly associated with worse radiologic outcome (P = .003).

In receiver operating characteristic analysis, increased rFTD was associated with 24-hour ASPECTS of ≤7 (area under curve = 0.79; 95% CI, 0.68–0.9; P < .001), 90-day mRS scores (3–6) (area under the curve = 0.77; 95% CI, 0.65–0.93; P = .001), and 90-day mortality (area under the curve = 0.79; 95% CI, 0.65–0.93; P = .002). The optimal threshold determined by the Youden index was 4.25 seconds for both functional and radiologic outcomes.

In multivariate logistic regression, rFTD was associated with functional and radiologic outcomes after adjustment for age, sex, and baseline NIHSS scores (Table 2).
quantitative rFTD could be obtained by using time-attenuation
appearance time between raters was generally
ment for rFTD. The variability in the assessment of contrast-ap-
observer subjectivity and translated to excellent inter-rater agree-
simplicity of rating the first appearance of contrast minimized
oped rFTD as a marker to assess the collateral circulation. The
ischemic stroke.17-19 Collateral blood flow plays a pivotal role in
supply in the prediction of clinical and radiologic outcome after
vessel occlusion.

FIG 3. Longer median rFTD was significantly associated with poor functional and radiologic outcomes.

Table 2: Multivariate logistic regression for clinical and radiologic outcome

<table>
<thead>
<tr>
<th>Poor Outcomes</th>
<th>Predictors</th>
<th>β</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-Day mRS 3–6</td>
<td>Age</td>
<td>0.097</td>
<td>0.043</td>
<td>.024</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.548</td>
<td>0.816</td>
<td>.501</td>
</tr>
<tr>
<td></td>
<td>Baseline NIHSS</td>
<td>0.207</td>
<td>0.091</td>
<td>.023</td>
</tr>
<tr>
<td>90-Day death</td>
<td>Age</td>
<td>0.185</td>
<td>0.074</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Baseline NIHSS</td>
<td>0.239</td>
<td>0.116</td>
<td>.028</td>
</tr>
<tr>
<td></td>
<td>rFTD</td>
<td>0.302</td>
<td>0.158</td>
<td>.039</td>
</tr>
<tr>
<td>24-Hour ASPECTS ≤7</td>
<td>Baseline NIHSS</td>
<td>0.114</td>
<td>0.065</td>
<td>.082</td>
</tr>
<tr>
<td></td>
<td>rFTD</td>
<td>0.456</td>
<td>0.162</td>
<td>.005</td>
</tr>
</tbody>
</table>

85%), a specificity of 76% (95% CI, 52%–91%), and a positive predictive value of 84% (95% CI, 68%–94%).

DISCUSSION

We found that a simple visual rating of collateral flow by using CTP source images is significantly associated with clinical and radiologic outcome in ischemic stroke. The relative filling time delay assessed in the Sylvian fissure represents the abundance of leptomeningeal collateral supply. Longer rFTD was associated with adverse outcomes, independent of standard prognostic variables, including age and baseline NIHSS scores. These results suggest that rFTD, especially >4 seconds, may be clinically useful as a marker of poor prognosis after ischemic stroke with proximal vessel occlusion.

Several studies have established the importance of collateral supply in the prediction of clinical and radiologic outcome after ischemic stroke.17-19 Collateral blood flow plays a pivotal role in the pathophysiology of cerebral ischemia but is difficult to quantify due to its complexity. In this study, we developed a method to evaluate the collateral status in patients with acute ischemic stroke with MCA or ICA occlusions by using CTP-SI. In contrast to standard CTA, which is a single “snapshot” of cerebral blood flow, CTP-SI provides a dynamic view of filling in the intracranial collateral arteries. Additionally, previous CTA studies used a variety of methods for grading leptomeningeal collateral flow, and limited data on interobserver agreement are available.20 We developed rFTD as a marker to assess the collateral circulation. The simplicity of rating the first appearance of contrast minimized observer subjectivity and translated to excellent inter-rater agreement for rFTD. The variability in the assessment of contrast-appearance time between raters was generally <2 seconds. A more quantitative rFTD could be obtained by using time-attenuation curve analysis with a manually positioned region of interest, though this would require dedicated software. Because rFTD is normalized to contralateral delay, factors such as the contrast injection and cardiac output, which affect the absolute delay to filling, are negated.

Studies of CTP in acute stroke commonly focus on 4 perfusion map–based parameters: cerebral blood volume, cerebral blood flow, mean transit time, and time-to-peak enhancement, with the aim of distinguishing salvageable tissue (penumbra) from the irreversibly injured ischemic core. The use of CTP-SI in evaluating collateral blood flow has been largely untested but has the advantage of combining anatomic information with temporal resolution to assess both the structure and function of collateral pathways. Assessing rFTD based on CTP-SI is also robust to motion in uncooperative patients. No special software is needed to perform CTP-SI assessment, so the method is feasible in most hospitals.

Recently, timing-invariant CTA was used to obtain CTA images from the CT perfusion source data that are insensitive to the timing of contrast arrival21 and, therefore, display collateral vessels that are undetectable on standard CTA. With a visual 4-point grading scale, poor retrograde collateral flow on timing-invariant CTA was associated with poor clinical outcome.21 However, the temporal information provided by CTP is a key strength, and timing-invariant CTA does not consider the potential impact of delay, which, in our data, seems highly predictive of outcome. There are more sophisticated methods to assess collateral flow by using whole-brain CTP.22 However, these require 320-slice CT, which would limit their applicability. In contrast, rFTD assessment can be performed by using any CT scanner technology and is simple and robust in clinical practice.

There are several limitations of this study. First, this is a retrospective study in a selected population of patients with ischemic stroke with ICA or MCA occlusion. Second, the rFTD method is limited to large-vessel-occlusion stroke, and the utility and value of rFTD requires validation in an independent cohort. rFTD focuses on the Sylvian fissure and does not account for more peripherally located collateral flow. Finally, recanalization following treatment was not analyzed in this study because repeat vascular imaging was not routinely performed in clinical practice. Variable recanalization and the mix of IV-tPA and endovascular therapy may have potentially affected the outcome independent of collateral status. The recent neutral endovascular trials such as the Intervventional Management of Stroke III trial23 and the Mechanical
Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) trial\textsuperscript{2,3} suggest that rates of recanalization between IV and intra-arterial-treated patients during the period of our study were not likely to be very different. However, any effect of recanalization heterogeneity would have reduced the strength of association observed between rFTD and the clinical and radiologic outcomes, and our results would, therefore, be a conservative estimate of the prognostic value of rFTD.

CONCLUSIONS

rFTD obtained by CTP-SI is a simple method to quantify cerebral collateral circulation and help overcome the lack of temporal resolution of CTA for collateral assessment. Patients with longer rFTD are at increased risk of developing adverse radiologic and functional outcomes in the future. However, further studies are needed to validate our findings in an independent cohort of patients.

Disclosures: Stephen M. Davis—UNRELATED: Consultancy: Boehringer Ingelheim, EVER Pharma, Covidien. Payment for Lectures (including service on Speakers Bureau): Boehringer Ingelheim, EVER Pharma, Covidien.

REFERENCES

Low Alberta Stroke Program Early CT Score (ASPECTS) Associated with Malignant Middle Cerebral Artery Infarction

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\textsuperscript{a}Melbourne Brain Centre at Royal Melbourne Hospital, \textsuperscript{b}Department of Radiology at Royal Melbourne Hospital, The University of Melbourne, \textsuperscript{c}The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Key Words
Stroke · CT · Malignant middle cerebral artery infarction · ASPECTS · Hemicraniectomy

Abstract
Background: Early decompressive hemicraniectomy following malignant middle cerebral artery (MCA) infarction reduces mortality and improves clinical outcome. Imaging predictors of malignant infarction may serve as ‘red flags’, prompting intensive neurological monitoring and timely intervention. Our objective is to investigate whether lower ASPECTS (Alberta Stroke Program Early CT Score) is associated with malignant MCA infarction.

Methods: A retrospective cohort study of all patients with MCA territory ischemic strokes who were admitted to the Royal Melbourne Hospital (RMH) between 1 January 2009 and 31 December 2009 (226 patients included). The main outcome measures were ASPECTS on admission for each patient and the development of malignant MCA infarction.

Results: One-hundred-and-eight patients out of 226 (48%) developed malignant MCA infarction. Good (>0.8) inter-rater agreement between observers scoring ASPECTS was observed using weighted kappa, intra-class correlation coefficient and Lin’s concordance coefficients. Using receiver operating characteristic (ROC) curve analysis, we validated that ASPECTS 7 was the optimal cut-off score to determine progression to malignant infarction, providing 50% sensitivity and 86% specificity. One hundred and fifty six patients had ASPECTS >7 (69%) and 70 patients had ASPECTS ≤7 (31%). Patients with ASPECTS ≤7 were significantly younger than those with ASPECTS >7, with the median age of each group being 72.5 and 78 respectively (p = 0.02); otherwise the groups were well-matched. With ASPECTS ≤7, 54 out of 70 patients (77%) developed malignant MCA infarction, compared with 54 out of 156 patients (35%) with ASPECTS >7 (age-adjusted OR = 0.12, 95% CI: 0.06, 0.25; p < 0.0001). If ASPECTS ≤7 is a positive result, then the positive predictive value is 77% and the negative predictive value is 65%. The median ASPECTS for developing malignant MCA infarction was 7.5 (IQR: 5 to 10), while the median ASPECTS for not developing MCA infarction was 10 (IQR: 8 to 10), resulting in a significant age-adjusted median difference of 2 (95% CI: 0.8, 3.2; p < 0.0001). We also found that coma on admission is associated with the development of malignant MCA infarction (OR = 22.63, 95% CI: 1.3, 393.7; p = 0.0323) and that a history of hypertension is not associated with the development of malignant MCA infarction (OR = 0.9707, 95% CI: 0.54, 1.75; p = 0.9213).

Conclusions: ASPECTS ≤7 on initial brain CT in a patient with MCA infarction is associated with the development of malignant MCA infarction. We recommend close monitoring of, and early consideration of decompressive hemicraniectomy for, acute stroke patients with ASPECTS ≤7.
Introduction

Malignant middle cerebral artery (MCA) infarction refers to an MCA territory infarction in which there is extensive cerebral edema leading to increased intracranial pressure and brain herniation [1, 2]. The conversion to malignant MCA infarction occurs in up to 50% of all MCA infarctions [3–6]. The consequences of malignant MCA infarction are dire, with a mortality rate of up to 80% without surgical intervention [3, 7], and survivors suffering severe disabilities. The pooled analysis of three European randomized controlled trials demonstrated that decompressive hemicraniectomy to treat malignant MCA infarction reduces mortality and improves functional outcomes [5, 8–10]. The general consensus is that early decompression is important for optimal outcomes [11–15]. To ensure prompt treatment, it is critical to determine the predictors, both clinical and radiological, of whether an MCA infarction will become malignant. Previous studies have investigated predictors but have reported poor positive predictive value [16–19]. ASPECTS (Alberta Stroke Program Early CT score) is a scoring system that provides a methodical and reproducible way to identify the extent of dead tissue and cytotoxic edema on CT following a stroke [20, 21]. The original ASPECTS study showed that ASPECTS of 7 or below differentiated patients who were highly unlikely to achieve independent functional outcome [22–28], although this study focused on stroke patients who received thrombolytic therapy. A later study similarly showed that ASPECTS ≤ 7 for an early CT predicts a high risk for parenchymal hematoma following acute ischemic stroke, in patients without thrombolysis [29]. ASPECTS may be used as a diagnostic tool for subsequent malignant MCA infarction. Our study aims to investigate the relationship between ASPECTS and malignant MCA infarction. We hypothesize that (a) ASPECTS 7 provides an optimal diagnostic cut-off point for subsequent malignant MCA infarction and (b) lower ASPECTS is associated with malignant MCA infarction.

Methods

Patients

This is a retrospective study of all patients with MCA territory ischemic strokes who were admitted to the Royal Melbourne Hospital (RMH) between 1 January 2009 and 31 December 2009. The inclusion criteria for this study were (i) acute MCA ischemic stroke, (ii) clinical data availability, and (iii) imaging data available, specifically data obtained from an initial CT scan on admission and a follow-up CT scan or MRI scan during the admission. The exclusion criterion was a hemorrhagic stroke.

Data

We collected clinical data for each patient by using a specific stroke registry maintained at RMH, and through extraction from medical records. These data include patient demographics; cardiovascular risk factors; stroke type using the TOAST classification; neurological features at onset and deterioration; Glasgow Coma Scale (GCS) at onset and deterioration; treatment received including intravenous or intra-arterial thrombolysis, intra-arterial clot retrieval or decompressive hemicraniectomy; the modified Rankin Scale on admission, on discharge and three months after onset of stroke; and mortality status one month after presentation.

Imaging

Baseline non-contrast CT scans were performed on admission. Follow-up non-contrast CT scans or MRI scans were performed during admission; we only used the next-in-time follow-up CT scan or MRI scan. This neuroimaging data were acquired through the Pictures and Archiving System (PACS) and were retrospectively reviewed. All CT scans were independently reviewed by three independent observers (PJMJ, RJM and BY) who were blinded to the clinical information. The first two observers are neuroradiologists, one with twenty years (PJMJ) and the other with ten years (RJM) neuroradiology experience respectively. The third observer is a neurologist and neurointerventionist (BY), with ten years neuroradiology experience.

The Alberta Stroke Program Early CT Score (ASPECTS) system was used to analyze the admission CT scans. ASPECTS is a 10-point quantitative topographic CT scan score, which is determined by evaluating two standardized regions of the MCA territory, the basal ganglia level and the supraganglionic level, for ischemic changes [22]. These areas are divided into 10 distinct regions. Evidence of early ischemic change in one of these areas amounts to 1 point. In order to compute ASPECTS, a patient starts with a maximum score of 10 (no ischemic changes) and 1 point is subtracted for each area involving ischemic change (see fig. 1 for examples).

Definition of Malignant MCA Infarction

The primary endpoint of malignant MCA infarction was defined as clinical signs of large middle cerebral artery territory infarction with either (a) secondary neurological deterioration including decline of consciousness (GCS fall of 1 or more points) or new neurological deficit (anisocoria, Babinski reflex, worsening hemiparesis, dysarthria, dysphasia) (‘neurological deterioration’), or (b) GCS ≤12 based on GCS on admission (‘low admission GCS’).

Statistical Analysis

Weighted kappa, intra-class correlation coefficient and Lin’s concordance coefficient were used to estimate the inter-rater agreement between the ASPECTS scorers. Youden’s index (J = sensitivity+specificity-1) for the receiver operating characteristic (ROC) curve was used to validate ASPECTS 7 as the optimal cut-off level of ASPECTS to allow for differentiation between malignant and nonmalignant MCA infarctions. Baseline characteristics, such as demographics, cardiovascular risk factors, stroke type, GCS at onset and deterioration, thrombolysis, and mortality status at one
month were compared between patients with ASPECTS ≤7 and ASPECTS >7 based on data from admission CT scan using either Wilcoxon-Mann-Whitney ranksum test or Fisher’s exact test depending on the nature of the underlying distribution. The association between dichotomized ASPECTS (≤7 vs. >7) and malignant MCA infarction was investigated using Fisher’s exact test and logistic regression. In addition, the association between ASPECTS on the full scale and malignant MCA infarction was investigated using Wilcoxon-Mann-Whitney ranksum test and median regression.

All statistical analysis was performed using Stata v12 IC software. p values less than 0.05 were considered indicative of statistical significance.

Results

Two hundred and fifty nine patients with MCA infarction who presented to Royal Melbourne Hospital between 1 January 2009 and 31 December 2009 were eligible for the final analysis. Twelve were excluded due to lack of imaging and 21 were excluded due to incomplete data. Overall, 226 patients with complete imaging and data were included in our analysis. In order to exclude selection bias, we compared the baseline characteristics of the included patients as against the characteristics of the excluded patients. We found that these results were comparable, except for the gender factor where there was a significant difference with more males than females in the included group (55%), but fewer males in the excluded group (28%) (p = 0.01).

The demographics for our patients are recorded in table 1. Out of 226 patients, 124 patients (55%) were male and the median age was 74.20 (IQR 69 to 83.8). In terms of cardiovascular risk factors, 71 (31%) were smokers, 85 (38%) had atrial fibrillation, 70 (31%) had ischemic heart disease, 55 (24%) had diabetes mellitus, 166 (73%) had hypertension, 56 (25%) had suffered a previous stroke, and 19 (8%) had suffered a previous TIA. We found that the median ASPECTS for the whole sample was 9 (IQR 7 to 10). One hundred and eight patients out of 226 (48%) developed malignant MCA infarction. Out of 108 patients with malignant MCA infarction, 69 (64%) patients were classified as being malignant due to GCS ≤12 on presentation, 28 (26%) due to a fall in GCS of 1 point or more, 8 (7%) due to a new neurological deficit, and 3 (3%) due to a simultaneous fall in GCS and a new neurological deficit. The median time of the first CT scan for each patient after ischemic onset was 3 h and 32 minutes (IQR: 1 hour 28 minutes, 10 hours). For patients who developed malignant MCA infarction, the median time of malignant MCA infarction after ischemic onset was three hours and 45 minutes (IQR: 1 hour 57 minutes, 9 hours 28 minutes). The scans were analyzed by three independent observers. There was good inter-rater agreement between the scores, with agreement above 0.8 using three methods – weighted kappa (0.82, 95% CI: 0.724, 0.89), intra-class coefficient (0.82, 95% CI: 0.77, 0.86), and Lin’s concordance correlation coefficient (0.819, 95% CI: 0.77, 0.861). Therefore, for the sake of consistency, only one observer’s scores were used for the analysis. Using the receiver operating characteristic curve analysis, we validated that ASPECTS 7 was the most appropriate cut-off score to allow for differentiation between malignant and nonmalignant MCA infarctions, as described earlier in the litera-
ture[22]. Our analysis showed that a cut-off point of 7 provides the best combination of diagnostic specificity and sensitivity as to whether an MCA infarction will become malignant (50% sensitivity, 86% specificity, Youden’s index = 0.36, AROC = 0.74, 95% CI: 0.68, 0.8).

Table 1 provides the summary of differences in baseline characteristics between patients with ASPECTS ≤7 and ASPECTS >7 on admission CT scan. One hundred and fifty six patients had an ASPECTS score >7 (69%) and 70 patients had an ASPECTS score ≤7 (31%). Patients with ASPECTS ≤7 were significantly younger than those with ASPECTS >7, with the median age of each group being 72.5 and 78 respectively (p = 0.02). The groups were well-matched in terms of the other demographics recorded.

Table 2 compares the distribution of MCA infarction in the groups of ASPECTS ≤7 and ASPECTS >7. There were 70 patients with an ASPECTS score ≤7, out of which 54 (77%) developed malignant MCA infarction and only 16 (23%) did not. Out of 156 patients with an ASPECTS score >7, 54 (35%) patients developed malignant MCA infarction and 102 (65%) patients did not. This is a statistically significant difference: OR = 0.16 (95% CI: 0.08, 0.3; p < 0.0001), Age-adjusted Odds Ratio = 0.12 (95% CI: 0.06, 0.24; p < 0.0001). MMI = Malignant middle cerebral artery infarction; NMMI = nonmalignant middle cerebral artery infarction.

### Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 226)</th>
<th>ASPECTS ≤7 (n = 70)</th>
<th>ASPECTS &gt;7 (n = 156)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR)</td>
<td>74.20 (69, 83.8)</td>
<td>72.5 (61, 84)</td>
<td>78 (71, 83.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>124 (55%)</td>
<td>41 (58%)</td>
<td>83 (53%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>71 (31%)</td>
<td>20 (29%)</td>
<td>51 (33%)</td>
<td>0.64</td>
</tr>
<tr>
<td>AF</td>
<td>85 (38%)</td>
<td>24 (34%)</td>
<td>61 (39%)</td>
<td>0.55</td>
</tr>
<tr>
<td>IHD</td>
<td>70 (31%)</td>
<td>23 (33%)</td>
<td>47 (30%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55 (24%)</td>
<td>13 (19%)</td>
<td>42 (27%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>56 (25%)</td>
<td>15 (21%)</td>
<td>41 (26%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>19 (8%)</td>
<td>4 (6%)</td>
<td>15 (10%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>166 (73%)</td>
<td>49 (70%)</td>
<td>117 (75%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>31 (14%)</td>
<td>12 (17%)</td>
<td>19 (12%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>81 (36%)</td>
<td>25 (36%)</td>
<td>56 (36%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Undetermined</td>
<td>115 (51%)</td>
<td>35 (50%)</td>
<td>80 (51%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2%)</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV thrombolysis</td>
<td>60 (27%)</td>
<td>21 (30%)</td>
<td>39 (25%)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

AF = Atrial fibrillation; IHD = ischemic heart disease; TIA = transient ischemic attack; IV = intravenous; Other = stroke of other etiology, examples including carotid dissection and cerebral vasculitis.* p values are from Fisher’s exact test for all comparisons apart from the age, where p value is from Wilcoxon-Mann-Whitney test.

### Table 2. Fisher’s Exact test – ASPECTS dichotomized to ≤7 and >7

<table>
<thead>
<tr>
<th></th>
<th>≤7 (n = 70)</th>
<th>&gt;7 (n = 156)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMI</td>
<td>54 (77%)</td>
<td>54 (35%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NMMI</td>
<td>16 (23%)</td>
<td>102 (65%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Odds Ratio = 0.16 (95% CI: 0.08, 0.3; p < 0.0001), Age-adjusted Odds Ratio = 0.12 (95% CI: 0.06, 0.24; p < 0.0001). MMI = Malignant middle cerebral artery infarction; NMMI = nonmalignant middle cerebral artery infarction.
for a patient who did develop malignant MCA infarction was 7.5 (IQR: 5, 10), while the median ASPECTS for a patient who did not develop malignant MCA infarction was 10 (IQR: 8, 10), resulting in the median difference of 3 (95% CI: 2, 4; p < 0.0001). This result is statistically significant using both Wilcoxon-Mann-Whitney test and a median regression model, with a lower ASPECTS indicating that a patient is more likely to develop malignant MCA infarction. This difference also remains statistically significant when adjusted for age (median difference = 2, 95% CI: 0.8, 3.2, median regression p < 0.0001).

We also found that coma on admission is associated with the development of malignant MCA infarction (OR = 22.63, 95% CI: 1.3, 393.7; p = 0.0323) and that a history of hypertension is not associated with the development of malignant MCA infarction (OR = 0.9707, 95% CI: 0.54, 1.75; p = 0.9213).

Discussion

We found that ASPECTS ≤7 on initial CT scan was associated with the development of malignant MCA infarction. In this study, we investigated the use of ASPECTS as a tool for predicting malignant MCA infarction. We hypothesized that lower ASPECTS on admission is associated with malignant MCA infarction, and aimed to validate that an ASPECTS score of 7 is an optimal diagnostic cut-off point for malignant MCA infarction.

The original ASPECTS study showed that 7 is the optimal cut-off point for predicting functional outcome. We used the ROC curve to validate the most appropriate cut-off point in the 10-point ASPECTS system. We performed statistical analysis on our data on the basis that ASPECTS ≤7 is a positive test result and ASPECTS >7 is a negative test result, and that malignant MCA infarction is a dependent outcome and nonmalignant MCA infarction is a negative outcome (see table 2). On this basis, the sensitivity of this test is poor, at 50%. The implication is that if the test is positive, namely ASPECTS ≤7, then in 50% of cases the patient will develop malignant MCA infarction. The specificity of this test is better, with a value of 86%. It follows that if the test is negative (ASPECTS >7), then 86% of cases the patient will not develop malignant MCA infarction. The positive predictive value of this diagnostic test is 77%, supporting a 77% probability that a patient will develop malignant MCA infarction in the setting of ASPECTS ≤7. The lack of sensitivity means that a negative test does not effectively rule out the risk of malignant infarction. Therefore, there is a significant group of patients who may need to be monitored, but who are not identified as requiring monitoring by the ASPECTS ≤7 cut-off test. While the ASPECTS ≤7 cut-off test is useful in identifying one group of patients who are at risk of developing malignant infarction, clinicians should still regularly assess patients with ASPECTS >7 and look for the development of malignant infarction.

Our results also showed that the median ASPECTS for patients who developed malignant MCA was 7.5 (IQR: 5 to 10), while the median ASPECTS for patients who did not was 10 (IQR: 8 to 10) (p < 0.001). In terms of demographics, it is interesting to note that patients with ASPECTS ≤7 are on average younger than patients with ASPECTS >7.

The aim of this project was to identify a diagnostic tool for the development of malignant MCA infarction in order to guide treatment decisions regarding hemispherectomy and to determine which patients to monitor closely. There have been many studies with a similar aim. Clinical predictors include high NIHSS on admission [19], coma on admission [16], early nausea and vomiting [17], history of hypertension [30], and history of heart failure [30], but these provide poor predictive value. Serum markers including high white cell count [20] and the presence of S100B [31, 32] are also predictive of poor outcome in MCA infarction, but again the predictive value is low. There are many studies relating to imaging predictors, which include an infarct size of >50% of the MCA territory on early CT [17, 30, 33–35], the ratio of infarct volume to CSF volume using perfusion CT and routine CT [6], the lesion volume of >145 ml on diffusion-weighted imaging (DWI) [18, 19], and the volume of severe perfusional deficit is more predictive of malignant edema than the total perfusional deficit, as measured by 11C-flumazenil PET [36]. The first two predictors are problematic because measuring the infarct size on CT is a crude test, which is open to inter-observer variability. Another problem with the latter three predictors is that DWI-MRI, perfusion CT and PET are not widely available imaging tools. Further, while the specificity relating to the infarct size predictors using CT and DWI-MRI is high, both these predicting systems have low sensitivity. It is noted that using the ratio of infarct volume to CSF volume as a predictor provides both good specificity and sensitivity (97% for both).

Our method offers an alternative to these challenges. First, ASPECTS is a system which attempts to provide good inter-rater agreement between users. This was confirmed in our study where agreement was excellent using three different statistical tests (weighted kappa = 0.819,
CI 0.724–0.890, intra-class coefficient = 0.82, 0.77–0.86, and Lin’s concordance correlation coefficient = 0.819, CI 0.77–0.861). Second, CT is widely available in clinical practice, meaning that the ASPECTS system can be used in more remote facilities where more advanced imaging technologies may not be available. Third, as with the other imaging predictors, an ASPECTS score ≤7 provides good specificity (86%) but poor sensitivity (50%), which makes it a practical test to determine which patients to monitor closely for the development of malignant infarction, but it does not reliably predict that patients with ASPECTS >7 will not develop malignant MCA infarction.

There are strengths and limitations in this study. One strength is that CT is a widely available imaging modality. Another strength is that we used three independent investigators who were blinded for the ASPECTS scoring. One limitation is that this is a retrospective study, and selection bias is a problem. The study is limited by the population of patients included in the analysis, in that there may be selection bias because some patients were not included on the basis of lack of imaging and lack of clinical data. We compared the baseline demographics of these patients and found that the only significant difference between the included and excluded patients was gender, because there was a higher proportion of males in the included patients (55 vs. 28%, p = 0.01).

The prediction of whether an MCA infarction becomes malignant is important for the ongoing treatment and close monitoring of the patient, and specifically to understand whether that patient will be a candidate for decompressive hemicraniectomy. It is generally understood that there are better outcomes associated with early surgery; therefore, early predictors are clinically useful. We found that there is an association between low ASPECTS on admission CT and development of malignant MCA infarction, and specifically found that ASPECTS <7 is positively associated with malignant MCA infarction.

**Conclusion**

We validated that ASPECTS ≤7 on initial brain CT in a patient with MCA infarction is associated with the development of malignant MCA infarction. It is important to identify early patients who are at risk of malignant MCA infarction in order to inform decisions on monitoring intensity and decompressive hemicraniectomy. We believe that the application of ASPECTS on initial brain CT is a clinically useful tool in this regard.

**References**

Leukoaraiosis and Early Neurological Recovery after Intravenous Thrombolysis

Heidi McAlpine, MBBS,* Leonid Churilov, PhD,†‡ Peter Mitchell, FRANZCR,§
Richard Dowling, FRANZCR,§ Sarah Teo, BSc (Hons),* and Bernard Yan, FRACP*

Background: Early neurological recovery after intravenous thrombolysis (IVT) is associated with favorable outcome after acute ischemic stroke. Leukoaraiosis, a marker of chronic ischemia, is a possible negative predictive factor of early recovery. However, its negative attenuating effects remain inadequately studied, leading to uncertainty in the prediction of outcomes after IVT. We aim to determine the influence of leukoaraiosis on early neurologic recovery. Methods: We included consecutive acute ischemic stroke patients who received IVT between 2007 and 2011. The following data were included: demographics, vascular risk factors, stroke type, National Institutes of Health Stroke Scale (NIHSS) at onset, and at 24 hours after IVT. Baseline computed tomography (CT) brain scans were analyzed. Two blinded assessors rated the CT scans using the van Swieten scale for leukoaraiosis. Median regression was used to assess the relationship between leukoaraiosis and neurologic recovery. Results: We included 158 patients. The median (interquartile range [IQR]) age was 77 (68-84) and 71 (45%) were female. The median (IQR) NIHSS was 13 (7-18.75) at baseline and 7.5 (2-16) at 24 hours. After taking into account variables independently associated with leukoaraiosis, median regression analysis failed to demonstrate the association between the presence of leukoaraiosis and early neurologic recovery (NIHSS relative one) after IVT, for either of the 3 prespecified dichotomization-based definitions of leukoaraiosis. Conclusions: In our sample, there was no evidence of the association between the degree of leukoaraiosis and early neurological recovery after IVT. Key Words: Leukoaraiosis—stroke—recovery—thrombolysis—white matter hyperintensity of presumed vascular origin.

Introduction

Ischemic stroke is a significant cause of morbidity and mortality in the community.1 Intravenous tissue plasminogen activator is the mainstay of current treatment, and has vastly improved outcomes for stroke patients presenting within 4.5 hours of ictal onset.2-5 However, there is significant variation in patient response to thrombolytic therapy. Between 18% and 33% experience early neurological recovery,6-12 which is associated with reduced mortality rate and the likelihood of a favorable functional outcome at 3 months.5,7,8,11,13 There is increasing interest to identify clinical and radiological factors, which might predict clinical outcome. It has been demonstrated that leukoaraiosis is an important factor for determining outcome after cerebral infarct.14,15 This is evidenced by the pathologic correlates of leukoaraiosis, which include structural vascular abnormalities such as vessel wall thickening and by clinical studies, which demonstrate that patients with leukoaraiosis show a poorer outcome after infarct.16-18 The clinical effects of leukoaraiosis may be
substantial. Podgorska et al. reported 1 year poststroke mortality rate of 28% in those without leukoaraiosis and 45.8% with leukoaraiosis. It follows that leukoaraiosis may be included as part of an algorithm to determine suitability for thrombolytic therapy. 

In the setting of thrombolytic therapy for ischemic stroke, patients with baseline leukoaraiosis have been shown to have a poorer functional outcome at 3 months. However, it has been proposed that this discrepancy in functional recovery is not because of the thrombolytic therapy itself, but more likely a reflection of the higher prevalence of comorbidities in patients with leukoaraiosis and the subsequent susceptibility of these patients to complications after stroke. Therefore, concern remains that leukoaraiosis may negate the beneficial effects of intravenous thrombolysis (IVT) on clinical outcomes. It is possible that early neurologic recovery is a more sensitive measure of determining the influence of leukoaraiosis on the efficacy of IVT in these patients.

The present study aims to investigate the relationship between the degree of leukoaraiosis and early neurologic recovery after IVT. We hypothesize that severe leukoaraiosis present on baseline computed tomography (CT) is associated with lack of early recovery after IVT and with poor clinical outcomes.

**Methods**

*Data Collection*

This was a single center retrospective study undertaken at Royal Melbourne Hospital between 2007 and 2011. This study received approval by the Human Research Ethics Committee at the hospital. Cases included in the present study were selected from a pre-existing database containing data from consecutive patients who received IVT for ischemic stroke. Patients were included if they had presented within 4.5 hours of the onset of neurologic symptoms and had a baseline CT available for analysis. One hundred ninety-five patients met the inclusion criteria. Clinical data collected for the patient population included the following: (1) demographic data; (2) baseline characteristics; (3) risk factors including presence of hypertension, diabetes mellitus (DM), ischemic heart disease (IHD), atrial fibrillation (AF), and hypercholesterolemia; (4) National Institutes of Health Stroke Scale (NIHSS) quantifying stroke severity at baseline and 24 hours; (5) mRS (Modified Rankin Scale) at onset and at 3 months; (6) Oxford stroke scale classification; and (7) Trial of Org 10172 in Acute Stroke Treatment classification. A total of 37 patients were excluded: 18 had no documented NIHSS 24, 14 with no mRS documented at 3 months, 1 without baseline NIHSS, and 4 as baseline CT undertaken at a different centre. The final number of patients included in this study was 158.

**Imaging Data**

Noncontrast CT images were obtained using the ischemic stroke protocol. Axial, nonhelical CT was performed using a Siemens Sensation 16 (Siemens Medical Solutions, Malvern, PA) using 120 kV, 320 mAs, 1.0 seconds rotation time, 4.5 mm slice thickness, and 12 x 0.75 mm detector combination.

**Assessment of Scans**

Leukoaraiosis was assessed using the van Swieten scale (vSS) for leukoaraiosis. This simple scale is used regularly in leukoaraiosis research and has been verified for reliability. The scale examines the severity of white matter changes on 3 sequential axial CT slices and is graded separately for the regions anterior and posterior to the central sulcus: 0 = no white matter hypodensity, 1 = hypodensity partly involving the white matter, and 2 = confluent white matter hypodensity extending up to the gray matter. The scores for the 2 regions are added together for the final vSS. Dicom images were analyzed from a single workstation by 2 independent rater. Assessors were blinded to the outcome of each patient.

**Outcome Measures**

Early neurologic outcome was defined as observed change in NIHSS score over 24 hours. This was defined in 3 alternative ways to reduce the likelihood of type II error:

1. Absolute NIHSS change was determined by comparing NIHSS at baseline with NIHSS at 24 hours and was calculated as (NIHSS24 − NIHSSbl), where NIHSSbl and NIHSS24 are the observed NIHSS scores at baseline and at 24 hours, respectively. Absolute NIHSS change has been criticized as a measure of early neurologic recovery as it is vulnerable to the scale ceiling effect.

2. Change in NIHSS relative to the potential change in NIHSS over 24 hours. This could occur either toward 0 (if the patients are recovering) or toward 42 (if they are deteriorating). This measure takes into account the ordinal noninterval nature of the NIHSS score. It was calculated as follows: (NIHSSbl − NIHSS24)/NIHSSbl if NIHSS24 < NIHSSbl and (NIHSSbl − NIHSS24)/ (42 − NIHSSbl) if NIHSS24 > NIHSSbl.

3. Change in NIHSS relative to NIHSS at baseline. It is calculated as follows: (NIHSSbl − NIHSS24)/ NIHSSbl if NIHSS24 < NIHSSbl and (NIHSSbl − NIHSS24)/NIHSSbl if NIHSS24 > NIHSSbl.

The vSS for leukoaraiosis was used to grade baseline CT for presence of leukoaraiosis. As depicted in Figure 1, scores are determined by a consistent change present on 3 consecutive CT slices and range from 0 (no
leukoaraiosis) to 4 (severe leukoaraiosis extending out to the cortex in the anterior and posterior fossa). Leukoaraiosis scores were dichotomized to reflect the proportion of patients with a low or absent burden of leukoaraiosis and those who had a present or significant burden of leukoaraiosis. Consistent with the exploratory nature of this research, 3 alternative dichotomization thresholds were used to reduce type II error:

1. To assess presence versus absence of leukoaraiosis, we use the dichotomization of vSS 0 versus other values.
2. To assess very mild versus more significant leukoaraiosis, vSS $<2$ versus vSS $\geq2$.
3. To compare mild versus severe leukoaraiosis, vSS $\leq2$ versus vSS $>2$.

Functional outcome was assessed using the mRS at 3 months. Poor functional outcome was defined as mRS score greater than or equal to 3.

**Statistical Analysis**

Data analysis was performed using STATA12IC (StataCorp, College Station, TX). The value of $P = .05$ was selected as a threshold for statistical significance. Inter-rater agreement among raters was assessed using interclass correlation coefficient and further validated with Lin coefficient on a randomly selected subsample of 40 scans. Univariate analysis was undertaken on potential confounding factors related to leukoaraiosis for all 3 definitions of leukoaraiosis scores using Mann–Whitney $U$ (age, gender) and 2-tailed Fisher exact tests (AF, IHD, DM, smoking, hypertension, and hypercholesterolemia).

Median regression was used to investigate the association between leukoaraiosis and early neurologic recovery adjusting for potential confounders identified in univariate analysis stage. Binary logistic regression was used to investigate the association between leukoaraiosis and functional outcome adjusting for potential confounders identified in univariate analysis stage.

**Results**

A total of 158 patients with acute ischemic stroke treated with IVT at the Royal Melbourne Hospital during the study period were included in the analysis. Demographic and baseline characteristics are given in Table 1. The median (interquartile range [IQR]) age of the patients included in the study was 77 years (68-84 years) and there were 71 (45%) females. The prevalence of vascular risk factors in these patients includes hypertension 74%, DM 30%, IHD 24%, smoking 24%, hypercholesterolemia 45%, and AF 31%. The median NIHSS was 13 (7-18.75) at baseline and 7.5 (2-16) at 24 hours. The median mRS was 0 (0-2) at baseline and 3 (1-5) at 3 months.

<table>
<thead>
<tr>
<th>Table 1. Baseline patient demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
</tr>
<tr>
<td>NIHSS baseline, median (IQR)</td>
</tr>
<tr>
<td>NIHSS 24, median (IQR)</td>
</tr>
<tr>
<td>mRS preadmission, median (IQR)</td>
</tr>
<tr>
<td>mRS 3 months, median (IQR)</td>
</tr>
<tr>
<td>Oxford, n (%)</td>
</tr>
<tr>
<td>TACI</td>
</tr>
<tr>
<td>PACI</td>
</tr>
<tr>
<td>POCI</td>
</tr>
<tr>
<td>LACI</td>
</tr>
<tr>
<td>TOAST, n (%)</td>
</tr>
<tr>
<td>Large artery</td>
</tr>
<tr>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Small vessel</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Undetermined risk factors, n (%)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; LACI, lacunar infarct; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; Oxford, The Oxford Community Stroke Project classification; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; TACI, total anterior circulation infarct; TOAST, Trial of Org 10172 in Acute Stroke Treatment scale.
The proportion of patients with each leukoaraiosis score was vSS0 = 45.66%, vSS1 = 13.92%, vSS2 = 12.03%, vSS3 = 12.66%, and vSS4 = 15.82%. Excellent agreement was found for leukoaraiosis scoring between the 2 raters (Intraclass correlation coefficient, .86; 95% confidence interval [CI], 75.75-92.57; Lin concordance coefficient, .86; 95% CI, 78.94).

All dichotomizations of the vSS were separately analyzed for possible association with age and the vascular risk factors of hypertension, smoking, hypercholesterolemia, AF, and IHD. Results are presented in Table 2, which demonstrates that within the first dichotomization (vSS1) age, hypertension, IHD, DM, and hypercholesterolemia were all independently associated with the vSS1. Smoking was also related; however, this was a negative association. Within the second dichotomization (vSS2) age and hypertension demonstrated an association with vSS2. In the final dichotomizations (vSS3), age and hypertension were found to be associated with vSS3.

Median regression analysis was undertaken to determine the relationship between vSS and NIHSS at 24 hours, adjusting for potential imbalances due to confounding variables identified in the univariate analysis. No association was found between neurologic recovery, using any of the 3 definitions of recovery, under any dichotomizations of vSS. NIHSS absolute change = vSS1 (median difference, .00; 95% CI, −2.44 to 2.44; P > .999), vSS2 (median difference, .00; 95% CI, −3.54 to 3.54; P > .999), vSS3 (median difference, .00; 95% CI, −3.29 to .29; P > .999), vSS4 (median difference, .00; 95% CI, −2.07 to 2.07; P > .999), NIHSS relative change 1 = vSS1 (median difference, −.07; 95% CI, −.29 to .15; P = .54), vSS2 (median difference = .00; 95% CI, −.23 to .23; P > .999), and vSS3 (median difference, .13; 95% CI, −.10 to .35; P = .26) and NIHSS relative change 2 = vSS1 (median difference, −.07; 95% CI, −.28 to .14; P = .53), vSS2 (median difference, .00; 95% CI, −.33 to .33; P > .999), and vSS3 (median difference, .13; 95% CI, −.11 to .36; P = .29).

Table 2. Univariate analysis of baseline characteristics (age, gender, vascular risk factors, and atrial fibrillation) and relationship to van Swieten scale (vSS)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>vSS1 (0 vs. 2, 3, 4) Effect size</th>
<th>95% CI</th>
<th>P value</th>
<th>vSS2 (&lt;2 vs. 2, 3, 4) Effect size</th>
<th>95% CI</th>
<th>P value</th>
<th>vSS3 (&lt;3 vs. 3, 4) Effect size</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (per year)</td>
<td>11</td>
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<td>.00*</td>
<td>11</td>
<td>5.05, 16.95</td>
<td>.00*</td>
<td>10</td>
<td>5.15, 14.85</td>
<td>.00*</td>
</tr>
<tr>
<td>Gender</td>
<td>.09</td>
<td>−.71, .25</td>
<td>.32</td>
<td>.08</td>
<td>−.12, .284</td>
<td>.54</td>
<td>−.04</td>
<td>−.21, .13</td>
<td>.72</td>
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<td>Vascular risk factors</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>.09</td>
<td>−.06, .25</td>
<td>.28</td>
<td>.09</td>
<td>−.1, .29</td>
<td>.37</td>
<td>.13</td>
<td>−.03, .3</td>
<td>.13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>.17</td>
<td>.05, .30</td>
<td>.02*</td>
<td>.19</td>
<td>.05, .33</td>
<td>.04*</td>
<td>.24</td>
<td>.12, .36</td>
<td>.00*</td>
</tr>
<tr>
<td>Smoking</td>
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<td>−.27, .02</td>
<td>.05*</td>
<td>−.13</td>
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<td>.23</td>
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<td>Ischemic heart disease</td>
<td>.17</td>
<td>.12, .32</td>
<td>.03*</td>
<td>.17</td>
<td>−.2, .36</td>
<td>.09</td>
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<td>.22</td>
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<td>Hypercholesterolemia</td>
<td>.18</td>
<td>.01, .34</td>
<td>.04*</td>
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<td>.30</td>
<td>.15</td>
<td>−.02, .32</td>
<td>.11</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>.14</td>
<td>−.02, .29</td>
<td>.10</td>
<td>.04</td>
<td>−.15, .23</td>
<td>.66</td>
<td>.15</td>
<td>−.1, .32</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
Effect sizes are reported as follows: for age—median difference and are analyzed using median regression, for all other variables—as risk differences and are analyzed using Fisher exact test.
*Two-tailed P < .05 is considered as an indication of statistically significant differences.

Binary logistic regression analysis was performed to investigate the relationship between leukoaraiosis severity and mRS scores at 3 months. With the first dichotomization of vSS a statistically significant relationship was identified, with higher vSS corresponding to a poorer mRS at 3 months (odds ratio [OR], .38; 95% CI, .16-93; P = .03); however, this relationship was not apparent in the second (OR, .55; 95% CI, .20-1.52; P = .25) or third (OR, .50; 95% CI, 21-1.22; P = .13) dichotomizations of the vSS.

Discussion

The present study demonstrates that baseline leukoaraiosis is unlikely to become a predictor of early neurologic recovery after IVT in the setting of acute ischemic stroke.

Leukoaraiosis is a radiological phenomenon, which represents white matter change in the brain. The underlying cause for this white matter hypodensity is likely hypoperfusion ischemia. Significant research exists to support this, including early studies in rat models of ischemia and more recently the elucidation of pathologic correlates of leukoaraiosis in the human brain, including structural vascular abnormalities such as vessel wall thickening. It is thought that structural vascular abnormalities characterized by vessel wall thickening lead to hemodynamic ischemia, which generates leukoaraiosis. Perfusion imaging studies further support the ischemic origin of leukoaraiosis, demonstrating reduced white matter cerebral blood flow in patients with ischemic leukoaraiosis and impaired perfusion reserve in advanced leukoaraiosis. These findings suggest that leukoaraiosis would likely be indicative of poor functional reserve and would lead to poor outcomes after stroke. The present study uses the term leukoaraiosis synonymously with the Standards for Reporting Vascular...
changes on Neuroimaging (STRIVE) terminology of white matter hyperintensity of presumed vascular origin.28

Patients with leukoaraiosis are at higher risk of developing ischemic stroke.15 Furthermore, it has been demonstrated that leukoaraiosis is more common and more severe in patients with ischemic stroke, compared with healthy persons.29 They experience worse functional outcome after IVT compared with patients without leukoaraiosis and experience more complications, such as hemorrhage.14,19,22 These findings have the potential to influence the clinicians’ decision to treat with IVT; it is important that thorough investigation be undertaken to determine the efficacy of this treatment in patients with leukoaraiosis. This will allow clinicians to undertake informed and appropriate use in these patients.

This study serves to inform decision making for clinicians prescribing IVT for patients with leukoaraiosis in ischemic stroke. It resolves the speculation surrounding the suitability of these patients for this potentially life saving therapy. Despite the evidence that patients with baseline leukoaraiosis have a higher risk of intracranial hemorrhage, and generally do worse after stroke, we demonstrated that leukoaraiosis has no impact on short-term functional outcome.14,30 Presence of leukoaraiosis should therefore not impact on clinical decision making regarding the administration of IVT in the setting of acute stroke.

Previous studies have demonstrated that presence of leukoaraiosis leads to poor functional recovery at 3 months.14 However, the study by Aries et al14 relied on only 1 definition of leukoaraiosis, whereas the present study attempted to look deeper into the relationship using 3 alternate dichotomizations for leukoaraiosis. The present study determined the relationship between leukoaraiosis and poor functional recovery at 3 months to exist in only 1 of the 3 dichotomizations of leukoaraiosis. Given these heterogeneous findings, we cannot assert that a stable relationship exists between mRS and leukoaraiosis.

The primary outcomes of the present study, which examined the relationship between early recovery and leukoaraiosis, are unlikely to be false negative findings, as most of the point estimates of the effect sizes are very close to 0. Thus, the negative findings are unlikely to be because of the low estimate precision and are more likely to be because of no trend toward a more adverse outcome in the leukoaraiosis cohort. The data were analyzed using multiple definitions of neurologic recovery and multiple dichotomizations for leukoaraiosis. Despite this, the results remain unchanged; no evidence of the association between leukoaraiosis and early functional recovery was detected.

We believe our results add certainty to the safety of IVT in stroke patients with leukoaraiosis. We do not believe that the presence of leukoaraiosis should be part of the decision making process of determining suitability for IVT.15

References
5. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. The Lancet;379:2352-2363.
The Impact of Arterial Collateralization on Outcome after Intra-Arterial Therapy for Acute Ischemic Stroke

S. Seeta Ramaiah, L. Churilov, P. Mitchell, R. Dowling, and B. Yan

ABSTRACT

BACKGROUND AND PURPOSE: Although intra-arterial therapy for acute ischemic stroke is associated with superior recanalization rates, improved clinical outcomes are inconsistently observed following successful recanalization. There is emerging concern that unfavorable arterial collateralization, though unproven, predetermines poor outcome. We hypothesized that poor leptomeningeal collateralization, assessed by preprocedural CTA, is associated with poor outcome in patients with acute ischemic stroke undergoing intra-arterial therapy.

MATERIALS AND METHODS: We retrospectively analyzed patients with acute ischemic stroke with intracranial ICA and/or MCA occlusions who received intra-arterial therapy. The collaterals were graded on CTA. Univariate and multivariate analyses were used to investigate the association between the dichotomized leptomeningeal collateral score and functional outcomes at 3-months mRS/H11349, mortality, and intracranial hemorrhages.

RESULTS: Eighty-seven patients were included. The median age was 66 years (interquartile range, 54–76 years) and the median NIHSS score at admission was 18 (interquartile range, 14–20). The leptomeningeal collateral score 3 was found to have significant association with the good functional outcome at 3 months: OR/H11005 3.13; 95% CI, 1.25–7.825; P = .016. This association remained significant when adjusted for the use of IV tissue plasminogen activator: alone, OR/H11005 2.998; 95% CI, 1.154–7.786; P = .024; and for IV tissue plasminogen activator and other confounders (age, baseline NIHSS score, and Thrombolysis in Cerebral Infarction grades), OR = 2.985; 95% CI, 1.027–8.673; P = .045.

CONCLUSIONS: We found that poor arterial collateralization, defined as a collateral score of <3, was associated with poor outcome, after adjustment for recanalization success. We recommend that future studies include collateral scores as one of the predictors of functional outcome.

ABBREVIATIONS: IAT = intra-arterial therapy; IQR = interquartile range

Intravenous tissue plasminogen activator is the only proved reperfusion therapy for acute ischemic stroke. However, a narrow therapeutic time window (<4.5 hours) limits its use because the clinical effectiveness is critically time-dependent.1–3 In addition, recanalization rates with IV-tPA are low in the setting of large-artery occlusion, (eg, ICA occlusion <10%).4–6 Intra-arterial therapy (IAT) has higher recanalization rates than intravenous thrombolysis, but this result has not been matched by concordant improvement in clinical outcomes.7–9 Two recent randomized trials comparing IAT with IV-tPA, the Interventional Management of Stroke III trial and the Local versus Systemic Thrombolysis for Acute Ischemic Stroke trial, did not demonstrate superiority.10,11

Inadequate arterial collateralization is a possible mechanism to explain the mismatch between recanalization success and clinical outcome, apart from the presence of an already infarcted ischemic core and an incomplete microcirculatory reperfusion after focal cerebral ischemia.12,13 A favorable arterial collateralization as determined by a robust leptomeningeal anastomoses profile may enhance recanalization, improve downstream reperfusion, reduce the extent of infarct core and ischemic lesion growth, decrease hemorrhagic transformation, and improve outcome postrevascularization.14–16

The leptomeningeal collateral scoring system based on CTA correlates with clinical outcome.17–21 However, its role in IAT is unclear. We hypothesized that a poor leptomeningeal CTA score predicts clinical futility in patients undergoing IAT independent of recanalization status.
MATERIALS AND METHODS

Study Design and Patient Cohort

This was a single-center retrospective review of 104 patients with acute ischemic stroke with ICA and/or MCA occlusion who received IAT at the Royal Melbourne Hospital from January 2008 to March 2013. The local research and ethics committee granted the study approval.

Clinical parameters, identified through computerized databases, were prospectively collected. The following parameters were recorded in a specific data bank: 1) demographics (age, sex); 2) medical history and risk factors such as hypertension (previous clinical diagnosis or regular treatment with antihypertensive medication), diabetes mellitus (previous diagnosis or current treatment with insulin or oral hypoglycemic medication), hypercholesterolemia (previous diagnosis or current treatment with lipid-lowering medication), atrial fibrillation (previous diagnosis or evident on admission), coronary artery disease, history of previous stroke or TIA; 3) “time from onset of symptoms to CTA” (defined from the time of symptom onset or from the time when the patient was last seen neurologically well, to the time of CTA), “time from onset of symptoms to recanalization” (defined from the time of symptom onset, or from the time when the patient was last seen neurologically well, to the time of intervention with any form of IAT), administration of IV-tPA before endovascular therapy, administration of intra-arterial tPA; and 4) clinical outcome variables: 3-month mRS score, intracranial hemorrhage, and 1-month mortality. The baseline severity of neurologic deficits was graded on admission according to the NIHSS.

CTA and DSA Analysis

CTAs of all patients were reviewed by 3 neurointerventionists (B.Y., P.M., and R.D.), with consensus opinion reached on collateral supply. The reviewers were blinded to all clinical information during the consensus collateral grading. The CTA source images (20-mm, axial) were edited with MPR technique for assessment of leptomeningeal collaterals based on distribution of vessels at the Sylvian fissure and the leptomeningeal convexity. The MPR images were assessed with an MIP technique at 32 mm to evaluate the leptomeningeal collaterals. Collateral statuses were divided into 4 categories (Fig 1): score 0 = absence of contrast reaching the cortical surface of the affected hemisphere; score 1 = contrast reaching the cortical surface but not the Sylvian fissure; score 2 = contrast reaching the Sylvian fissure but opacifying <50% of hemisphere; score 3 = contrast reaching the Sylvian fissure and opacifying >50% of hemisphere.

The Thrombolysis in Cerebral Infarction system was used to grade recanalization success.22 TICI grade 0 is no perfusion and no antegrade flow beyond the point of occlusion. TICI grade 1 is penetration with minimal perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run. TICI grade 2 is partial perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction or its rate of clearance from the distal bed or both are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel (eg, the opposite cerebral artery or the arterial bed proximal to the obstruction). In TICI grade 2a, only partial filling (less than two-thirds) of the entire vascular territory is visualized; in TICI grade 2b, complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal. TICI grade 3 is complete perfusion; antegrade flow into the bed distal to the obstruction occurs as promptly as that into the obstruction and clearance.

Statistics

Statistical analysis was performed by using the STATA, Version 12 IC statistics package (StataCorp, College Station, Texas). We in-
cluded the following baseline clinical variables: age, sex, comorbidities (history of hypertension, diabetes, atrial fibrillation, coronary artery disease, TIA, or stroke), baseline NIHSS score, IV-tPA, intra-arterial tissue plasminogen activator, onset time to CTA, and onset time to recanalization. Continuous variables were reported as median ± interquartile range (IQR). Categoric variables were reported as proportions. P values were reported by using the Fisher exact test for categoric variables and the Wilcoxon-Mann-Whitney rank sum test for continuous variables (age, NIHSS score, and time-to-event data). Receiver operating characteristic analysis curves were used to determine the collateral score threshold with functional outcome (3-month mRS score). Univariate and multivariate analyses were used to investigate the association between the dichotomized leptomeningeal collateral score with functional outcomes, mortality, and intracranial hemorrhages. Given the strong clinical association with clinical outcomes, we planned a priori to include the following independent variables in the model: age, baseline NIHSS score, TICI grade, and IV-tPA. A 2-sided P value <.05 was considered significant.

**RESULTS**

Of the initial 104 patients with acute ischemic stroke with ICA and/or MCA occlusion who underwent IAT, CTA was not available for 14 patients before IAT. Three patients had poor image quality on CTA, and these patients were excluded. Eighty-seven patients with both adequate CTA and angiographic data with clinical outcome (mRS) at 90 days available were entered into the leptomeningeal collateral assessment. The baseline characteristics did not differ in a statistically significant manner between the patients with and without CTA (Table 1). In the CTA group, the median age was 66 years (IQR, 54–76 years). Fifty (57%) patients were men. The median NIHSS score at admission was 18 (IQR, 14–20). Forty (46%) subjects were treated with IV-tPA; 13 subjects (15%) received intra-arterial tPA. Sixty-five patients (75%) were treated with the Solitaire device (Covidien, Irvine, California), 10 (12%) patients were treated with the Merci retriever (Concentric Medical, Mountain View, California), and 3 (3%) were treated with the Penumbra System (Penumbra, Alameda, California).

**Leptomeningeal Collaterals**

According to the leptomeningeal score, 34 subjects (39%) were graded as three, 30 subjects (35%) were graded as two, 12 subjects (14%) were graded as one, and 11 subjects (13%) were graded as zero. Receiver operating characteristic analysis

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### Table 1: Baseline characteristics of the patient cohort with and without CTA

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Patients with CTA (n = 87)</th>
<th>Patients without CTA (n = 17)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (median) (IQR)</td>
<td>66 (54–76)</td>
<td>65 (56–73)</td>
<td>.954</td>
</tr>
<tr>
<td>Male sex</td>
<td>50 (58%)</td>
<td>11 (65%)</td>
<td>.788</td>
</tr>
<tr>
<td>Baseline NIHSS score, (median) (IQR)</td>
<td>18 (14–20)</td>
<td>21 (14–24)</td>
<td>.083</td>
</tr>
<tr>
<td>IV-tPA</td>
<td>40 (46%)</td>
<td>5 (29%)</td>
<td>.286</td>
</tr>
<tr>
<td>IA-tPA</td>
<td>13 (15%)</td>
<td>2 (12%)</td>
<td>&lt;.999</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (13%)</td>
<td>3 (18%)</td>
<td>.697</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 (30%)</td>
<td>1 (6%)</td>
<td>.286</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>29 (33%)</td>
<td>2 (12%)</td>
<td>.089</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (13%)</td>
<td>0 (0%)</td>
<td>.204</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13 (15%)</td>
<td>1 (6%)</td>
<td>.457</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>60 (69%)</td>
<td>11 (65%)</td>
<td>.779</td>
</tr>
<tr>
<td>TICI grade 2b–3</td>
<td>Onset to CTAb (min) (median) (IQR)</td>
<td>90 (72–136)</td>
<td>90 (70–130)</td>
</tr>
<tr>
<td>Onset to recanalizationc (min) (median) (IQR)</td>
<td>329 (274–398)</td>
<td>360 (322–395)</td>
<td>.286</td>
</tr>
</tbody>
</table>

**Note:**—IA-tPA indicates intra-arterial tissue plasminogen activator.

a P values reported using the Fisher exact test for categoric variables and the Wilcoxon-Mann-Whitney rank sum test for continuous variables (age, NIHSS score, and time-to-event data).

b Symptom onset or from the time when the patient was last seen neurologically well to the time of CTA.

c Time from symptom onset or from the time when the patient was last seen neurologically well to the time of intervention with any form of IAT.

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### Table 2: Comparison of patients for the dichotomized leptomeningeal collateral score

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Collateral Score 3 (n = 34)</th>
<th>Collateral Score 0–2 (n = 53)</th>
<th>Effect Sizea (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>16 (47%)</td>
<td>34 (64%)</td>
<td>2.013 (0.844–4.802)</td>
<td>.127</td>
</tr>
<tr>
<td>NIHSS score, median (IQR)</td>
<td>15.5 (11–20)</td>
<td>18 (14–22)</td>
<td>1.585 (0.671–3.750)</td>
<td>.379</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (53%)</td>
<td>22 (42%)</td>
<td>0.544 (0.146–2.067)</td>
<td>.517</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (9%)</td>
<td>8 (15%)</td>
<td>0.964 (0.381–2.442)</td>
<td>&lt;.999</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10 (29%)</td>
<td>16 (30%)</td>
<td>0.746 (0.299–1.863)</td>
<td>.643</td>
</tr>
<tr>
<td>AF</td>
<td>10 (30%)</td>
<td>19 (36%)</td>
<td>2.057 (0.606–6.975)</td>
<td>.327</td>
</tr>
<tr>
<td>CAD</td>
<td>6 (18%)</td>
<td>5 (9%)</td>
<td>0.652 (0.195–2.204)</td>
<td>.556</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>4 (12%)</td>
<td>9 (17%)</td>
<td>3.565 (1.455–8.729)</td>
<td>.008</td>
</tr>
<tr>
<td>Process-of-care characteristics</td>
<td>IV-tPA</td>
<td>22 (65%)</td>
<td>18 (34%)</td>
<td>0.239 (0–1.042)</td>
</tr>
<tr>
<td>IA-tPA</td>
<td>2 (6%)</td>
<td>11 (21%)</td>
<td>1.429 (0.552–3.696)</td>
<td>.488</td>
</tr>
<tr>
<td>Onset to CTAb (min) (median) (IQR)</td>
<td>90 (63–124)</td>
<td>90 (75–137)</td>
<td>0.239 (0–1.042)</td>
<td>.070</td>
</tr>
<tr>
<td>Recanalizationc (min) (median) (IQR)</td>
<td>146 (86.5–274)</td>
<td>175 (128.68–276.5)</td>
<td>1429 (0.552–3.696)</td>
<td>.488</td>
</tr>
</tbody>
</table>

**Note:**—IA-tPA indicates intra-arterial tissue plasminogen activator; AF, atrial fibrillation; CAD, coronary artery disease.

a Effect sizes reported as odds ratios for categoric variables and Hodges-Lehman median differences for continuous variables (age, NIHSS score, and time-to-event data).

b P values reported using the Fisher exact test for categoric variables and the Wilcoxon-Mann-Whitney rank sum test for continuous variables (age, NIHSS score, and time-to-event data).

c Symptom onset or from the time when the patient was last seen neurologically well to the time of CTA.

d Time from symptom onset or from the time when the patient was last seen neurologically well to the time of intervention with any form of intra-arterial therapy.
demonstrated the suitability of the collateral score ≥3 for determining good functional outcome of mRS ≤2 with an area under the curve of 0.6513 (sensitivity, 51.1%; specificity, 73.8%). The leptomeningeal score was dichotomized into good (score = 3) and poor (score = 0–2) on the basis of the receiver operating characteristic analysis. A higher percentage of IV-tPA was administered for a collateral score of 3 than for a collateral score of 0–2, (P = .008). The remainder of the baseline clinical variables did not differ in a statistically significant way between the 2 groups (Table 2).

Outcome
Three-month outcome was favorable (mRS 0–2) in 47 subjects (54%), and the remaining 40 subjects (46%) had mRS scores of 3–6 (Fig 2). Patients with a good collateral score of 3 had higher odds of good functional outcome than patients with a collateral score of 0–2 (OR = 3.130; 95% CI, 1.252–7.825; P = .016). This finding remained significant after adjustment for administration of IV-tPA (OR = 2.998; 95% CI, 1.154–7.786; P = .024). In the multivariate analysis, patients with a collateral score of 3 had significantly higher odds of good outcome at 3-month follow-up after adjustment for age, baseline NIHSS score, IV-tPA, and TICI grades (adjusted OR = 2.985; 95% CI, 1.027–8.673; P = .045) (Table 3).

Survival
Of the 13 deaths at 1 month, patients with poor collateral scores of 0–2 exhibited a trend toward a higher death rate than those with a collateral score of 3 (11 versus 2) (OR = 0.239; 95% CI, 0.049–1.153; P = .070), though no statistically significant differences were found.

**FIG 2.** Distribution of mRS scores according to the leptomeningeal collateral scores.

### Table 3: Univariate analysis of associations for outcomes for the dichotomized leptomeningeal collateral score

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Collateral Score 3 (n = 34)</th>
<th>Collateral Score 0–2 (n = 53)</th>
<th>ORs (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted for IV-tPA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical outcome mRS ≤2 at 3 months</td>
<td>24 (71%)</td>
<td>23 (43%)</td>
<td>3.13 (1.252–7.825)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>4 (12%)</td>
<td>13 (25%)</td>
<td>0.41 (0.122–1.385)</td>
</tr>
<tr>
<td>Mortality at 1 month</td>
<td>2 (6%)</td>
<td>11 (21%)</td>
<td>0.239 (0.049–1.153)</td>
</tr>
</tbody>
</table>

* Fisher exact test.
* Logistic regression.
* Adjusted for age, baseline NIHSS score, IV-tPA, and TICI grades.

### Intracranial Hemorrhage
Although patients with a good collateral score of 3 had fewer episodes of intracranial hemorrhage than patients with a poor collateral score of 0–2 (4 versus 13), no statistically significant difference was detected (OR = 0.41; 95% CI, 0.122–1.385; P = .174).

**DISCUSSION**
We found that a favorable pattern of leptomeningeal collaterals, as measured by CTA on admission, was associated with improved functional outcomes at 3 months in a cohort of patients with acute ischemic stroke with ICA or proximal MCA occlusion. In a multivariate model, a good leptomeningeal collateral score remained independently associated with good clinical outcome after adjustment for age, baseline NIHSS score, IV-tPA, and recanalization status.

Various studies have used CTA to score collaterals status14,17,19,20,23 with either CTA source images or by using MIP. Tan et al17 demonstrated that CTA-MIP was the best technique to quantify the degree of collateral circulation. In their retrospective analysis, they reported a good correlation between the CTA-based collateral score and the final infarct volume within 6 months.17 In another study, Miteff et al14 assessed retrograde filling of the MCA by 3 categories of collateral scoring and concluded that a good collateral status was one of the significant univariate predictors of favorable outcome.14 Menon et al21 included 138 patients (MCA-M1 and/or intracranial occlusion) in a retrospective single-center study and demonstrated good regional leptomeningeal anastomoses scores in 37.6% of patients, which correlated strongly with the size of the infarct core at baseline and were a strong independent predictor of final infarct and clinical outcome.

In a recent study, Souza et al23 found that CTA collaterals correlate with admission diffusion-weighted imaging infarct size and that a malignant collateral profile is highly specific for large admission DWI lesion size and poor functional outcome. In another study, Angermaier et al24 demonstrated that the CTA collateral grade was an independent predictor of final infarct volume in patients with stroke treated with endovascular therapy. On the other hand, Rosenthal et al18 reported that CTA collaterals had a positive impact on the outcomes of patients who did not achieve complete recanalization and had no impact in patients who were completely recanalized. Tan et al25 reported that good CTA collaterals correlated with improved outcomes in uni- but not in multivariate analyses. Our study reveals that a good CTA collateral score had a positive impact on the outcomes of patients in...
both uni- and multivariate analyses independent of recanalization status.

The system of leptomeningeal anastomoses is anastomotic connections between distal branches of the cerebral arteries on the surface of the brain that permit blood flow from the territory of an unobstructed artery into the territory of an occluded artery and constitute the secondary network of cerebral collateral circulation apart from the circle of Willis. 26 Although the criterion standard for the assessment of leptomeningeal anastomoses is conventional DSA, the extent of leptomeningeal anastomoses formation seen on conventional DSA and with clinical outcome correlates well with collateral blood flow as assessed by CTA.15,27,28 CTA is quicker, simpler, and noninvasive and uses IV-administered contrast to visualize the extent of leptomeningeal anastomoses with intra- and extracranial vasculature.19,21 There is currently no consensus on what the presence or absence of collateral circulation means with respect to treatment choices for patients with acute ischemic stroke. Some authors believe a minority of patients with robust leptomeningal collateral circulation will have minimal damage and experience excellent recovery without recanalization.29 On the other hand, some neurointerventionalists may want to try more aggressive IAT because there may be salvageable tissue in patients with good collateral vessel formation. Given the risks inherent in the therapeutic procedure and the clinical risk of futile recanalization,30 practitioners need a way to consistently select patients whom IAT is likely to benefit rather than harm. Given the significance of leptomeningeal collaterals, they should be taken into account with other validated scoring systems, namely the Houston Intra-Artial Therapy 30 and the Totaled Heath Risks in Vascular Events score,31 in patient selection for IAT.

Our study has some limitations. First, selection bias is unavoidable in a retrospective single-center study. We sought to minimize reading bias by blinding the observers to clinical data and consensus achieved for the collateral grading. The CTA collateral scoring system was modified from Tan et al.17 Although our collateral grading derived from a consensus by 3 experienced neurointerventionists, the utility and value of the score requires further validation in a larger study before collateral scores are used as a primary means of selecting patients for revascularization therapy. Potential biases may have influenced the selection of cases for IAT on the basis of the CTA and clinical data.

CONCLUSIONS
Evaluation of the leptomeningeal collateral blood supply before IAT for anterior circulation intracranial arterial occlusion stroke (ICA and/or MCA) with a collateral score based on CTA-MIP reconstructions is independently associated with functional outcome at 3 months. We believe that leptomeningeal collateral assessment should be included in future trials investigating the clinical efficacy of IAT.

REFERENCES

is highly specific for large admission DWI infarct core and poor outcome in acute stroke. *AJNR Am J Neuroradiol* 2012;33:1331–36


Proximal Hyperdense Middle Cerebral Artery Sign Predicts Poor Response to Thrombolysis

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Abstract

The aim of our study was to compare the rapid neurological improvement after intravenous recombinant tissue-type plasminogen activator (rtPA) in patients with proximal hyperdense middle cerebral artery sign (p-HMCAS) to those without the sign and those with the distal hyperdense middle cerebral artery sign (d-HMCAS). Admission and 24 hour non-contrast CT scans of 120 patients with middle cerebral artery (MCA) territory stroke who were treated with intravenous rtPA were assessed for the presence of p-HMCAS and d-HMCAS. The sign was classified according to the site of occlusion. Rapid neurological recovery was defined as ≥50% improvement in the NIHSS score at 24 hours after thrombolysis. Rapid neurological recovery after thrombolysis was assessed and compared between the subgroups. Rapid neurological recovery was less common in the pooled group of patients with either p-HMCAS or d-HMCAS than those without the sign (p<0.01). Patients with p-HMCAS were less likely to have rapid neurological recovery than those with d-HMCAS (p<0.01). However, there was no difference in early neurological recovery between patients with d-HMCAS and those without any hyperdense sign. Our study showed that poor neurological recovery post rtPA was confined to p-HMCAS and not to d-HMCAS, indicating that these signs have quite different prognostic significance.

Methods

This study was approved by the Ethics Committee of the Royal Melbourne Hospital and informed consent was obtained. Consecutive patients with MCA territory stroke who were treated with intravenous rtPA at the Royal Melbourne Hospital between October 2007 and October 2010 were included. All patients were treated with intravenous rtPA at 0.9 mg/kg within 3 hours of the onset of symptom and then 4.5 hours after approval of the extended time window.

The patient data were recorded in a specific stroke registry which includes patient demographics, vascular risk factors, laboratory and relevant outcome variables. Baseline non-contrast CT scans were performed within 4.5 hours after onset of
symptoms. Follow-up non-contrast CT scans were performed 24 hours after the intravenous rtPA treatment. All CT scans were performed by using a Siemens Sensation scanner (Siemens Sensation 64, Erlangen, Germany), covering the whole brain. The technical parameters of the CT acquisition were as follows: 100 kv, 200 mAs, pitch 1.25, 0.5 sec rotation time, slice thickness 0.75 mm, and slice spacing 0.4 mm.

The All CT scans were independently reviewed by two independent experienced neurologists who were blinded to the clinical information. In case of disagreement, they discussed until a consensus was reached. The admission non-contrast CT scans were assessed for the presence of p-HMCAS, d-HMCAS and early ischemic changes.

The p-HMCAS was defined as hyperattenuating signals along the course of the middle cerebral artery M1 segment (Figure 1A). The d-HMCAS, which has been termed the MCA dot sign [4], was defined as hyperattenuating dot sign in the Sylvian fissure (Figure 1B). Patients with hyperattenuating signs were classified as p-HMCAS or d-HMCAS. The follow-up CT scans were compared with the baseline non-contrast CT for the persistence of hyperattenuating signs and ischemic infarcts.

The severity of stroke was assessed by using the National Institute of Health Stroke Scale (NIHSS) for each patient on admission and 24 hours after thrombolysis. The neurological improvement was estimated by the difference between admission and the 24 hour NIHSS scores. Early neurological improvement was defined as NIHSS score improvement ≥4 points at 24 hour follow-up. Dramatic neurological improvement was defined as NIHSS score improvement ≥8 points at 24 hour follow-up. Rapid neurological improvement was defined as ≥50% improvement in the NIHSS score at 24 hours after thrombolysis.

Demographic data, vascular risk factors, results of CT scans and neurological assessment were compared between patients with hyperdense artery sign and those without the sign. The chi square test was used to assess categorical variables. For continuous variables, the dependent Student’s t-test was used. The possible false discovery during multiple comparisons was controlled by Benjamini and Hochberg method. Interobserver agreement for determining hyperdense artery sign was determined by calculating kappa values, with kappa value = 0.81–1.00 defined as excellent agreement; 0.61–0.80, good agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; 0.01–0.20, slight agreement; and 0, poor agreement.

All statistical analysis was done by using the statistical product and service solutions (SPSS) 16.0 package, with assistance of a medical statistician. P value less than 0.05 was considered statistically significant.

Results

Of the 148 patients with middle cerebral artery territory stroke who were treated with intravenous rtPA between Oct 2007 and Oct 2010, 120 patients were eligible for the final analysis. The remaining 28 patients were excluded from our study due to incomplete data at follow-up. The study population consisted of 70 men and 50 women (mean age, 73.4 years; age range, 26–94 years). For all patients, the median pre-treatment NIHSS score was 13 (IQR, 8–18). The median time to intravenous rtPA thrombolysis was 155 minutes (IQR, 121–189).

Results of baseline data and univariate comparison of early neurological improvement after thrombolysis between patients with hyperdense artery sign and those without the sign are shown in Table 1. Patient age, gender, vascular risk factors and time to treatment did not differ between patients with hyperdense artery sign and those without the sign. Patients with hyperdense artery signs have more severe neurological deficit on admission than those without the sign (p<0.05). Early ischemic changes on initial CT scans are more common in patients with hyperdense artery signs (p<0.01).

Early neurological improvement by ≥4 NIHSS points was observed in 29.7% of patients with hyperdense artery sign as compared to 48.2% of patients without the sign. Dramatic neurological improvement, which was defined as NIHSS score improvement ≥8 points at 24 hours after thrombolysis, was less common in patients with hyperdense artery sign than those without the sign (p<0.05). Rapid neurological improvement, which as defined as ≥50% improvement in the NIHSS score within 24 hours of thrombolysis, was observed in 18.9% of patients with hyperdense artery signs as compared to 44.6% of patients without the sign. Patients with hyperdense artery signs are less likely to have rapid neurological recovery than those without the sign (p<0.01).

Of the 120 patients treated with rtPA, hyperdense artery sign was seen in 37 (30.8%) patients. P-HMCAS was seen in 21 (17.5%) of 120 patients, whereas 16 (13.3%) patients had d-HMCAS on the initial CT scan. The p-HMCAS and d-HMCAS coexisted in 6 patients. The hyperdense artery sign disappeared in

Figure 1. Hyperdense artery sign on noncontrast CT. (A) Transverse CT scan showing a proximal hyperdense artery sign (arrow) in the M1 segment of MCA. (B) Noncontrast CT showing a distal hyperdense artery sign in the sylvian fissure (arrowhead), which was also referred to as the MCA dot sign.

doi:10.1371/journal.pone.0096123.g001
7 of 21 patients with p-HMCAS. The MCA dot sign disappeared in 12 of 16 patients with d-HMCAS. The interobserver agreement for hyperdense artery sign was excellent (kappa value = 0.83).

Patients with p-HMCAS were compared with d-HMCAS (Table 2). Patient age, gender, vascular risk factors and time to treatment did not differ between the two groups. The p-HMCAS is associated with more severe initial neurological deficit (p, 0.0001) and worse NIHSS score at 24 hours (p, 0.0001). Disappearance of hyperdense artery sign is more common in patients with d-HMCAS than those with p-HMCAS (p, 0.05). Patients with p-HMCAS are less likely to have rapid neurological recovery than those with d-HMCAS (p, 0.01). The p-HMCAS on baseline CT scan was significantly associated with poor early neurological recovery on univariate analysis (p, 0.01). Univariate analysis did not demonstrate any association of d-HMCAS with rapid neurological recovery (OR = 1.042, p = 0.941).

Patients with d-HMCAS were compared with those without any hyperdense artery signs (Table 3). The patient demographics and vascular risk factors did not differ between the two groups. Early ischemic signs are approximately twice as common in patients with d-HMCAS. The admission and 24 hour NIHSS score were virtually the same between patients with d-HMCAS and those without any hyperdense sign. The rate of rapid neurological improvement was similar in patients with d-HMCAS and those with no hyperdense sign.

### Discussion

In previous reports, the hyperdense artery sign has been reported in 17% to 50% of patients with MCA territory stroke. The reported prevalence of hyperdense artery signs is consistent with previous reports [3,4]. We classified hyperdense artery signs as either p-HMCAS or d-HMCAS according to the site of occlusion. A proximal hyperdense artery sign was seen in 17.5% of patients. The reported incidence of d-HMCAS was 13.3% in our case series, which is similar to the findings described by Barber and colleagues [12].

The rate and extent of recanalization after intravenous rtPA thrombolysis was dependent on the site and amount of thrombus. Recent study suggested that thrombus volume were significantly larger in patients with hyperdense artery signs than in those without the sign [13]. Furthermore, the authors also reported the mean thrombus volume was significantly larger in the p-HMCAS than those with d-HMCAS. Our results suggested that patients with hyperdense artery signs are less likely to have rapid neurological recovery than those without the sign. This could be well explained by the larger thrombus volume associated with the hyperdense artery signs. In our study, we compared the early neurological improvement after rt-PA thrombolysis in patients with p-HMCAS and d-HMCAS. Patient age, gender, vascular risk factors and time to treatment did not differ between patients with
In addition, we also observed that patients with d-HMCAS were more likely to have early neurological improvement (median NIHSS improvement 3.5 point) than those with p-HMCAS signs (median NIHSS improvement 0 point). The results of our study suggested that intravenous rtPA is less effective in recanalizing patients with p-HMCAS. The efficacy of rtPA in patients with hyperdense artery signs has been debated in previous reports [14]. Few studies have investigated the association of rtPA in patients with hyperdense artery signs. In a secondary analysis of 620 patients in the European Cooperative Acute Stroke Study I, Manelfe and colleagues found that patients with HMCAS who received rtPA had better neurological recovery than those who received placebo [10]. A limitation of the study is that the authors did not differentiate between proximal and distal hyperdense artery signs. The results of our study suggested that the response to rtPA was different between patients with proximal and distal hyperdense artery signs. More recently, Barber and colleagues described the efficacy of rtPA in patients with proximal and distal hyperdense artery signs. They found that 5/5 (100%) of patients with proximal HMCAS and 64% of distal HMCAS patients were either dead or dependent at 3 months [12]. However, the number is too small to draw any conclusion. The results of our study support the concept that MCA stem occlusions are less likely to benefit from rtPA treatment than MCA branch occlusions.

### Table 2. Baseline data and response to rt-PA between patients with proximal hyperdense artery sign and distal hyperdense artery sign.

<table>
<thead>
<tr>
<th></th>
<th>p-HMCAS</th>
<th>d-HMCAS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of patients</strong></td>
<td>21</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>9 (42.9%)</td>
<td>10 (62.5%)</td>
<td>0.325</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>73 (69–84)</td>
<td>74 (62–76)</td>
<td>0.770</td>
</tr>
<tr>
<td><strong>Vascular Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (71.4%)</td>
<td>14 (87.5%)</td>
<td>0.436</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (23.8%)</td>
<td>9 (52.6%)</td>
<td>0.091</td>
</tr>
<tr>
<td>IHD</td>
<td>5 (23.8%)</td>
<td>5 (31.2%)</td>
<td>0.785</td>
</tr>
<tr>
<td>AF</td>
<td>6 (28.6%)</td>
<td>4 (25%)</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (14.3%)</td>
<td>7 (43.8%)</td>
<td>0.085</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>8 (38.1%)</td>
<td>11 (68.8%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1 (4.8%)</td>
<td>2 (12.5%)</td>
<td>0.576</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>0 (0%)</td>
<td>1 (6.2%)</td>
<td>0.443</td>
</tr>
<tr>
<td><strong>Neuroradiological Features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Ischemic Signs</td>
<td>18 (85.7%)</td>
<td>10 (62.5%)</td>
<td>0.143</td>
</tr>
<tr>
<td>Disappearance of hyperdense artery sign</td>
<td>7 (33.3%)</td>
<td>12 (75%)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Neurological Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission NIHSS (median, IQR)</td>
<td>19 (15–21.5)</td>
<td>10.5 (7–15.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24 hour NIHSS (median, IQR)</td>
<td>19 (14.5–21)</td>
<td>6 (2.25–10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Early NIHSS improvement (median, IQR)</td>
<td>0 (0–2)</td>
<td>3.5 (0–6)</td>
<td>0.035</td>
</tr>
<tr>
<td>NIHSS Recover ≥4</td>
<td>3 (14.3%)</td>
<td>8 (50%)</td>
<td>0.038</td>
</tr>
<tr>
<td>NIHSS Recover ≥8</td>
<td>1 (4.8%)</td>
<td>3 (18.8%)</td>
<td>0.312</td>
</tr>
<tr>
<td>NIHSS Recover ≥50%</td>
<td>1 (4.8%)</td>
<td>6 (37.5%)</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>Thrombolysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to rt-PA (median, IQR)</td>
<td>164 (107.5–193)</td>
<td>133.5 (102.5–162.75)</td>
<td>0.255</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; IQR indicates interquartile range.

Differentiation between p-HMCAS and d-HMCAS is important because they have different prognostic implications. In a study of 186 patients with MCA territory stroke, Somford and colleagues reported that patients with p-HMCAS have a worse short-term outcome than those with d-HMCAS [11]. A limitation of their study is that all patients did not receive rtPA treatment in their cohort. In our study, we compared the efficacy of intravenous rtPA between p-HMCAS patients and d-HMCAS patients. We found a strong association between the presence of p-HMCAS and poor early neurological recovery after intravenous rtPA. Interestingly, we failed to find any association between d-HMCAS and poor early neurological recovery.

Previous angiographic studies suggested that disappearance of hyperdense artery sign after rtPA treatment indicates recanalization of occluded vessels [15,16]. Disappearance of hyperdense artery sign has been associated with good functional outcome in patients who underwent thrombolysis. In a recent study, Kharitonova and colleagues reported that hyperdense artery sign disappeared in 48% of patients treated with rtPA [17]. However, the authors did not differentiate between p-HMCAS and d-HMCAS in their study. In our study, we observed that the hyperdense artery sign disappeared in 51.3% of patients treated with rtPA, which is similar to Kharitonova’s finding. Furthermore, we found that disappearance of hyperdense artery sign is more common in patients with distal hyperdense artery sign than those
with proximal hyperdense sign. One possible explanation is that patients with p-HMCAS may have longer clots or tandem internal carotid occlusion. Regular dose intravenous rtPA is difficult to fully recanalize those patients with a heavy clot burden [18–20].

The d-HMCAS sign has been verified in angiographic studies with high specificity [21]. It is well established as a reliable early CT marker of acute ischemia. However, the prognostic significance of d-HMCAS remains unclear. In previous reports, the d-HMCAS patients were pooled with p-HMCAS patients to analyse the effect of rtPA in MCA territory stroke patients. In our study, we observed that the initial neurological deficit and early neurological improvement were similar in patients with d-HMCAS and those without any hyperdense sign. Our results suggest that intravenous rtPA is equally effective in patients with d-HMCAS and those without any hyperdense artery sign. Based on our findings, we suggest that patients with hyperdense artery signs should not be investigated as a whole in future studies.

Recently, more aggressive treatment such as intra-arterial or interventional clot retrieval has been available in clinical practice [22]. The clot length is associated with the rates of intravenous tissue-type plasminogen activator recanalization. In a recent study, Kamalian et al. found that patients with internal carotid artery-terminus occlusion are likely to have clot length ≥8 mm [23]. In an observational study, Mattle and colleagues found that intraarterial thrombolysis was more beneficial than intravenous thrombolysis in stroke patients presenting with HMCAS on CT [24]. Patients with hyperdense artery signs have a heavy clot burden and should be treated with more aggressive procedures [25,26].

Our study has several limitations. First, the data of recanalization was not assessed based on CT angiographic findings. Second, this is a single center study and the sample size is relatively small. Third, the carotid clot burden was not investigated in our present study.

In conclusion, patients with hyperdense artery signs on admission CT are less likely to have rapid neurological recovery than those without the sign. Patients with p-HMCAS are associated with more severe neurological deficit and less rapid neurological recovery than patients with d-HMCAS. P-HMCAS and d-HMCAS have different prognostic implications in patients treated with rtPA.

**Table 3.** Baseline data and response to rt-PA between patients with d-HMCAS and patients without any hyperdense sign.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Solitary d-HMCAS</th>
<th>No Hyperdense</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>16</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>10 (62.5%)</td>
<td>51 (61.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>74 (62–76)</td>
<td>75 (67–83)</td>
<td>0.332</td>
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**Vascular Risk Factors**

<table>
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<th>P Value</th>
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</thead>
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<tr>
<td>Hypertension</td>
<td>14 (87.5%)</td>
<td>65 (78.3%)</td>
<td>0.523</td>
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<tr>
<td>Diabetes</td>
<td>9 (52.6%)</td>
<td>27 (32.5%)</td>
<td>0.098</td>
</tr>
<tr>
<td>IHD</td>
<td>5 (31.2%)</td>
<td>24 (28.9%)</td>
<td>1</td>
</tr>
<tr>
<td>AF</td>
<td>4 (25%)</td>
<td>30 (36.1%)</td>
<td>0.573</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (43.8%)</td>
<td>22 (26.5%)</td>
<td>0.085</td>
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<td>Hypercholesterolemia</td>
<td>11 (68.8%)</td>
<td>47 (56.6%)</td>
<td>0.271</td>
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<td>Previous stroke</td>
<td>2 (12.5%)</td>
<td>15 (18.1%)</td>
<td>0.746</td>
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<tr>
<td>Previous TIA</td>
<td>1 (6.2%)</td>
<td>9 (10.8%)</td>
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**Neuroradiological Features**

<table>
<thead>
<tr>
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<th>Solitary d-HMCAS</th>
<th>No Hyperdense</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Early Ischemic Signs</td>
<td>10 (62.5%)</td>
<td>29 (34.9%)</td>
<td>0.059</td>
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**Neurological Status**

<table>
<thead>
<tr>
<th></th>
<th>Solitary d-HMCAS</th>
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<th>P Value</th>
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<tr>
<td>Admission NIHSS (median, IQR)</td>
<td>10.5 (7–15.5)</td>
<td>11 (7–17)</td>
<td>0.653</td>
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<tr>
<td>24 hour NIHSS (median, IQR)</td>
<td>6 (2.25–10)</td>
<td>6 (2–13)</td>
<td>0.963</td>
</tr>
<tr>
<td>NIHSS improvement (median, IQR)</td>
<td>3.5 (6–66)</td>
<td>3 (6–8)</td>
<td>0.316</td>
</tr>
<tr>
<td>NIHSS Recover ≥4</td>
<td>8 (50%)</td>
<td>40 (48.2%)</td>
<td>1</td>
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<tr>
<td>NIHSS Recover ≥8</td>
<td>3 (18.8%)</td>
<td>25 (30.1%)</td>
<td>0.556</td>
</tr>
<tr>
<td>NIHSS Recover ≥50%</td>
<td>6 (37.5%)</td>
<td>37 (44.6%)</td>
<td>0.792</td>
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</table>

**Thrombolysis**

<table>
<thead>
<tr>
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<th>Solitary d-HMCAS</th>
<th>No Hyperdense</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to rt-PA (median, IQR)</td>
<td>133.5 (102.5–162.75)</td>
<td>164 (130–190)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; IQR indicates interquartile range.

doi:10.1371/journal.pone.0096123.t003

**Author Contributions**

Conceived and designed the experiments: QL SD BY. Performed the experiments: QL SD PM RD BY. Analyzed the data: QL SD PM RD BY. Contributed reagents/materials/analysis tools: PM RD. Wrote the paper: QL SD BY.
References

Does Large Vessel Occlusion Affect Clinical Outcome in Stroke with Mild Neurologic Deficits after Intravenous Thrombolysis?

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Bruce C. V. Campbell, PhD, FRACP;† Monica Lin, BSc,† Xinfeng Liu, MD, PhD,*
Stephen M. Davis, MD, FRACP;† and Bernard Yan, FRACP†

**Background:** Large vessel occlusion (LVO) is associated with poor functional outcome in acute ischemic stroke. Given the uncertainty whether LVO has the same significance in mild and severe stroke, we compared functional outcomes after intravenous thrombolysis, based on severity and LVO. **Methods:** Ischemic stroke patients were thrombolysed in less than 4.5 hours after onset between 2007 and 2013. LVO was defined as occlusion of one of the following arteries: internal carotid, middle cerebral (M1/M2), anterior cerebral (A1), posterior cerebral (P1), basilar, or vertebral (V4) arteries on prethrombolysis computed tomography angiography. Mild stroke was defined as baseline National Institutes of Health Stroke Scale (NIHSS) score 0-6. Favorable outcome was defined as modified Rankin Scale (mRS) score 0-1 at 3 months or equal to the prestroke mRS. **Results:** There were 175 acute stroke patients, median age 74 years (interquartile range [IQR], 64-83), median baseline NIHSS = 11 (IQR, 5-16), and 63 of 175 patients (36%) with mild stroke. LVO was associated with worse outcome in severe stroke (age-adjusted odds ratio [OR] of favorable outcome, .42; 95% confidence interval [CI], .19-.93; \( P = .033 \)) and mortality (age-adjusted OR, 3.52; 95% CI, 1.08-11.48; \( P = .037 \)). Although the difference in favorable outcome between mild stroke patients with and without LVO was not significant (55.6% vs. 74.1%, \( P = .262 \)); age-adjusted OR of favorable outcome, .42; 95% CI, .1-.84; \( P = .251 \)), the similarity of effects across both subgroups cannot be excluded (LVO-by-stroke severity interaction test, \( P = .906 \)). **Conclusions:** LVO is associated with worse functional outcome and mortality in severe stroke after intravenous thrombolysis. Although significant association between LVO and outcome in mild stroke was not found, there were similar effects on outcome and a larger study might well confirm a relationship. **Key Words:** Ischemic stroke—mild stroke—intravenous thrombolysis—CT angiography—modified Rankin Scale.

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Introduction

Intravenous tissue plasminogen activator (IV tPA) leads to improved functional outcomes for patients with acute ischemic stroke. Of patients who receive IV tPA within 3 hours of symptom onset, 61.1% have a favorable outcome, and of those who receive IV tPA within 4.5 hours of stroke onset, 52.4% have a favorable outcome. Large vessel occlusion (LVO) is associated with poor outcome in acute stroke, and IV tPA leads to successful recanalization in only 21.3% of acute stroke patients with LVO. The effect of IV tPA diminishes in the setting of large clot burden. Successful recanalization at 2 hours after tissue plasminogen activator is achieved in only 6% of patients with terminal internal carotid artery (ICA) occlusion, and only 18% of patients in this group achieve a favorable outcome.

Up to half of acute stroke patients in the United States have mild neurologic deficit, defined by a National Institutes of Health Stroke Scale (NIHSS) less than 6. Patients with low NIHSS scores were excluded from tPA treatment in randomized clinical trials, for example, National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator stroke trial (NIHSS ≤5 exclusion) and European Cooperative Acute Stroke Study III trial (NIHSS <5 exclusion). Current guidelines for acute ischemic stroke management from the American Heart Association/American Stroke Association state that the use of IV tPA in patients with mild stroke remains controversial and may be considered. However, approximately one third of patients who did not receive IV tPA because of mild or rapidly improving stroke symptoms have a poor outcome. It is important to examine the reasons behind poor outcome in mild stroke. It has been postulated that LVO exerts a negative effect on outcomes in mild stroke.

The aim of our study was to investigate the effects of LVO in stroke patients with mild and severe deficits treated with IV tPA. We hypothesized that there will be different LVO effects on outcomes in stroke patients with mild and severe neurologic deficits.

Methods

Patients

Clinical and demographic details of acute ischemic stroke patients who presented and were treated with IV tPA at Royal Melbourne Hospital within 4.5 hours after stroke onset, between December 2007 and February 2013, were prospectively recorded in a database. Patients with acute ischemic stroke meeting clinical and noncontrast computed tomography (CT) eligibility criteria were administered 0.9 mg/kg IV tPA within 4.5 hours after onset of symptoms. We included only those patients who had received computed tomography angiography (CTA) before thrombolysis. The following parameters were included: (1) demographics (age and sex); (2) vascular risk factors (such as hypertension, diabetes, hypercholesterolemia, atrial fibrillation, smoking, and ischemic heart disease); (3) previous stroke history; (4) baseline NIHSS score; (5) onset to treatment time; (6) CTA before tPA; (7) CT/magnetic resonance imaging after tPA; and (8) modified Rankin Scale (mRS) prestroke and 3 months. Mild neurologic deficit was defined as baseline NIHSS score 0-6 and severe neurological deficit as baseline NIHSS score greater than or equal to 7. Patients eventually diagnosed with stroke mimics and those patients who received IV tPA plus intra-arterial (IA) therapy were excluded from the analysis. The study was approved by our institutional human research ethics committee.

Imaging Assessment

From December 2007, CTA was routinely performed in acute ischemic stroke patients before IV tPA at Royal Melbourne Hospital, unless contraindicated (eg, renal impairment or known contrast allergy). All patients underwent CT or magnetic resonance imaging scan approximately 24 hours after IV tPA to assess hemorrhagic transformation and extent of infarction. Symptomatic intracerebral hemorrhage (sICH) was defined as blood at any site in the brain associated with clinical deterioration, resulting in greater than or equal to 4 point increase in the NIHSS score. LVO was defined by proximal vessel occlusion in any of the following arteries: ICA, middle cerebral artery (M1 and M2 segment), anterior cerebral artery (A1 segment), V4 segment of vertebral artery, basilar artery, and posterior cerebral artery (P1 segment). LVO was assessed on CTA image by 2 independent experienced stroke neurologists (W.Z., B.Y.). LVO was considered relevant only if the site of occlusion correlated with acute ischemic stroke symptoms.

Outcome

The primary outcome was mRS score at 3 months. Favorable outcome was defined as mRS 0-1 at 3 months or equal to prestroke mRS. Secondary outcomes were mortality at 3 months and sICH after IV tPA treatment.

Statistical Analysis

Statistical analysis was performed using Stata (v13IC; StataCorp, College Station, TX). Continuous variables were expressed as mean values ± standard deviation or median values (interquartile range [IQR]) depending on the nature of the underlying distribution. Differences between groups were assessed using the Student t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Multivariable logistic regression analysis was
used to explore the association of LVO with outcomes in stroke patients with mild and severe neurologic deficits. The interaction effect between LVO and neurologic deficit severity (measured using either dichotomized [NIHSS score 0-6 vs. NIHSS score ≥7] or original NIHSS scale) was tested using a logistic regression model with an appropriate interaction term. A 2-tailed $P$ value less than .05 was considered significant.

**Results**

**Baseline Characteristics**

In our tPA database, we identified 243 acute ischemic stroke patients who underwent CTA before IV tPA therapy (243 of 359 thrombolysis patients, 67.7%). Sixty-eight patients were excluded from the study: 40 patients received IV tPA plus IA therapy (including IA thrombolysis and mechanical thrombectomy), 17 patients did not have clinical follow-up, 6 patients did not have a baseline NIHSS score, and 5 patients were stroke mimics (1 migraine and 4 psychogenic pseudostrokes). There were 175 patients included in this study. The baseline characteristics of the 175 included patients and 68 excluded patients are listed in Table 1. The median age of included patients was 74 years (IQR, 64-83), 59.4% were male, and median baseline NIHSS score was 11 (IQR, 5-16). There were 126 patients with pre-mRS score 0, 3 patients with pre-mRS score 1, 13 patients with pre-mRS score 2, 19 patients with pre-mRS score 3, and 14 patients with pre-mRS score 4. There was no significant difference in baseline characteristics between the included and excluded patients, except for age. The included patients were older than the excluded patients ($P = .007$), reflecting the younger age of patients receiving IA therapy.

There were 63 mild stroke patients (median age, 72 years [IQR, 60-81] and median baseline NIHSS score, 4 [IQR, 4-6]) and 112 severe stroke patients (median age, 76.5 years [IQR, 67-83] and median baseline NIHSS score, 14 [IQR, 9-19]). Full baseline characteristics and outcomes of mild stroke and severe stroke patients are listed in Table 2. LVO occurred more frequently in severe stroke patients than in mild stroke patients (54.5% [95% confidence interval [CI], 44.8-63.9] vs. 14.3% [95% CI, 6.7-25.4], $P < .001$). Atrial fibrillation was more frequent in severe stroke patients than in mild stroke patients (36.6% vs. 22.2%, $P = .049$).

**Follow-up**

Forty-five mild stroke patients (71.4% [95% CI, 59-82]) had a favorable functional outcome. Death occurred in 4 patients (6.3% [95% CI, 1.8-15]) within 3 months after stroke onset. One patient (1.6% [95% CI, .04-8.5]) developed an sICH after IV tPA. A higher rate of favorable outcome was seen in mild stroke patients than in severe stroke patients (71.4% [95% CI, 59-82] vs. 37.5% [95% CI, 29-47], $P < .001$). Mortality was more frequent in severe stroke patients than in mild stroke patients (17.9% [95% CI, 11-26] vs. 6.3% [95% CI, 1.8-15], $P = .039$; Table 2).

**Relationship between LVO and Outcome**

The rates of favorable outcome at 3 months in mild and severe stroke patients post IV tPA, stratified by the presence or absence of LVO, are listed in Table 3. LVO was observed in 9 mild stroke patients (14.3% [95% CI, 6.7-25]). There were 3 patients with ICA occlusion, 2 patients with M1 occlusion, 3 patients with M2 occlusion, and 1 patient with P1 occlusion. Five of mild stroke patients (55.6% [95% CI, 21-86]) with LVO showed favorable outcome. The difference in favorable outcome between mild stroke patients without LVO and those with LVO was not statistically significant (74.1% [95% CI, 60-85] vs. 55.6% [95% CI, 21-86], $P = .262$; age-adjusted odds ratio [OR], 42; exact 95% CI, 1.1-84; $P = .251$). In severe stroke patients, favorable outcome was more common in patients without LVO compared with those with LVO.

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**Table 1. Baseline characteristics of included and excluded stroke thrombolysis patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Included patients, N = 175</th>
<th>Excluded patients, N = 68</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>104 (59.4)</td>
<td>38 (55.9)</td>
<td>.615</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>74 (64-83)</td>
<td>70 (59.5-76.5)</td>
<td>.0035*</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>114 (65.1)</td>
<td>36 (52.9)</td>
<td>.079</td>
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<tr>
<td>Diabetes, n (%)</td>
<td>42 (24.0)</td>
<td>14 (20.6)</td>
<td>.571</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>90 (51.4)</td>
<td>28 (41.2)</td>
<td>.151</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>55 (31.4)</td>
<td>23 (33.8)</td>
<td>.720</td>
</tr>
<tr>
<td>Previous stroke history, n (%)</td>
<td>22 (12.6)</td>
<td>8 (11.8)</td>
<td>.864</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>37 (21.1)</td>
<td>16 (23.5)</td>
<td>.686</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>40 (22.9)</td>
<td>9 (13.2)</td>
<td>.093</td>
</tr>
<tr>
<td>Onset to treatment time, mean (SD), min</td>
<td>160.2 (55.9)</td>
<td>149.1 (62.6)</td>
<td>.180</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; SD, standard deviation.

* $P < .05$.
(49.0% [95% CI, 35-63] vs. 27.9% [95% CI, 17-41], \( P = .031 \); age-adjusted OR, .42; exact 95% CI, .19-.93; \( P = .033 \)). No significant interaction between LVO and stroke severity on the rate of favorable outcome was observed after adjustment for age (\( P = .906 \)). LVO was associated with higher mortality in severe stroke patients (age-adjusted OR, 3.52; exact 95% CI, 1.08-11.48; \( P = .037 \)).

**Discussion**

The results of our study demonstrated that LVO was associated with worse functional outcome and mortality in severe stroke patients after intravenous thrombolysis. Although no significant difference in favorable outcome between mild stroke patients with LVO and without LVO was found, there was no significant interaction between LVO and stroke severity on favorable outcome (\( P = .906 \); Table 3). Moreover, because of the similar effect sizes in both subgroups, the similarity of effects across both mild and severe stroke subgroups cannot be excluded and might as well be confirmed with a larger study.

A previous observational study suggested that mild stroke patients treated with intravenous thrombolysis had more favorable outcome compared with those without thrombolysis.\(^6\) In a transient ischemic attack and mild stroke population who did not receive thrombolysis, Coutts et al\(^8\) demonstrated that baseline LVO predicted stroke progression and poor outcome. However, there has been limited data on the effect of LVO in mild stroke after intravenous thrombolysis. Köhrmann et al\(^3\) investigated the safety and outcome of IV tPA in mild stroke (without comparison with severe stroke) and found no effect of baseline vessel occlusion on 3-month functional outcome. However, there were important differences to our study. Köhrmann et al\(^3\) had a smaller sample size with CTA in only 18 patients and magnetic resonance angiography in 8 patients and accepted any “visible vessel occlusion” including M3, M4 segment of middle cerebral artery or P2 segment of posterior cerebral artery. Therefore, the rate of vessel occlusion in mild stroke was higher (35%) compared with 14.3% in our study, as we mandated complete occlusion as our criterion for LVO. The definition of “mild stroke” according to NIHSS score varies\(^24\) and various NIHSS score thresholds of 3,\(^5\) 4,\(^4\) 5,\(^25\) 6,\(^6\) 7,\(^6\) or 10\(^27\) have been used. Köhrmann et al\(^3\) defined mild stroke as NIHSS score less than or equal to 4, and this probably contributed to the higher rate of favorable outcome of mild stroke patients after intravenous thrombolysis (94%) compared with 71.4% in our study using the definition of NIHSS score less than or equal to 6.

Our results indicated that LVO was significantly associated with worse functional outcome across the spectrum of severity in stroke thrombolysis patients. The lack of statistical significance in the mild stroke subgroup may be simply because of the study being underpowered, as there were only 9 mild stroke patients with occlusion. However, it is also likely that mild stroke severity in the presence of LVO indicates excellent collateral flow, sufficient to maintain neuronal function in much of the affected territory.\(^28\) Such collateral flow may persist in some patients, leading to favorable outcome despite a lack of recanalization. Nonetheless, persistent LVO poses

### Table 2. Baseline characteristics and outcomes of mild (NIHSS \(\leq 6\)) versus severe (NIHSS \(\geq 7\)) stroke thrombolysis patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NIHSS (\leq 6), N = 63</th>
<th>NIHSS (\geq 7), N = 112</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
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<td>Male, n (%)</td>
<td>42 (66.7)</td>
<td>62 (55.4)</td>
<td>.144</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>69.8 (14.4)</td>
<td>73.6 (12.3)</td>
<td>.069</td>
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<tr>
<td>Baseline NIHSS score, median (IQR)</td>
<td>4 (4-6)</td>
<td>14 (9-19)</td>
<td>(&lt; .001^*)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>41 (65.1)</td>
<td>73 (65.2)</td>
<td>.989</td>
</tr>
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<td>Diabetes, n (%)</td>
<td>13 (20.6)</td>
<td>29 (25.9)</td>
<td>.434</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>32 (50.8)</td>
<td>58 (51.8)</td>
<td>.900</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>14 (22.2)</td>
<td>41 (36.6)</td>
<td>.049*</td>
</tr>
<tr>
<td>Previous stroke history, n (%)</td>
<td>5 (7.9)</td>
<td>17 (15.2)</td>
<td>.165</td>
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<tr>
<td>Smoking, n (%)</td>
<td>15 (23.8)</td>
<td>22 (19.6)</td>
<td>.517</td>
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<tr>
<td>Ischemic heart disease, n (%)</td>
<td>14 (22.2)</td>
<td>26 (23.2)</td>
<td>.881</td>
</tr>
<tr>
<td>Periperal vascular disease, n (%)</td>
<td>2 (3.2)</td>
<td>5 (4.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Onset to treatment time, mean (SD), min</td>
<td>167.9 (59.7)</td>
<td>155.9 (53.3)</td>
<td>.173</td>
</tr>
<tr>
<td>Large vessel occlusion, n (%)</td>
<td>9 (14.3)</td>
<td>61 (54.5)</td>
<td>(&lt; .001^*)</td>
</tr>
<tr>
<td>mRS 0-1, n (%)</td>
<td>41 (65.1)</td>
<td>34 (30.4)</td>
<td>(&lt; .001^*)</td>
</tr>
<tr>
<td>Favorable outcome, n (%)</td>
<td>45 (71.4)</td>
<td>42 (37.5)</td>
<td>(&lt; .001^*)</td>
</tr>
<tr>
<td>sICH, n (%)</td>
<td>1 (1.6)</td>
<td>6 (5.4)</td>
<td>.424</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>4 (6.3)</td>
<td>20 (17.9)</td>
<td>.039*</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; sICH, symptomatic intracerebral hemorrhage.

\*\( P < .05 \)
a risk as collateral flow does often fail over time leading to infarct growth.\cite{29} Of note, in patients with severe stroke, it is likely that collaterals may not adequately compensate. Given that the rates of favorable outcome (55.6\%) in our mild stroke patients with LVO remain suboptimal despite intravenous thrombolysis, this group may warrant more aggressive therapy.

The 51 patients with severe NIHSS, yet no vessel occlusion, deserve consideration. These patients had significantly more favorable outcome compared with those with LVO (49.0\% vs. 27.9\%, P = .021). Given the high sensitivity and specificity of CTA, unrecognized LVO is very unlikely.\cite{30,32} Some of these patients may have already reperfused with clinical recovery lagging behind (“stunned brain”), hence the improved outcome. Others may be because of more distal arterial lesions such as M3, M4 occlusions that supply brain regions that are heavily represented in the NIHSS. These smaller occlusions are more likely to dissolve with tPA and lead to clinical recovery.

There were some limitations to our study. First, this is a relatively small single-center cohort. Our findings need to be confirmed in a study with a larger population. Currently, ongoing trials such as Tenecteplase Evaluation for Minor Ischemic Stroke with Proven Occlusion-1 (ClinicalTrials.gov NCT01654445) will assess the safety and feasibility of thrombolysis in patients with minor stroke and intracranial occlusion. Second, 40 patients who received IV tPA plus IA therapy were excluded in our study, to rule out the impact of IA therapy on the outcome of the patients. However, exclusion of these patients may have introduced select bias in the proportion of LVO in our population study. Third, differentiating between acute occlusion and chronic occlusion may be an important factor in the assessment of collaterals. In our study, LVO was considered relevant only if the site of occlusion correlated with acute ischemic stroke symptoms. However, it may not be possible to differentiate between acute occlusion and chronic occlusion. Fourth, 46 patients with premorbid mRS score 2 or higher were included in this study. Depending on the nature of the disease process that led to a higher premorbid mRS score (eg, previous stroke), the baseline NIHSS could be because of either premorbid mRS or the severity of the current stroke or both. To account for the premorbid mRS effect, we defined favorable outcome in our study as either mRS score 0-1 or as equal to the premorbid mRS. As we are interested in the overall neurologic deficit reflected by the NIHSS score, rather than solely by the severity of the stroke episode, which could not be easily separated from pre-existing deficits consequent of a previous neurologic event, we used the NIHSS score as a measure of such a neurologic deficit and conducted an interaction test not only using mild versus severe dichotomy, but also across the full scale spectrum of NIHSS.

### Table 3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stroke severity</th>
<th>No LVO, n (%)</th>
<th>LVO, n (%)</th>
<th>OR (95% CI)</th>
<th>P value for interaction</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>Mild</td>
<td>40 (74.1)</td>
<td>5 (55.6)</td>
<td>.438 (1.00-1.86)</td>
<td>.438</td>
<td>.422 (1.00-1.86)</td>
<td>.251</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>25 (69.0)</td>
<td>17 (52.9)</td>
<td>.602 (1.13-1.80)</td>
<td>.023</td>
<td>.419 (1.18-3.90)</td>
<td>.333</td>
</tr>
<tr>
<td>sICH</td>
<td>Mild</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00 (0.00-1.00)</td>
<td>0.997</td>
<td>0.10 (0.00-1.00)</td>
<td>0.997</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>2 (3.9)</td>
<td>4 (6.6)</td>
<td>1.719 (702-1.33)</td>
<td>.006</td>
<td>1.697 (293-9.83)</td>
<td>.006</td>
</tr>
<tr>
<td>Mortality</td>
<td>Mild</td>
<td>3 (5.6)</td>
<td>1 (11.1)</td>
<td>2.125 (156-23.02)</td>
<td>.035</td>
<td>2.09 (158-23.49)</td>
<td>.035</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>5 (9.8)</td>
<td>15 (24.6)</td>
<td>3.00 (1007-3.06)</td>
<td>.049</td>
<td>3.518 (179-11.47)</td>
<td>.037</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; sICH, symptomatic intracerebral hemorrhage.

Model 1: not adjusted for age.
Model 2: adjusted for age.

*P < .05.
In conclusion, LVO is associated with worse functional outcome and mortality in severe stroke after intravenous thrombolysis. Although the effect of LVO in mild stroke after intravenous thrombolysis could not be confirmed, the effects were similar to those with LVO and severe stroke, and larger studies are required. Finally, the rates of favorable outcome in patients with mild stroke and LVO remain suboptimal and may warrant consideration of more aggressive treatment in the future, such as mechanical embolectomy if confirmed in randomized controlled trials.

References


Remote intracerebral haemorrhage post intravenous thrombolysis: Experience from an Australian stroke centre

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Intravenous thrombolysis
Modified Rankin Scale
Previous ischaemic attack
rICH
tPA

Remote intracerebral haemorrhage (rICH) is defined as intracerebral haemorrhage (ICH) post thrombolysis in brain regions without visible ischaemic changes. There is uncertainty that clinical outcomes and risk factors for rICH are different to those for local ICH. We investigated the morbidity, mortality and factors associated with rICH. We hypothesised that a previous history of cerebral ischaemic events is associated with increased risk of rICH. We included consecutive acute ischaemic stroke patients from 2003 to 2012 who were treated with intravenous thrombolysis. Clinical data included demographics, stroke classification, vascular risk factors and laboratory results. Clinical outcome was defined by modified Rankin Scale (mRS) score at 3 months. Baseline and follow-up CT scans were analysed for all ICH, and further dichotomised to rICH and local ICH. Clinical outcomes between rICH and local ICH were compared after adjustment for confounding factors. Four hundred and two patients were included in the study. The median age was 71 (interquartile range 60–79) years, and 54% were male. ICH (local ICH and rICH) was detected in 21.6% (87/402) of all patients post thrombolysis. The incidence of rICH was 2.2% (9/402). Most rICH were classified as haemorrhagic infarct category 2 (HI2) (p = 0.002). The proportion of patients with previous transient ischaemic attacks was significantly higher in the rICH group (33.33% versus 2.56%; odds ratio [OR] 18.75, 95% confidence interval [CI] 3.06–114.38; p = 0.007). The proportion of mRS scores 0–2 at 3 months was significantly higher in the rICH group (33.33% versus 2.56%; adjusted OR 10.469, 95%CI 1.474–74.338; p = 0.007). The 3 month mortality rate was 22.2% (2/9) in the rICH group and 36% (27/75) in the local ICH group (OR 0.53, 95%CI 0–2.51, p = 0.703). rICH was an infrequent complication after intravenous thrombolysis in our series. The clinical outcome of rICH was significantly better than local ICH. Of note, previous episodes of transient ischaemic attack were significantly higher in the rICH group, suggesting previous ischaemic injury as an underlying mechanism.

1. Introduction

Symptomatic (or severe) intracerebral haemorrhage (sICH) is a major complication after the administration of tissue plasminogen activator (tPA) for acute ischaemic stroke [1]. The incidence of intracerebral haemorrhage (ICH) ranges from 6.2% to 43% according to different studies [2]. sICH is defined as ICH coinciding with neurological deterioration. The incidence of sICH within 24 to 36 hours after the onset of ischaemic stroke among patients given tPA ranges from 1.7% to 6.4% [1,3–5]. The mortality rate of sICH within 3 months in the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) was 11.3%, and 45.2% of sICH patients were functionally dependent at 3 months [5].

The mechanism of post tPA ICH has been attributed to ischaemia-reperfusion injury [6]. At the onset of brain ischaemia, a cascade of events is initiated by the release of cytokines by astrocytes and endothelial cells, leading to leucocyte recruitment and activation [7]. Free radicals and proteolytic enzymes released by leucocytes in turn disrupt the blood–brain barrier, causing blood extravasation towards the brain tissue [8,9]. Further damage to the blood–brain barrier follows during reperfusion, whereby leucocyte–endothelial interaction, complement activation and reactive oxygen species cause damage to cellular proteins, DNA and the plasma membrane [10]. Restored blood flow also causes further cerebral oedema or haemorrhage [10]. tPA itself may impact haemorrhagic transformation rates by amplifying matrix
metallopeptidase 9, increasing excitotoxicity and impacting vasoreactivity [10].

Remote intracerebral haemorrhage (rICH) is defined as ICH in a brain region without visible ischaemic damage [11]. Previous studies suggested that rICH was infrequent but possibly had more severe clinical sequelae [12]. The incidence of rICH is reported to range from 1.3% to 2.8% [11,13]. However, the morbidity and mortality of rICH is unclear. Furthermore, the clinical characteristics of rICH have not been documented in an Australian population to our knowledge.

We conducted a retrospective analysis of all patients who received intravenous tPA at a single Australian stroke centre. We aimed to investigate the incidence, associated factors and clinical outcome of rICH. We hypothesised that a previous history of cerebral ischaemic events would be associated with an increased risk of rICH.

2. Methods

The data of all acute ischaemic stroke patients treated with tPA at the Royal Melbourne Hospital between January 2003 and January 2012 were retrospectively analyzed. All patients from 2003 to 2008 were treated within 3 hours after onset of stroke symptoms, and within 4.5 hours in patients treated from 2008 to 2012. Baseline patient information collected included demographics (age, sex), stroke risk factors (smoking, hypertension, hyperlipidaemia, diabetes, ischaemic heart disease, structural heart disease, atrial fibrillation, peripheral vascular disease, history of previous stroke or transient ischaemic attack [TIA]) and time interval between onset of symptoms and tPA admission. Oxfordshire Community Stroke Project (OCSAP) classification was utilised for stroke type allocation [14]. Neurological assessment was performed using National Institutes of Health Stroke Scale (NIHSS) score on admission, modified Rankin Scale (mRS) score at 3 months and mortality.

Follow-up CT scans were analyzed for ICH (Fig. 1, 2). The CT scans were reviewed by one assessor (B.Y.) who received dual training in neuroradiology and neurology. ICH was assigned to one of the European Cooperative Acute Stroke Study (ECASS) groups, either haemorrhagic infarcts (HI1: small petechiae; HI2: confluent petechiae) or parenchymal haematoma (PH1: <30% of the infarcted area with mild space-occupying effect; PH2: >30% of the ischaemic area with significant mass effect), based on CT scan [15]. rICH was defined as any extra-ischaemic cerebral haematoma (multiple or single focus). rICH was subclassified into rHI1, rHI2, rPH1, and rPH2. Presence of sICH was defined according to the SITS-MOST classification, namely the presence of a local or remote PH2 type lesion on CT scan 22–36 hours after treatment combined with a neurological deterioration of 4 or more points on the NIHSS or death. Good functional outcome was defined as achieving mRS score 0–2 at 3 months.

2.1. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA) and Stata version 12IC (StataCorp, College Station, TX, USA). Continuous data were expressed as median and interquartile range (IQR). Baseline patient data and stroke risk factors were compared between rICH and local ICH groups using Pearson’s chi-squared test (with Yates’ correction for 2 × 2 tables or, in the case of small expected frequencies, Fisher’s exact test) for categorical variables and the Mann–Whitney U test for continuous variables. Comparison was also conducted between rICH and non-rICH (local ICH and non-ICH) groups. Corresponding effect sizes were estimated using odds ratios (OR) and the Hodges–Lehmann median shift.
estimator with corresponding 95% confidence intervals (CI). To control for Type I error when investigating factors associated with rICH, a multiplicity-corrected two-sided p value <0.01 was considered statistically significant. For outcome analyses, a two-sided p value <0.05 was considered statistically significant for all tests.

3. Results

Four hundred and two patients were included in the study. The median age was 71 (IQR 60–79) years and 54% were male. The median NIHSS score at onset was 12 (IQR 8–18) and the mean time from onset of symptoms to treatment was 160 (IQR 120–182) minutes. According to the OCSP classification, 40.8% (149/402) of patients had a total anterior circulation infarct (TACI), 46.3% (169/402) had partial anterior circulation infarct (PACI), 7.7% (28/402) had posterior circulation infarct (POCI), and 5.2% (19/402) had lacunar circulation infarct (LACI). According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, the aetiology of the stroke was large artery atherosclerosis in 12.5% (49/402) of patients, cardioembolism in 43.9% (172/402) of patients, other determined or undetermined aetiology in 43.7% (168/402) of patients, small-vessel occlusion in 0.8% (3/402) of patients, and ischaemic stroke. rICH was regarded as a rare but severe complication in previous studies [16]. In this retrospective study of 402 patients treated with recombinant tPA in a single Australian stroke centre, the incidence of rICH was 2.2%, which was consistent with corresponding results in the National Institute of Neurological Disorders and Stroke (NINDS), ECASS and SITS-MOST studies [1,5,12]. However, those studies did not report the mortality rate or neurological outcomes of rICH. The mortality rate of rICH in our study was 22% (2/9). The neurological outcome was significantly better in rICH, though the mortality rate was not significantly different between rICH and local ICH. rICH was predominantly lobar in location. The proportion of severe haemorrhage with mass effect (PH1, PH2) was lower in our study than in the SITS-MOST study [5]. A rICH study by a Spanish group reviewed 210 patients with tPA treatment from 1999 to 2008. They reported that rICH prognosis was poor with early deterioration and unfavourable neurological outcome [16]. In our study, the morbidity and mortality rates of rICH were comparatively lower.

Table 1

Data of nine remote intracerebral haemorrhage patients

<table>
<thead>
<tr>
<th>Patient</th>
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<th>5</th>
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<td>4</td>
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<td>2</td>
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<td>OCSP</td>
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<td>TACI</td>
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<td>TACI</td>
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</table>

AF = atrial fibrillation, DM = diabetes mellitus, F = female, LACI = lacunar circulation infarct, M = male, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, OCSP = Oxford Community Stroke Project, PACI = partial anterior circulation infarct, POCI = posterior circulation infarct, TACI = total anterior circulation infarct, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

Thrombolysis is the only approved effective treatment for acute ischaemic stroke. rICH was regarded as a rare but severe complication in previous studies [16]. In this retrospective study of 402 patients treated with recombinant tPA in a single Australian stroke centre, the incidence of rICH was 2.2%, which was consistent with corresponding results in the National Institute of Neurological Disorders and Stroke (NINDS), ECASS and SITS-MOST studies [1,5,12]. However, those studies did not report the mortality rate or neurological outcomes of rICH. The mortality rate of rICH in our study was 22% (2/9). The neurological outcome was significantly better in rICH, though the mortality rate was not significantly different between rICH and local ICH. rICH was predominantly lobar in location. The proportion of severe haemorrhage with mass effect (PH1, PH2) was lower in our study than in the SITS-MOST study [5]. A rICH study by a Spanish group reviewed 210 patients with tPA treatment from 1999 to 2008. They reported that rICH prognosis was poor with early deterioration and unfavourable neurological outcome [16]. In our study, the morbidity and mortality rates of rICH were comparatively lower.

Little is known about the mechanisms and risk factors for rICH. Although there is a large number of studies on identifying predictors of ICH [15], none of them covered the study of rICH to our knowledge. As rICH occurs outside of the infarct area, reperfusion injury may not completely explain the underlying pathophysiology. It is possible that rICH is associated with the toxic effects of tPA. It has been suggested that tPA leads to neurotoxicity by altering extracellular protease and signalling actions, leading to degradation of extracellular matrix integrity and endothelial cell death, blood–brain barrier leakage, oedema, and haemorrhage.
factors may exist for rICH.

Similar risk factors have been postulated to be risk factors for multifocal haematoma after thrombolysis for myocardial infarction. Pre-existing brain pathology may have occurred in areas harbouring microangiopathy, predisposing these areas to rICH. It is also possible that rICH is due to reperfusion into unrecognised infarcted areas. The strong correlation with prior TIA may suggest that many TIAs could be in fact small ischaemic cortical strokes which go undetected (for lack of MRI, or simply because they are below current imaging resolution), which could turn into areas of haemorrhage from local blood–brain barrier disturbance if exposed to thrombolytics. Cardioembolic source was reported as an independent risk factor for the unrecognised ischaemic area with mild space-occupying effect, PH2 = >30% of the ischaemic area with significant mass effect, POCI = posterior circulation infarct, PH1 = <30% of the infarcted area with mild space-occupying effect, PH2 was reported as a marker of bad outcome. Therefore, the outcome of the rICH group was statistically better than the local ICH group, though there was no significant difference in mortality rate. The percentage of PH2 was lower in the rICH group compared with the local ICH group. This may explain why our rICH group had a lower mortality rate than the local ICH group. This study includes a reasonable sample size and a high mortality rate. In our study, the neurological outcome of rICH patients may depend on the characteristics of the haematoma and mass effect rather than the nature of remoteness itself. The percentage of PH2 was lower in the rICH group, though there was no significant difference in mortality rate. The multifocal haematomas account for 15% to 38% of the ICH in thrombolysis for myocardial infarction. Pre-existing brain pathology has been postulated to be a risk factor for multifocal haematoma after thrombolysis for myocardial infarction. Similar risk factors may exist for rICH.

The Spanish study reported poor neurological outcome of rICH and a high mortality rate. In our study, the neurological outcome of the rICH group was statistically better than the local ICH group, though there was no significant difference in mortality rate. The Spanish study reported poor neurological outcome of rICH and a high mortality rate. In our study, the neurological outcome of the rICH group was statistically better than the local ICH group, though there was no significant difference in mortality rate. PH2 was reported as a marker of bad outcome. Therefore, the neurological outcome of rICH patients may depend on the characteristics of the haematoma and mass effect rather than the nature of remoteness itself. The percentage of PH2 was lower in the rICH group, though there was no significant difference in mortality rate. The multifocal haematoma after thrombolysis for myocardial infarction. Pre-existing brain pathology has been postulated to be a risk factor for multifocal haematoma after thrombolysis for myocardial infarction. Similar risk factors may exist for rICH.

AF = atrial fibrillation, APTT = activated partial thromboplastin time, BP = blood pressure, HI1 = small petechiae, HI2 = confluent petechiae, HTN = hypertension, ICH = intracerebral haemorrhage, IHD = ischaemic heart disease, INR = international normalized ratio, IQR = interquartile range, LACI = lacunar circulation infarct, NIHSS = National Institutes of Health Stroke Scale, OCSP = Oxford Community Stroke Project, OTT = onset to treatment, PACI = partial anterior circulation infarct, PH1 = <30% of the infarcted area with mild space-occupying effect, PH2 = >30% of the ischaemic area with significant mass effect, POCI = posterior circulation infarct, PVD = peripheral vascular disease, rICH = remote intracerebral haemorrhage, SHD = structural heart disease, TACI = total anterior circulation infarct, TIA = transient ischaemic attack, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

| Table 2 | Comparison of baseline factors between remote intracerebral haemorrhage patients and local intracerebral haemorrhage patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age (median; IQR) | 70 (59–77) | 79 (62–80) | 3.5 (4–11) | 0.407 |
| Baseline NIHSS (median; IQR) | 17 (12–20) | 17 (11–20.50) | 0 (4–4) | 0.926 |
| Platelet (median; IQR) | 225.5 (181–265) | 319 (259–340) | 77 (4–144) | 0.019 |
| INR (median; IQR) | 1.1 (1–1.15) | 1 (1–1) | 0 (0.1–1) | 0.681 |
| APTT (median; IQR) | 25.45 (24–28.5) | 25.8 (24.1–28.5) | 0.2 (1.7–2.5) | 0.810 |
| Admission systolic BP (median; IQR) | 125 (85–142.5) | 145 (130–150) | 10 (5–30) | 0.634 |
| Admission diastolic BP (median; IQR) | 72 (45–80) | 77.5 (70–80) | 0 (5–8) | 0.734 |
| OTT, minutes (median; IQR) | 160 (120–180) | 182 (126–195) | 20 (10–53) | 0.633 |
| Smoking | 25.64% | 33.33% | 1.46 (0.36–5.88) | 0.694 |
| HTN | 69.23% | 77.78% | 1.56 (0.3–8.05) | 0.719 |
| AF | 35.9% | 11.1% | 0.22 (0.14–0.48) | 0.261 |
| SHD | 6.41% | 11.1% | 1.83 (0–13.89) | 0.491 |
| IHD | 21.79% | 33.33% | 1.79 (0.45–7.36) | 0.424 |
| PVD | 3.85% | 11.1% | 3.13 (0–25.58) | 0.359 |
| Dyslipidaemia | 51.28% | 55.56% | 1.19 (0.32–4.41) | 1.000 |
| Previous stroke | 10.26% | 22.2% | 2.5 (0.12–7.9) | 0.275 |
| Previous TIA | 2.56% | 33.33% | 18.75 (3.06–114.38) | 0.007 |
| Diabetes | 23.08% | 22.2% | 0.95 (0.4–4.48) | 1.000 |
| OCSF | | | | |
| TACI | 62.8% (49/78) | 44% (4/9) | | |
| LACI | 1.3% (1/78) | 22% (2/9) | | |
| PACI | 25.6% (20/78) | 22% (2/9) | | |
| POCI | 1.3% (1/78) | 11% (1/9) | | |
| TOAST | | | | |
| Large artery | 15.4% (12/78) | 22% (2/9) | | |
| Cardioembolic | 48.7% (38/78) | 22% (2/9) | | |
| Lacunar | 0% | 0% | | |
| Other | 1.3% (1/78) | 0% | | |
| Unknown | 33.3% (26/78) | 55.5% (5/9) | | |
| Type of haemorrhage | | | | |
| HI1 | 28.21% (22/78) | 0% | | |
| HI2 | 26.92% (21/78) | 88.89% (8/9) | | |
| PH1 | 24.36% (19/78) | 0% | | |
| PH2 | 20.51% (16/78) | 11.1% (1/9) | | |

AF = atrial fibrillation, APTT = activated partial thromboplastin time, BP = blood pressure, HI1 = small petechiae, HI2 = confluent petechiae, HTN = hypertension, ICH = intracerebral haemorrhage, IHD = ischaemic heart disease, INR = international normalized ratio, IQR = interquartile range, LACI = lacunar circulation infarct, NIHSS = National Institutes of Health Stroke Scale, OCSP = Oxford Community Stroke Project, OTT = onset to treatment, PACI = partial anterior circulation infarct, PH1 = <30% of the infarcted area with mild space-occupying effect, PH2 = >30% of the ischaemic area with significant mass effect, POCI = posterior circulation infarct, PVD = peripheral vascular disease, rICH = remote intracerebral haemorrhage, SHD = structural heart disease, TACI = total anterior circulation infarct, TIA = transient ischaemic attack, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

1 Reported as Hodges-Lehmann median shift estimator (95% confidence interval) for continuous variables and as odds ratio (95% confidence interval) for categorical variables.
patients were consecutively included from a single stroke centre. However, the limitations are that it is retrospective and data on pre-existing brain pathology were not available. In addition, given the small number of patients with rICH, definitive conclusions cannot be drawn regarding associative risk factors.

5. Conclusion

In our cohort, patients with rICH were found to do better than those with local ICH. In our patients, the only strong association with rICH was a history of prior TIA.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

Assessment of Arterial Collateralization and Its Relevance to Intra-arterial Therapy for Acute Ischemic Stroke

Siva Seeta Ramaiah, MBBS, MMed,*† Peter Mitchell, FRANZCR,‡ Richard Dowling, FRANZCR,‡ and Bernard Yan, FRACP†‡

Evidence from recent randomized controlled studies comparing intra-arterial (IA) therapy with intravenous tissue plasminogen activator highlighted the mismatch between recanalization success and clinical outcomes in patients presenting with acute ischemic stroke. There is emerging interest in the impact of arterial collateralization, as determined by leptomeningeal anastomoses (LMAs), on the treatment outcomes of IA therapy. The system of LMA constitutes the secondary network of cerebral collateral circulation apart from the Circle of Willis. Both anatomic and angiographic studies confirmed significant interindividual variability in LMA. This review aims to outline the current understanding of arterial collateralization and its impact on outcomes after IA therapy for acute ischemic stroke, underpinning the possible role of arterial collateralization assessment as a selection tool for patients most likely to benefit from IA therapy. Key Words: Leptomeningeal anastomoses—acute ischemic stroke—intra-arterial therapy—mismatch.

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Brief Overview of Revascularization for Acute Ischemic Stroke: Intravenous Thrombolysis and Intra-arterial Therapy

Intravenous Thrombolysis

The guiding principle of acute stroke treatment is the timely recanalization of occluded arteries, leading to restoration of cerebral blood flow. Intravenous tissue plasminogen activator (IV-tPA) is shown to improve outcomes as shown by the National Institute of Neurological Disorders and Stroke trial and the Safe Implementation of Thrombolysis in Stroke Monitoring Study registry.1-3 Following the European Cooperative Acute Stroke Study III trial and pooled data from the large IV-tPA trials, IV thrombolysis up to 4.5 hours from stroke symptom onset is now accepted as the standard of care.4-6 However, recanalization rates with IV-tPA are low in the setting of large artery occlusion with rates ranging from 4% to 68% depending on the location of occlusion.7-9

Intra-arterial Therapy

Alternative strategies to intravenous thrombolysis have been developed to address the low recanalization rates of IV-tPA. These strategies, termed intra-arterial (IA) therapy, include a myriad of techniques: IA thrombolysis, percutaneous transluminal angioplasty, aspiration thrombectomy, and mechanical thrombectomy.10-13 In the recently concluded Interventional Management of Stroke III14 trial, the investigators randomized acute ischemic stroke (AIS) patient who had received IV-tPA
within 3 hours after symptoms onset to receive additional IA therapy or IV-tPA alone. The study demonstrated equivalent, favorable clinical outcomes (40.8% in IA therapy group and 38.7 in IV-tPA alone) despite a higher recanalization rate in the endovascular group. In another long-awaited randomized trial, Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) trial, the investigators assigned 362 patients with AIS, within 4.5 hours after onset to IA therapy or IV-tPA alone. The clinical outcomes were similar in both treatment groups (42% favorable clinical outcome in IA therapy and 46.4% in IV-tPA alone) though median time from stroke onset to the start of treatment was only 1 hour longer in the former. In the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial, the investigators randomly assigned 127 patients between the ages of 18 and 85 years, with National Institutes of Health Stroke Scale scores of 6-29 who had a previous history of ischemic stroke within 8 hours after the onset of symptoms to undergo either mechanical embolectomy (MERCI Retriever or Penumbra System) or standard medical care. The rate of recanalization at 7 days was 71% for endovascular therapy group and 87% for the standard care group. The reported rate of disability-free survival at 90 days was 14% in penumbral group and 9% in non-penumbral group for endovascular therapy and 23% in penumbral group and 10% in non-penumbral group for standard care group. The proposed explanation for better outcomes of patients with an ischemic penumbra than patients without a penumbral pattern was the ability of collateral vessels to maintain sufficient perfusion to limit the infarct size.

Poor Clinical Outcomes Despite Good Recanalization

Although endovascular techniques have shown better recanalization rates than intravenous thrombolysis, this has not been matched by a corresponding improvement in clinical outcomes (Table 1). In the MultiMERCI trial, recanalization rate of 69.5% was achieved, but good clinical outcome remained 36% with a mortality rate of 34%. The Penumbra Pivotal Stroke trial demonstrated an 81.6% recanalization rate with only 25% positive clinical outcome. Several possible mechanisms have been put forward to explain the mismatch between recanalization success and clinical sequelae: (1) the presence of an incomplete microcirculatory reperfusion after focal cerebral ischemia; the presence of an already infarcted ischemic core; and inadequate arterial collateralization. Recent advances in imaging of patients undergoing IV thrombolysis and IA therapy suggested the role of arterial collateralization as a significant prognostic factor. A favorable arterial collateralization profile may enhance recanalization, improve downstream reperfusion, reduce the extent of infarct core and ischemic lesion growth, decrease hemorrhagic transformation, and improve outcome after revascularization.

Cerebral Collateral Circulation

Human

The development of the cerebral collateral circulatory channels during embryonic stages parallels development of the nervous system. At the fifth week of gestational age, 4 pairs of presegmental arteries originate from the primitive internal carotid artery (ICA): the trigeminal arteries, the otic arteries, the hypoglossal arteries, and the proatlantal intersegmental arteries. By the sixth gestational week, dorsal to the presegmental arteries, bilateral longitudinal neural arteries unite to form the basilar artery. The posterior communicating arteries (PCoAs) develop from caudal division of the ICA at the same period and begin to serve as a communication between the ICA and the arteries of the primitive hindbrain. During the early eighth gestational week, the posterior cerebral artery (PCA) develops during the posterior expansion of the forebrain as a posterior continuation of the PCoA and the ICA. Early in development, the PCoA and the proximal branches of the PCA (posterior choroidal, diencephalic, and mesencephalic arteries) are prominent. During embryogenesis, the distal PCA elongates and increases in caliber as the occipital lobes expand, outgrowing the once prominent proximal branches. The PCoA undergoes relative regression. This shift in dependence from the carotid to the basilar system in the final stages of embryonic development is not constant. In some adult brains, the embryonic pattern persists, with the PCA remaining a branch of the ICA, which occurs in approximately 20%-30% of cases.

The system of leptomeningeal anastomoses (LMA), which is first described by Heubner in 1874, constitutes the secondary network of the cerebral collateral circulation apart from the Circle of Willis (primary network). LMA are primary collateral pathways between distal branches of the cerebral arteries found along the surface of the brain that permit blood flow from the territory of an unobstructed artery into the territory of an occluded artery. The most significant anastomoses are between anterior cerebral artery (ACA) and middle cerebral artery (MCA) (Fig 1), in terms of number and size with smaller and fewer connections between MCA and PCA (Fig 2) and even less prominent terminal anastomoses between PCA and ACA. In recent years, both anatomic and angiographic studies confirmed the presence of LMA in every brain. Great interindividual variability in distribution, size, and number of LMA existed, but the range and compensatory capacity still remained unanswered.
Table 1. Major trials of intra-arterial therapy demonstrating mismatch between recanalization rates and good clinical outcomes

<table>
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<tr>
<th>Trials</th>
<th>N</th>
<th>Time (min)</th>
<th>NIHSS</th>
<th>Angiography</th>
<th>Type of IA</th>
<th>Recanalization rate (%)</th>
<th>Good clinical outcomes (mRS score ≤2) (%)</th>
<th>Mortality (%)</th>
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<td>IMS I/II (2004/2007)</td>
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<td>0-180</td>
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<td>Occlusion of ACA, MCA, PCA, or BA</td>
<td>Combined IV + IA t-PA</td>
<td>56/60</td>
<td>43/46</td>
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<td>0-360</td>
<td>≥4 and ≤30</td>
<td>TIMI grade 0-1 of MCA M1/M2</td>
<td>IA r-pro-UK</td>
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<td>MERCI (2005)</td>
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<td>≥8</td>
<td>Occlusion of VA, BA, ICA, MCA</td>
<td>MERCI retrieval system</td>
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<td>28</td>
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<tr>
<td>MultiMERCI (2008)</td>
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<td>180-480*</td>
<td>≥8</td>
<td>Occlusion of VA, BA, ICA, MCA</td>
<td>MERCI retriever X5, X6, L5</td>
<td>69.5</td>
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<td>Penumbra Pivotal Trial</td>
<td>125</td>
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<td>≥8</td>
<td>Treatable large intracranial occlusion</td>
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<td>81.6</td>
<td>25</td>
<td>32.8</td>
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Abbreviations: ACA, anterior cerebral artery; BA, basilar artery; IA, intra-arterial; ICA, internal carotid artery; IMS, Interventional Management of Stroke; IV-tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; PROACT II, prolyse in acute cerebral thromboembolism; r-pro-UK, recombinant pro-u-rokinase; VA, vertebral artery.

*0-180 min if ineligible or refractory to IV-tPA.

†434 participants in endovascular therapy group and 222 in IV-tPA alone in IMS III trial.

‡IV-tPA initiated within 3 h after stroke onset; randomization required within next 40 min.

§The results shown are for endovascular therapy group.

||Total of 362 participants equally divided into 2 groups (endovascular treatment and IV-tPA).
Leptomeningeal Collaterals

Animal Model

The dynamics of collateral blood flow during ischemic stroke remain little known owing to heterogeneity in patient demographics and treatment options despite of the advent of medical technology imaging. Animal model studies offer greater experimental control and facilitate an understanding of collateral vascular dynamics. Early studies in animal models showed that the pyriform branch of the MCA has collateral communication with the ACA and that the parietal and temporal branches collateralize with the PCA after MCA occlusion in Sprague–Dawley rats. Leptomeningeal arterial blood pressure correlates with blood flow in ischemic areas, and these arteries can further dilate to increase blood flow to the brain after an MCA or common carotid artery occlusion. In a recent study, Zhang et al investigated 15 different mouse strains to determine numbers of native collaterals and demonstrated statistically significant variation in collateral length, numbers of penetrating arterioles, and infarct volume after MCA occlusion. As expected, infarct volume correlated inversely with collateral number (P < 0.001), diameter (P < 0.001), and number of penetrating arterioles (P < 0.001). Faber et al demonstrated age- and dose-dependent loss of collateral number and diameter and increased tortuosity with a 3-fold larger infarct volume and a 6-fold increase in collateral resistance 3 days after permanent MCA occlusion in 24-month-old mice, which resulted from collateral insufficiency.

The uncertainty regarding role of collateral dynamics in neuroprotection remains as a result of paucity of research in humans. Nonetheless, in animal setting, dynamic mapping with laser speckle contrast imaging established extensive anastomotic connections between the ACA and MCA that develop after MCA occlusion in rats and persisted for 24 hours. Schaffer et al quantified blood flow reversals downstream of MCA occlusion in Sprague-Dawley rats using a 2-photon laser scanning microscope and showed that approximately half of the arterioles downstream of the occlusion showed flow reversal, as would result from retrograde flow from the ACA into the territory of the MCA, within the 2 hours after occlusion. The same author demonstrated overall reduction in the magnitude of the

Figure 1. Leptomeningeal collaterals between ACA and MCA. Abbreviations: ACA, anterior cerebral artery; LMA, leptomeningeal anastomose.

Figure 2. Leptomeningeal collaterals between MCA and PCA. Abbreviations: LMA, leptomeningeal anastomose; PCA, posterior cerebral artery.
speed of the red blood cells in 42 vessels across 11 rats with the volume flux reduced by 45% after the MCA and essentially unaffected vessel diameter. More recently, Shih et al demonstrated in similar rats that these flow reversals are restricted to surface arterioles and do not persist to penetrating arterioles. In addition, the author documented that, using 2-photon laser scanning microscope, the velocity of red blood cells in arterioles downstream MCA occlusion is reduced to 30% of baseline and lumen diameters in small surface arterioles (<23 um diameter) and penetrating arterioles increased by approximately 20% during acute ischemia and the vasodilation persisted over 90 minutes post-occlusions.

Changes in LMA were not limited to acute occlusion, but extreme collateralization was noted after 1 month of MCA occlusion in normotensive Wistar Kyoto rats and stroke-prone spontaneously hypertensive rats that exhibited ~26 and ~27 anastomoses between the ACA and MCA, respectively. 43 Although both Wistar Kyoto and stroke-prone spontaneously hypertensive rats exhibited almost similar ACA–MCA anastomoses after 1 month of MCA occlusion, these connections were significantly narrower in the latter resulting in significant infarction. 43

However, certain differences are evident between the cerebrovascular systems (and reactions to different factors) of humans and animals before overzealous rendition into clinical practice. A more complete anatomic knowledge of the cerebral vessels of various model species is needed to develop more reliable models for objective results that improve knowledge of the pathology of stroke in both human and veterinary medicine. 44

Imaging Leptomeningeal Collateral Blood Flow

Modern imaging modalities are available to evaluate leptomeningeal collateral circulation including transcranial Doppler (TCD), positron emission tomography, single-photon emission computed tomography (CT), computed tomography angiography (CTA), magnetic resonance angiography (MRA), computed tomography perfusion (CTP), magnetic resonance (MR) perfusion, and digital subtraction angiography (DSA). The extent of LMA formation seen on conventional DSA and with clinical outcome correlates well with collateral blood flow as assessed by CTA, triphasic perfusion CT, Xenon CT, MR imaging, and single-photon emission CT. 45 The CT-based methods, CTA and CTP, can be performed rapidly and are widely available to clinicians. CTP is a dynamic technique, which provides maps of salvageable tissue (penumbra) and nonviable tissue (ischemic core). CTA uses IV administered contrast to visualize the intra- and extracranial vasculature including LMA, and it is noninvasive. CTA permits visualization of the extent of LMA despite of lack of dynamic information. The combination of CTP and CTA adds crucial dynamic information to confirm that collateral flow is truly retrograde with exceptional interobserver agreement. 23

TCD-Based Assessment of Leptomeningeal Collaterals

TCD has the advantage in assessment of LMA as it requires neither radiation nor contrast requirements though these are offset by the lack of uniformity for LMA definition on TCD and difficulty in finding acoustic window. 46

TCD-Based Leptomeningeal Scores and Validation

Six different assessment methods of LMA on TCD were incorporated in 7 publications, in which none assessed the reliability. 47 Zareie et al used TCD to measure ACA flow diversion, and it was considered present when the ipsilateral ACA mean blood flow velocity was at least 30% greater than that of the contralateral ACA.

Collateral Correlation with Clinical Outcomes

Zareie et al used TCD to measure ACA flow diversion of 53 patients presenting with acute anterior circulation ischemic stroke within 6 hours and correlated with leptomeningeal collateral flow on CTA. 48 Favorable outcome (modified Rankin Scale score 0-2) was higher (P < .001) in those with the presence of ACA flow diversion on TCD. ACA flow diversion was associated with good collateral flow on CTA (P < .001) and was an independent predictor of admission infarct core volume (P < .001) and 24-hour infarct volume (P < .001). 48

CTA-Based Assessment of Leptomeningeal Collaterals

CTA-Based Leptomeningeal Scores and Validation

Various studies have used CTA to score collaterals status. 23,49-54 In these studies, various collateral scoring grade has been used based on CTA source images and multiplanar reconstructed images using maximum intensity projections. Lee et al incorporated triphasic CTP in evaluations of collaterals with 2 grades assessing the extent of perfusion deficit (severe and moderate) without reliability assessment. Mitteff et al assessed retrograde filling of MCA by 3 categories of collateral scoring with a good reliability grade that was divided to good, moderate, and poor. Maas et al graded collateral flow viewed with CTA (source image) by comparing the vasculature in the ischemic hemisphere with that on the unaffected side with a 5-point scale with no assessment on the reliability method. Tan et al demonstrated that a CTA maximal intensity projection was the best technique to quantify the degree of collateral circulation with a good interobserver agreement. In a recent study by Menon et al, a semiquantitative system of leptomeningeal scoring using multiplanar reformatted CTA based
on the major anatomic regions of the anterior circulation that is comparable with the ASPECTS method of scoring head CT applied with a high inter-rater reliability.

Collateral Correlation with Clinical Outcomes

Of 92 patients with proximal anterior circulation stroke who underwent CTP and CTA within 6 hours, good collateral status was noted in 51 patients with reduced infarct expansion and more favorable outcomes (modified Rankin Scale score 0-2) in a study by Miteff et al. The National Institutes of Health Stroke Scale score was significantly lower in patients with good collaterals than in patients with collateral scoring of moderate and poor (P = .012). Good collateral status was one of the significant univariate predictors of favorable outcome. In another study, Maas et al included 134 patients with proximal MCA occlusion without evidence of occlusion in the contralateral MCA and compared with a group of 235 patients with anterior circulation ischemic symptoms. The effects of collaterals on prehospital clinical fluctuations, size of the ischemic stroke, and clinical outcome. There were no fluctuations in prehospital symptoms in patients with poor collaterals. However, in hospital, worsening of symptoms was 4 times more likely in patients with poor collaterals than in those with normal or exuberant collaterals. Menon et al included 138 patients (MCA-M1 and/or intracranial occlusion) in a retrospective single-center study and demonstrated a good regional LMA score in 37.6% of patients that correlates strongly with the size of infarct core at baseline and is a strong independent predictor of final infarct and clinical outcome.

**Dynamic and 4-Dimensional CTA Techniques to Assess Leptomeningeal Collaterals**

**Dynamic and 4-Dimensional CTA–Based Leptomeningeal Scores and Validation**

Menon et al used whole-brain dynamic time-resolved CTA to assess retrograde filling of leptomeningeal arteries which were divided into 2 groups based on origin from anterior or posterior circulation, namely ACA to MCA and PCA to MCA. The leptomeningeal arteries were analyzed on 3 properties: anatomical extent, prominence of pial arteries, and time for retrograde filling. Inter-rater reliability for all components of LMA assessment was good in this study except for retrograde filling time in the anterior MCA territory, which was described as fair. Frölich et al used thin-slice 4-dimensional (4D) CTA to assess the presence of antegrade contrast opacification distal to the occlusion site using multiplanar reformations and maximum intensity projections in 3 orthogonal planes with a high inter-rater reliability.

**Collateral Correlation with Clinical Outcomes**

In a retrospective study, Menon et al included 25 patients of AIS and MCA-M1 and/or intracranial ICA occlusions within 6 hours of onset undergoing dynamic time-resolved CTA and CTP. The investigators demonstrated functionally better interterritorial LMA between the posterior circulation and the MCA territory than those between the ACA and MCA territories. Significant variability in size and rate of backfilling of pial arteries were noted when compared with anatomically similar vessels in the contralateral hemispheres. In another retrospective study, Frölich et al used 4D CTA to 57 patients to differentiate antegrade flow across incomplete vessel occlusions from retrograde collateral flow with high sensitivity and specificity. The conclusions reached that patients with antegrade flow might have a higher chance of early vessel recanalization after IV thrombolysis.

**MR-Based Assessment of Leptomeningeal Collaterals**

**MR-Based Leptomeningeal Scores and Validation**

Various studies used different modalities of MR to grade LMA though none were assessed for reliability. In a retrospective study, Ruland et al demonstrated the utilization of quantitative MRA by using noninvasive optimal vascular analysis to assess leptomeningeal collateral flow. Sanossian et al incorporated the fluid-attenuated inversion recovery vascular hyperintensities sequences as a marker of collateral flow in 74 patients and demonstrated its presence in areas of blood flow proximal and distal to occlusion, and fluid-attenuated inversion recovery vascular hyperintensities were associated with more extensive collateral circulation.

**Collateral Correlation with Clinical Outcomes**

Lee et al demonstrated prominent distal hyperintense vessels in 46% of patients and subtle distal hyperintense vessels in 27% of patients out of 52 patients assessed within 3 hours of the onset of stroke with proximal intracerebral arterial occlusion. Patients with distal hyperintense vessels had smaller initial lesions, smaller 24-hour and subacute lesions, larger diffusion–perfusion mismatch, and smaller final lesions viewed with DWI than did patients with no distal hyperintense vessels.

**DSA-Based Assessment of Leptomeningeal Collaterals**

**DSA-Based Leptomeningeal Scores and Validation**

Conventional DSA is referred to as the gold standard for assessment of LMA using indirect assessment of the extent and rate of backfilling of pial arteries receiving blood flow.
through small interarteriolar connections. Apart from assessment of LMA, it also allows assessment of 2 other major collateral routes: extracranial–intracranial anastomoses and Willisian and LMA Fig 3. An American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology angiographic grading system has been established to measure the extent of collaterals in subjects with intracranial occlusion as proposed by Higashida et al that use a 5-point scale. There were only 2 studies with good intra-observer agreement despite of 41 different assessment methods of LMA using DSA. Limitations of DSA include its operator dependency, availability of DSA, and radiation exposure, and it is invasive with a risk of complications including embolism, dissection, hematoma, allergic reaction to contrast dye, and nephropathy.

Collateral Correlation with Clinical Outcomes

Bang et al demonstrated that good collaterals in 17 (39%) patients, intermediate collaterals in 20 (45%), and poor collaterals in 7 (16%) of 44 patients with acute stroke underwent endovascular recanalization therapy. The degree of collateral circulation had a positive effect on recanalization therapy with none of the patients with poor collateral circulation had complete recanalization. Complete recanalization was evident in 25% of patients with intermediate collateral circulation and in 41% of patients with good collateral circulation, and pretreatment collateral circulation was independently correlated with infarction growth in multiple regression analysis.

Best Imaging?

Collateral vessel assessment is inconsistent and often indirect in clinical practice. Imaging assessment of LMA in humans does not visualize these vessels directly but instead relies on an indirect assessment of the extent and rate of backfilling of leptomeningeal arteries receiving blood flow through small inter-arteriolar connections. CTA shows the anatomical configuration of collateral vessels and is becoming more routine as it is quicker, noninvasive, and simpler, but the low temporal resolution can result in overestimation of collateral flow. Conventional DSA is considered to be the reference standard for assessment of LMA; however, it is an invasive test and is not performed at presentation in the majority of patients with AIS as it is restricted for those patients considered for IA therapy. Furthermore, a detailed 4-vessel study requires a comprehensive assessment of collateral status, and it is time consuming and would not be feasible in an acute stroke setting although it provides excellent temporal and spatial resolution. Currently, MRA is limited in ability to evaluate leptomeningeal collaterals because of poor resolution of the distal intracranial vasculature and high sensitivity. The dynamic nature of collateral perfusion may be incompletely characterized with current imaging approaches that ignore temporal features. Hopefully, the explosion of technological advances in the field of neurovascular imaging with newer imaging techniques such as whole-brain dynamic time-resolved CTA and 4D CTA would be more widely available as the small sample size studies has shown promising result in addressing the dynamic nature of collaterals.

Best Methods of LMA Assessment?

In a recent systemic review, the issue of inconsistency in how LMA is graded, with a variety of grading scales and imaging modalities being used has been addressed. In total, 41 different criteria for grading LMA with conventional DSA (n = 3467 patients), with collateral assessments in anterior and posterior circulation, were recorded with good reliability assessments in only 2 methods. For CTA-based LMA assessments, 7 grading scales were identified with moderate-to-excellent interobserver agreement in 5 studies. MR imaging (n = 358}

Figure 3. (A) DSA of a 76-year-old man with right mid-M1 occlusion underwent clot retrieval in our centre. He presented with left side deficits with admission NIHSS 8 reduced to 5 after given intravenous tissue plasminogen activator. (B) Good leptomeningeal collaterals between right ACA and MCA of the same patients’ pre-clot retrieval. Abbreviations: ACA, anterior cerebral artery; NIHSS, National Institutes of Health Stroke Scale.
patients) and TCD (n = 268 patients) were used according to 9 and 6 grading methods, respectively, with no assessments of interobserver agreement. The inconsistency in imaging methods and grading limits the emphasis on LMA despite its linkage with positive outcome after stroke. Furthermore, ischemia in acute stroke is extremely complex and perhaps warrants distinction of primary ischemia resulting from a vessel occlusion versus secondary ischemia characterized by collateral blood flow and cerebral oxygen supply that is dependent on other parameters, including arterial blood pressure and arterial oxygen content.

Conclusions

There is accumulating evidence that clinical outcomes after IA therapy is critically dependant on arterial collateralization. However, the prognostic role of collateralization has not been definitively established given the lack of a uniform grading system consequent of poorly defined parameters and individual variability in the Circle of Willis. Notwithstanding advances in the imaging of collateral circulation, its validity requires standardization in assessment methods. Further trials are required to establish the role of collateral circulation as a predictor of outcome after IA therapy.

References

Association of Aspirin Resistance With Increased Stroke Severity and Infarct Size

Amy S. Y. Zheng, BSc(Hons); Leonid Churilov, PhD; Ruth E. Colley, BSc(Hons); Christine Goh, MBBS; Stephen M. Davis, MD; Bernard Yan, MD

Objective: To investigate the relationship between aspirin resistance and clinical and neuroimaging measures of stroke severity in acute stroke patients.

Design: Prospective single-center survey of acute ischemic stroke patients receiving aspirin therapy.

Setting: The Royal Melbourne Hospital, Parkville, Victoria, Australia.

Patients: Ninety acute stroke patients who previously received aspirin therapy were enrolled.

Main Outcome Measures: Clinical stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) and stroke infarct size was measured using the Alberta Stroke Program Early CT Score (ASPECTS). Aspirin resistance was measured using the VerifyNow system.

Results: The mean (SD) age was 75 (9.9) years and 64.4% were male. The median NIHSS score and ASPECTS were 4 (interquartile range [IQR], 3-10) and 9 (IQR, 6-10), respectively. Aspirin resistance was detected in 28.9% (95% CI, 0.19 to 0.38) of all patients. The median aspirin reaction unit (ARU) was 486.0 (IQR, 432.3-557.0). Every 1-point increase in ARU was associated with a 0.03-point increase in NIHSS score (95% CI, 0.01 to 0.04; \( P < .001 \)) and a 0.02-point decrease in ASPECTS (95% CI, -0.03 to -0.01; \( P < .001 \)). This corresponded to an approximate median increase of 1 point in NIHSS score for every 33-point increase in ARU or a decrease of 1 point in ASPECTS for every 50-point increase in ARU.

Conclusions: Aspirin resistance is associated with increased clinical severity and stroke infarct volume in acute stroke patients. Our results support the need for a randomized controlled study to investigate alternative antiplatelet therapy in patients with aspirin resistance.


Improving clinical outcome is the cornerstone of both acute stroke treatment and prevention. In addition to intravenous recombinant tissue plasminogen activator, short-term aspirin therapy significantly reduces death and dependency at 6 months. Pooled analysis of the International Stroke Trial and Chinese Acute Stroke Trial showed significant relative risk reduction of 11% of nonfatal stroke or death in patients treated with short-term aspirin. Further, prior use of aspirin has also been associated with lower National Institutes of Health Stroke Scale (NIHSS) scores on hospital admission as well as lower modified Rankin Scale scores at discharge. Prior antiplatelet therapy has been shown to decrease infarct growth in both animal models and human studies. Aspirin inhibits the conversion of arachidonic acid into prostaglandin H2 by acetylating cyclooxygenase-1, leading to decreased formation of thromboxane A2. The biological consequence is the inhibition of platelet aggregation and thrombus formation. This may reduce the size and extent of thromboses and emboli, leading to reduced infarct volume. Aspirin may also reduce stroke severity through anti-inflammatory and neuroprotective mechanisms.

However, a proportion of patients treated with aspirin demonstrate poor clinical outcomes, which may be attributable to aspirin resistance, an increasingly recognized clinical phenomenon. Aspirin resistance is the failure of aspirin to reduce platelet production of thromboxane A2 and therefore platelet activation and aggregation. Approximately 30% of patients with cardiovascular disease do not achieve an expected level of platelet inhibition with aspirin. A similar prevalence is found in stroke populations. These “aspirin-resistant” patients exhibit
an increased risk of vascular events such as myocardial infarction, transient ischemic attack, or stroke.\textsuperscript{20-21} The effect of aspirin resistance on stroke severity has been previously investigated, but the findings were inconclusive.\textsuperscript{22,23} Schwammenthal and colleagues\textsuperscript{22} found a significant association with admission NIHSS score; however, less than half their cohort were receiving long-term aspirin therapy. A different study\textsuperscript{23} found that aspirin resistance was significantly associated with functional outcome (modified Rankin Scale score), but not stroke severity (NIHSS score), within 72 hours of onset.

Consequently, there is a need to further investigate the effect of aspirin resistance on clinical stroke severity. There is also increasing interest to measure stroke severity with additional neuroimaging tools. In particular, area of infarct is an alternate measure of stroke severity. The Alberta Stroke Program Early CT Score (ASPECTS)\textsuperscript{24} is widely used for measuring the area of infarct seen on admission computed tomography.\textsuperscript{24}

We hypothesized that in patients receiving prior aspirin therapy with aspirin resistance stroke severity would be greater measured by a clinical impairment score and a radiological measurement. We therefore aimed to investigate the association between aspirin resistance and stroke severity measured by NIHSS and infarct volume as measured by ASPECTS.

METHODS

We obtained ethics approval to prospectively recruit consenting acute stroke patients presenting to the Royal Melbourne Hospital stroke care unit. The inclusion criteria were at least 7 days of aspirin therapy (acetylsalicylic acid, 100 mg daily) prior to stroke onset, evidence of ischemic infarct on computed tomography or magnetic resonance imaging, and age older than 18 years. Compliance was determined by interviews of patients and patient relatives. Patients were excluded if there was evidence of hemorrhage on computed tomography or magnetic resonance imaging or they had platelet function disorders or were concurrently taking an additional antplatelet, anticoagulant, or nonsteroidal anti-inflammatory medication.

Patient enrollment, blood sampling, and data collection occurred within 48 hours of hospital admission. Those who had aspirin withheld during this period were further excluded, as were those for whom an antplatelet other than aspirin or anticoagulant medication was added. Demographic and clinical information including duration of aspirin therapy, stroke subtype according to the Oxfordshire Community Stroke Project and Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and whether they were given tissue plasminogen activator were collected for all patients. History of myocardial infarction, ischemic stroke, and transient ischemic attack was assessed retrospectively over the previous 2 years.

Stroke severity was assessed using the NIHSS\textsuperscript{25} on admission by persons trained in the examination and blinded to the diagnosis of aspirin resistance. A severe stroke was defined as an NIHSS score of 16 or more and a mild to moderate stroke severity was defined as an NIHSS score less than 16. The size of infarction was measured on admission computed tomography scan using the ASPECTS\textsuperscript{24,26} scoring system by radiologists trained in the examination and blinded to the diagnosis of aspirin resistance. The ASPECTS scoring also relies on middle cerebral artery territory involvement; therefore, posterior infarctions were excluded from this analysis. A large area of infarction was defined as an ASPECTS less than 7 and a small area of infarction was defined as an ASPECTS of 7 or more.

Blood samples were taken no sooner than 2 hours and no later than 24 hours following last aspirin ingestion. A 2-mL blood sample was collected into a 3.2% sodium citrate vacuum-sealed tube. All patients were tested while receiving 100 mg of aspirin every morning as documented on ward records.

Aspirin resistance was measured using the VerifyNow system (Accumetrics), a type of rapid platelet function assay. The VerifyNow measures the change in light transmission across a whole-blood sample in response to agonist stimulation proportional to the level of platelet activation/aggregation in the sample. Results are produced in the form of an aspirin reaction unit (ARU). In line with previous definitions,\textsuperscript{27,28} a cutoff of 550 ARU was used to determine the presence of aspirin resistance. Raw ARU scores as continuous variables were also used to indicate the degree of platelet aggregation.

Statistical analysis was performed using statistical software SPSS version 16 (IBM SPSS) and Stata version 11IC (StataCorp). A Shapiro-Wilk test was used to assess the normality of distributions. Univariate analyses of sociodemographic and clinical variables, as well as vascular risk factors, were performed using the \( t \) test. Wilcoxon-Mann-Whitney rank sum test, or \( \chi^2 \) test as appropriate depending on the nature of the underlying distributions. Independent association between aspirin resistance and both NIHSS score and ASPECTS was assessed using the Spearman rank correlation coefficient. The magnitude of the association between aspirin resistance and both NIHSS score and ASPECTS (both unadjusted and adjusted for vascular risk factors and cardioembolic stroke) was estimated using median regression. The difference in both NIHSS score and ASPECTS between aspirin-resistant and aspirin-sensitive groups (dichotomized using the 550-ARU threshold) was assessed using the Wilcoxon-Mann-Whitney rank sum test and median regression was used to estimate corresponding effects (both unadjusted and adjusted for vascular risk factors and cardioembolic stroke). The difference in proportions of severe strokes between the aspirin-resistant and aspirin-sensitive groups was assessed using the Fisher exact test and corresponding effect sizes were estimated using corresponding odds ratios (ORs). A 2-comparison Bonferroni-corrected (corresponding to NIHSS score and ASPECTS), 2-sided \( P < .025 \) was used as a statistical significance threshold for testing the main hypotheses. A Kruskal-Wallis equality of populations rank test was used to assess whether NIHSS score or ASPECTS differed by TOAST categories. Stroke etiology was then dichotomized into cardioembolic and noncardioembolic.

RESULTS

Between October 1, 2006, and April 7, 2011, 710 acute ischemic stroke patients who were receiving aspirin therapy were screened. A total of 90 patients were enrolled. The mean (SD) age was 75 (9.9) years and 64.4% were male. Participants had been taking aspirin for a median duration of 5 years (interquartile range [IQR], 2-10 years). Demographic and clinical characteristics of the patient population are presented in Table 1.

Raw ARUs ranged from 385 to 653, with a median of 486.0 (IQR, 432.3-537.0). A total of 26 of 90 enrolled patients (28.9%; 95% CI, 0.19 to 0.38) were aspirin resistant, defined by more than 550 ARU. Demographic and clinical characteristics of the aspirin-resistant and aspirin-sensitive groups are given in Table 2. Aspirin-resistant patients were significantly more likely to have sustained...
a myocardial infarction, transient ischemic attack, or stroke within the last 2 years (OR, 8.04; 95% CI, 2.89 to 22.3; \( P = .001 \)). The Oxfordshire Community Stroke Project classification significantly varied with aspirin-resistance status. Five percent of aspirin-sensitive patients sustained a total anterior circulation infarct compared with 35% of the aspirin-resistant patients (OR, 1.093; 95% CI, 0.023 to 0.38; \( P = .001 \)). Patients who did not respond to aspirin were significantly more likely to have a history of smoking (OR, 3.08; 95% CI, 1.17 to 8.13; \( P = .02 \)). No other vascular risk factors differed significantly between the aspirin-sensitive and aspirin-resistant groups. Aspirin response status, NIHSS score, and ASPECTS did not differ significantly between patients with and without cardioembolic stroke.

The Spearman rank correlation indicated a significant association between raw NIHSS and raw ARU scores (\( r = 0.36; P < .001 \)). Median regression estimated a statistically significant increase in NIHSS score of 0.03 point for every 1-point increase in ARU (95% CI, 0.01 to 0.04; \( P = .001 \)). This corresponds to an approximate median increase of 1 point in NIHSS score for every 33-point increase in ARU or 8 points in NIHSS score over the entire range of ARUs observed in the present study. This association remained significant after adjusting for vascular risk factors. A Kruskal-Wallis rank test found no significant difference in NIHSS score between stroke etiology defined by TOAST criteria (\( H_4 = 7.09, P = .07 \)). The NIHSS score did not differ significantly when etiology was dichotomized into cardioembolic and noncardioembolic strokes (\( P = .62 \)).

Aspirin resistance (>550 ARU) was significantly associated with stroke severity (Figure 1). Observed median NIHSS score was 11 (IQR, 4-16) in the aspirin-resistant group compared with 4 (IQR, 2-6) in the aspirin-sensitive group, resulting in a statistically significant median difference of 7 (95% CI, 4.69 to 9.31; \( P < .001 \)), with the aspirin-resistant group having higher NIHSS scores. Adjustment for cardioembolic strokes did not alter the results (median difference, 7; 95% CI, 4.6 to 9.4; \( P < .001 \)). This difference increased further when adjusted for vascular risk factors (median difference, 8; 95% CI, 5.0 to 11.0; \( P < .001 \)). Aspirin-resistant patients were significantly more likely to sustain a severe stroke, defined as an NIHSS score of 16 or more (OR, 7.49; 95% CI, 1.49 to 48.0; \( P = .002 \)).

The Spearman rank correlation indicated a significant association between raw ARU scores and raw ASPECTS (\( r = −0.45; P < .001 \)). Median regression estimated a statistically significant decrease of 0.02 in ASPECTS for every 1-point increase in ARU (95% CI, −0.03 to −0.01; \( P < .001 \)). This corresponds to an approximate median decrease of 1 point in ASPECTS for every 50-point increase in ARU or a median decrease of 5.4 points in ASPECTS over the entire range of ARUs observed in the study sample. This association remained significant after adjusting for vascular risk factors and cardioembolic stroke.

Aspirin-resistance status was significantly associated with infarct size (Figure 2). Observed median ASPECTS was 5.5 (IQR, 4-6.5) in the aspirin-resistant group compared with a median ASPECTS of 10 (IQR, 8-10) in the aspirin-sensitive group, resulting in a statistically significant median difference of 5 (95% CI, −7.0 to −3.0; \( P < .001 \)). While remaining highly statistically significant, this difference decreased slightly when adjusted for vascular risk factors and cardioembolic stroke (median difference, −4.0; 95% CI, −4.8 to −3.3; \( P < .001 \)). The aspirin-resistant group was also significantly more likely to sustain a large stroke defined by an ASPECTS of 7 or less (OR, 60.0; 95% CI, 10.5 to 343.2; \( P = .001 \)).

**COMMENT**

Aspirin is widely used in the treatment of stroke. It significantly reduces the risk of recurrence and the severity of stroke. Long-term aspirin therapy has been estimated to have a cost-effectiveness ratio of $11 000 per quality-adjusted year of life gained. Resistance to aspirin could translate into a significant increase in health burden.

Aspirin resistance is the inability to decrease thromboxane A2 levels after aspirin therapy. It has been associated with increased risk of recurrent stroke and poor outcome after stroke. Drug interactions and compliance, which may fall to 75% at 3 months, have been previously proposed but not substantiated. Genetic polymorphisms in genes encoding collagen, glycoprotein, von Willebrand receptors, or enzymes of the platelet arachidonic acid cascade have also been suggested.
The present study shows that aspirin resistance is prevalent (28.9%; 95% CI, 0.19 to 0.38) in the ischemic stroke population. This is comparable with most previous reports in ischemic stroke populations. Previously reported prevalence has varied from 5% to 60%. The wide range of prevalence may be due to use of different tests of platelet function as well as clinical and demographic differences.

Our study showed that aspirin resistance was significantly associated with a higher median NIHSS score on admission. This was expected because aspirin therapy has previously been found to reduce stroke severity. Schwammenthal et al. found that aspirin resistance was associated with a lower NIHSS score on admission. However, less than half their cohort was receiving long-term aspirin therapy prior to the index event and aspirin doses varied between participants. Englyst et al. found aspirin resistance to be significantly associated with modified Rankin Scale score but not NIHSS scores. Their failure to find significance with clinical stroke severity can be attributed to small sample size within which only a subset took aspirin prior to the index event. The 72-hour time window to collect stroke severity scores may also have influenced their results; a score collected on admission to the hospital may not reflect the patient’s status prior to aspirin therapy.

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### Table 2. Baseline Demographic and Clinical Characteristics of Aspirin-Resistant and Aspirin-Sensitive Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin Resistant (n = 26)</th>
<th>Aspirin Sensitive (n = 64)</th>
<th>P Value</th>
<th>Group Difference (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>76 (70.8-85)</td>
<td>76.5 (72.3-86.5)</td>
<td>.88</td>
<td>0 (−3.53 to 3.53)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (77)</td>
<td>38 (59)</td>
<td>.12</td>
<td>18 (0.26 to 0.38)</td>
</tr>
<tr>
<td>Duration of aspirin therapy, y, median (IQR)</td>
<td>4.5 (2-10)</td>
<td>5 (2-10)</td>
<td>.77</td>
<td>0 (−3.50 to 3.50)</td>
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<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Smoking (current and past)</td>
<td>18 (69)</td>
<td>27 (42)</td>
<td>.02</td>
<td>0.27 (0.06 to 0.49)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>9 (35)</td>
<td>27 (42)</td>
<td>.51</td>
<td>−0.08 (−0.29 to 0.14)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (42)</td>
<td>17 (27)</td>
<td>.14</td>
<td>0.16 (−0.06 to 0.38)</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>8 (31)</td>
<td>13 (20)</td>
<td>.29</td>
<td>0.10 (−0.10 to 0.31)</td>
</tr>
<tr>
<td>Previous MI, TIA, or stroke</td>
<td>18 (69)</td>
<td>14 (22)</td>
<td>&lt;.001</td>
<td>0.47 (0.27 to 0.68)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (92)</td>
<td>60 (94)</td>
<td>.80</td>
<td>−0.01 (−0.13 to 0.10)</td>
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<td>Hypercholesterolemia</td>
<td>13 (50)</td>
<td>52 (81)</td>
<td>&lt;.001</td>
<td>0.31 (−0.53 to −0.10)</td>
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<td>Stroke subtype</td>
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<td>OCSP</td>
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<td></td>
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<tr>
<td>TACI</td>
<td>9 (35)</td>
<td>3 (5)</td>
<td>.01</td>
<td>0.51 (0.29 to 0.73)</td>
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<tr>
<td>PACI</td>
<td>11 (42)</td>
<td>36 (56)</td>
<td>&lt;.001</td>
<td>0.34 (0.12 to 0.56)</td>
</tr>
<tr>
<td>LACI</td>
<td>3 (11.5)</td>
<td>12 (19)</td>
<td>.47</td>
<td>0.31 (−0.05 to 0.67)</td>
</tr>
<tr>
<td>POCI</td>
<td>3 (11.5)</td>
<td>13 (20)</td>
<td>.74</td>
<td>0.06 (−0.20 to 0.32)</td>
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<td>TOAST</td>
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<td></td>
</tr>
<tr>
<td>LI</td>
<td>3 (11)</td>
<td>9 (14)</td>
<td>.47</td>
<td>0.26 (−0.01 to 0.54)</td>
</tr>
<tr>
<td>CE</td>
<td>9 (35)</td>
<td>17 (27)</td>
<td>.47</td>
<td>0.26 (−0.01 to 0.54)</td>
</tr>
<tr>
<td>OE</td>
<td>7 (27)</td>
<td>27 (42)</td>
<td>.47</td>
<td>0.26 (−0.01 to 0.54)</td>
</tr>
<tr>
<td>UE</td>
<td>0 (0)</td>
<td>0</td>
<td>.47</td>
<td>0.26 (−0.01 to 0.54)</td>
</tr>
<tr>
<td>LAA</td>
<td>7 (27)</td>
<td>11 (17)</td>
<td>.47</td>
<td>0.26 (−0.01 to 0.54)</td>
</tr>
</tbody>
</table>

Abbreviations: CE, cardioembolic; IQR, interquartile range; LAA, large artery atherosclerosis; LACI, lacunar infarction; LI, lacunar infarction; MI, myocardial infarction; OCSP, Oxfordshire Community Stroke Project; OE, other determined etiology; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; TACI, total anterior circulation infarction; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UE, undetermined etiology.

<sup>a</sup>Group difference for continuous variables is reported as median difference. Group difference for binary variables is reported as risk difference.

### Figure 1. Variation of baseline National Institutes of Health Stroke Scale (NIHSS) scores with aspirin reaction unit. The asterisks and circle represent individual participants who were outliers. They had a particularly high NIHSS score for aspirin-sensitive patients.

### Figure 2. Variation of Alberta Stroke Program Early CT Score (ASPECTS) between aspirin-sensitive and aspirin-resistant patients.
the third day may be different from that at onset. Furthermore, both studies used labor-intensive tests of platelet activity, which are impractical for clinical use. VerifyNow is a highly specific and sensitive point-of-care measure of platelet function, enabling testing at the patient’s bedside. VerifyNow also correlates well with clinical outcome. The association between stroke subtype and stroke severity and outcome is well established. Aspirin resistance was also significantly associated with infarct size measured by the ASPECTS. The aspirin-resistant group had a lower median ASPECTS compared with the aspirin-sensitive group, indicating larger infarct size. To our knowledge, this is a novel finding and has not been previously described.

Several theories have been postulated to explain the phenomenon whereby aspirin decreases stroke severity and size. Platelets are critical to thrombus formation, contributing as much as 50% of the total thrombus volume. Antiplatelet agents decrease platelet aggregation and, in turn, the size and frequency of thrombotic emboli. An animal study found that pretreatment with aspirin significantly reduced the surface area of carotid mural thrombosis. The increased severity and infarct size observed in the present study may be due to larger thrombus formation as a result of inadequate platelet inhibition. Aspirin also reduces platelet microaggregates and platelet-derived vasoconstricting products. This may ease ischemic injury by improving local blood flow. Aspirin-resistant patients may not experience the same therapeutic effect and, as a result, sustain a larger stroke. The effect of aspirin on stroke severity may be independent of its antiplatelet property. Joseph and colleagues found that aspirin decreased stroke severity but this decrease was not associated with platelet activity. Neuroprotective mechanisms have also been proposed as a mechanism by which aspirin therapy decreases stroke severity. Aspirin has been found to decrease glutamate-mediated excitotoxicity. The metabolite, salicylic acid, is also a free radical scavenger. These anti-inflammatory and neuroprotective mechanisms may be reduced or not present in aspirin-resistant patients and may reflect their increased stroke severity and size. It is also possible that larger tissue ischemia may also trigger a prothrombotic inflammatory reaction and incomplete response to aspirin. Causality is unclear and likely bidirectional.

Several clinical and demographic variables differed between the resistant and responsive groups. Aspirin resistance was more prevalent in patients who had a previous or current smoking history. This may be attributed to cigarette smoking increasing platelet aggregability in patients receiving aspirin therapy. Previous myocardial infarction, stroke, or transient ischemic attack in the last 2 years was also significantly more prevalent in the aspirin-resistant group. Similar to previous findings, aspirin-resistant patients were more likely to sustain a total anterior circulation infarct. This may be the result of inadequate platelet inhibition and the formation of larger thrombi. Larger thrombi translate into the occlusion of larger vessels and a larger infarct. This phenomenon may also be partly attributable to cardioembolic stroke. Atrial fibrillation was prevalent in the study cohort and aspirin therapy has a modest effect on stroke prevention.

Aspirin resistance should therefore have a larger influence on patients with noncardioembolic stroke than those with cardioembolic stroke. Previous studies have reported a higher prevalence of aspirin resistance in lacunar stroke compared with embolic stroke. However, the current study found no significant association with stroke etiology defined by TOAST criteria. The NIHSS score did not differ between patients with cardioembolic and noncardioembolic stroke. Atrial fibrillation also did not differ significantly between aspirin-sensitive and aspirin-resistant groups.

Our study has several strengths. First, to our knowledge, the association between aspirin resistance and ASPECTS has not previously been reported. Second is the prospective data collection, assessment of all patients within 48 hours of admission, and the strict inclusion and exclusion criteria. Third, ASPECTS is highly sensitive and specific for functional outcome, 0.78 and 0.96, respectively. However, our findings and conclusions should be interpreted in light of a small sample size. There was also a slight selection bias for patients with relatively milder symptoms. Furthermore, we are limited by the possible insensitivity of ASPECTS for early ischemic changes. Because ASPECTS was determined using admission computed tomography, allocated scores may not accurately represent the total area of ischemia.

The results of our study suggest that patients with aspirin resistance are more likely to sustain a more severe stroke than patients without. We recommend a randomized controlled study to compare alternative antiplatelet agents in patients with aspirin resistance.

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Author Contributions: Study concept and design: Davis and Yan. Acquisition of data: Zheng and Colley. Analysis and interpretation of data: Zheng, Churilov, Goh, Davis, and Yan. Drafting of the manuscript: Zheng, Colley, and Yan. Critical revision of the manuscript for important intellectual content: Zheng, Churilov, Goh, Davis, and Yan. Statistical analysis: Zheng, Churilov, and Yan. Administrative, technical, and material support: Zheng, Goh, Davis, and Yan. Study supervision: Davis and Yan.

Conflict of Interest Disclosures: Ms Colley received honoraria from Biometrictra, Australian distributor of VerifyNow, for educational presentations.

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3. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40 000 randomized patients from the


Warfarin-associated intracerebral hemorrhage: Volume, anticoagulation intensity and location

Minmin Ma, Atte Meretoja, Leonid Churilov, Gagan J. Sharma, Søren Christensen, Xinfeng Liu, Louise Weir, Stephen M. Davis, Bernard Yan

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Brain stem hemorrhage

Abstract
Background: Warfarin use increases mortality in patients with intracerebral hemorrhage (ICH). Larger hematoma volume and infratentorial location are both major determinants of poor outcome in ICH. Although warfarin-associated intracerebral hemorrhages have greater volumes, there is uncertainty about the effects of location. We aimed to investigate the influence of warfarin on hematoma volume and location.

Methods: We conducted a retrospective study of all patients hospitalized for ICH at a large stroke center from October 2007 to January 2012. Initial CT scans were used to quantify hematoma volumes using the computer-assisted planimetric analysis. Univariate and multivariable analyses determined the influence of warfarin on hemorrhage location. Median regression analysis was performed to estimate the effects of INR on hematoma volumes.

Results: We included 404 consecutive patients with ICH of whom 69 were on warfarin. Patients on warfarin had larger hematoma volumes (median 23.9 mL vs. 14.2 mL; P = 0.046). In patients excessively anticoagulated with warfarin (defined as INR > 3.0), compared with those in the therapeutic range, brainstem ICH was more frequent (24.0% vs. 6.1%; P = 0.005). Patients with INR > 3.0 had increased odds of infratentorial hemorrhage (OR 3.63; 95% CI 1.52-8.64; P = 0.004) when compared to non-warfarin ICH patients. After adjustment for hematoma location, there was no significant association between INR and hematoma volume.

Conclusions: Patients with warfarin-associated ICH have a predilection for brainstem ICH. After adjustment for ICH location, no relationship between admission INR and hematoma volume was found.

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1. Introduction

Warfarin-associated ICH is a major clinical problem, more common than subarachnoid hemorrhage in the United States [1]. The use of warfarin to prevent atrial fibrillation-related stroke is increasing with aging populations and better recognition [2–4]. Oral anticoagulant therapy (OAT) not only increases the risk of intracerebral hemorrhage (ICH) [5], but also worsens the severity of ICH in a dose-dependent manner [6]. The underlying mechanism by which warfarin worsens ICH prognosis has not been well established.

Larger baseline hematoma volume and infratentorial location are two major determinants of poor outcome in spontaneous ICH [7,8]. Given that the risk of ICH increases significantly with increasing international normalized ratio (INR) in patients taking warfarin [9], it is possible that intense anticoagulation may affect the size of ICH. However, previous studies have reported conflicting results on the effect of warfarin on hematoma volume [10–13]. In addition, the correlation of anticoagulant therapy and hematoma location is controversial [14–17]. Some studies have suggested a higher proportion of lobar and thalamic location [10,17], but others reported a higher rate of cerebellar hemorrhage [14–16]. It follows that the relationship of OAT with hematoma volume and location remains unresolved.

The aim of the present study was to investigate in ICH patients whether higher INR values are associated with larger baseline hematoma volumes, and to determine the relationship between warfarin therapy and hematoma location.
2. Methods

2.1. Study population

The study protocol was approved by the human research ethics committee of the Royal Melbourne Hospital. We identified all subjects aged ≥18 years who were hospitalized with ICH between October 1, 2007 and January 31, 2012 at this hospital. All potential cases were extracted from our prospective stroke database. Exclusion criteria were traumatic ICH, hemorrhagic transformation of cerebral infarction, ICH secondary to vascular malformation, aneurysm, vasculitis of the central nervous system, and recent endarterectomy. In addition, we excluded patients with primary intraventricular hemorrhage (IVH), liver cirrhosis, and those with missing INR values or CT scans on admission.

Patient demographics and putative risk factors, such as sex, age, hypertension, diabetes mellitus, atrial fibrillation, hypercholesterolemia, ischemic heart disease, previous transient ischemic attack (TIA) or stroke, and pre-ICH medications were abstracted from the stroke database and complemented by a chart review. Pre-ICH modified Rankin Scale (mRS), Glasgow Coma Scale (GCS) at presentation, mRS at discharge, and in-hospital mortality were retrieved. All presentations were within 7 days of symptom onset, including interhospital transfers. The initial baseline brain CT scans and INR values were evaluated. For warfarin-related ICH patients, initial INR values obtained before reversal were used for the analysis. Patients were both dichotomized by warfarin use and stratified by the level of anticoagulation (non-warfarin, warfarin therapy with INR ≥ 2.0, 2.0–3.0, > 3.0).

2.2. Neuroimaging analyses

All CT scans were reviewed and evaluated in consensus by two experienced neurologists (M.M, B.Y.) who were blinded to the patient’s clinical status. The ICH and IVH volumes were determined from available CT scans. Images were transmitted digitally in DICOM format to a workstation and analyzed with the Analyze 10.0 software (Mayo Clinic, Rochester, MN). ICH and IVH were defined and outlined separately by using the tracing tools in the region of interest module from the Analyze software for planimetric volume calculation. Intraventricular blood was not included in the volume calculation. The hematoma location was categorized into lobar (with or without involvement of subcortical white matter), deep (basal ganglia, thalamus, internal capsule), cerebellum and brainstem. Location was also dichotomized into supra- and infratentorial site.

2.3. Statistical analysis

Continuous variables and categorical variables were compared using the Mann-Whitney rank-sum test and Fisher exact test as appropriate. The association between the baseline INR category and hematoma location was determined using multiple logistic regression analysis, including the factors that were found to be associated with ICH location in univariate analysis (P < 0.20). The following factors were considered: age, hypertension, hyperlipidemia, diabetes, and ischemic heart disease. Spearman rank correlation was estimated to determine the association between the baseline INR and hematoma volume for each ICH location category. Due to nonparametric hematoma volume distributions, median regression analysis was used to estimate the effects of INR on hematoma volumes, adjusted for the ICH location. Statistical analyses were performed using Stata/IC software package, version 12.0 (StataCorp, College Station, TX). All P values are 2-tailed; P < 0.05 was considered significant.

3. Results

There were 553 ICH patients treated at our hospital from October 1, 2007 to January 31, 2012. Of these, 28 were excluded due to secondary ICH, 12 due to primary IVH, 68 due to unavailable baseline CT scans or CT films unfit for computerized image analysis, and 47 due to missing initial INR values, leaving a study population of 404. Baseline characteristics of the study patients are described in Table 1.

The median age of the cohort was 74 years (interquartile range [IQR] 63 to 81), 58.9% of patients were male, and 17.1% (69/404) were taking warfarin at the time of their ICH. Patients on warfarin were older and more frequently had diabetes, ischemic heart disease, atrial fibrillation, and previous acute ischemic stroke. Patients on
warfarin showed less frequent pre-admission use of antiplatelet drugs than non-warfarin patients. Among patients documented to be taking warfarin, 10 (14.5%) had subtherapeutic INR (1.4–1.9), 34 (49.3%) had therapeutic INR (2.0–3.0), and 25 (36.2%) had an spontaneously mildly elevated INR (range 1.2 to 1.4). Patients on warfarin had lower GCS on admission and higher in-hospital mortality than non-warfarin patients (Table 1).

Warfarin-associated hemorrhages were significantly larger than those unrelated to warfarin (median 23.9 mL vs. 14.2 mL; \( P = 0.046 \)). Among all the ICH patients, supratentorial hemorrhages had greater hematoma volumes than infratentorial ICH (median 21.6 mL vs. 3.7 mL; \( P < 0.001 \)). The baseline hematoma volume categorized by location and level of anticoagulation are presented in Fig. 1. Overall, there was no significant association between hematoma volume and anticoagulation intensity (INR). Although there was a trend toward the association between the initial INR and hematoma volume in lobar hemorrhages (Spearman rank 0.121; \( P = 0.120 \)), the effect was attenuated in deep (Spearman rank 0.041; \( P = 0.457 \)), cerebellar (Spearman rank 0.018; \( P = 0.845 \)) and brainstem hemorrhages (Spearman rank −0.047; \( P = 0.617 \)).

Using INR as a continuous variable and adjusting for location, median volume was increased by 1.9 mL per an increase of one unit in INR, but the increase was not significant in the median regression model (\( P = 0.285; 95\% \) CI −1.57–5.32).

Hematoma locations are presented in Table 2. There was a trend toward increased proportion of infratentorial location in patients on warfarin, than patients not on warfarin (24.6% vs. 15.8%; \( P = 0.086 \)). In the patients with excessive anticoagulation (INR \( \geq 3.0 \)), there was a greater proportion of brain stem hemorrhage, compared with the combined group of patients including those on warfarin with an INR \( \leq 3.0 \) and patients not taking warfarin (24.0% vs. 6.1%; \( P = 0.005 \)). Multivariable analysis demonstrated that patients with INR \( > 3.0 \) had a markedly increased odds of infratentorial hemorrhage (OR 3.63; 95% CI 1.52–8.64; \( P = 0.004 \)) when compared to non-warfarin ICH patients (Table 3).

4. Discussion

Patients with warfarin-related ICH have worse outcomes, chiefly attributed to larger hematoma volumes. In this study, we have also found a relationship between warfarin-associated ICH and infratentorial location, which may contribute to the worse prognosis in this group.

ICH is the most feared and lethal complication of warfarin therapy. It accounts for approximately 90% of the deaths from warfarin-associated intra- and extracranial hemorrhages and the majority of major functional disability among survivors [18]. Patients with advanced age, prior ischemic stroke, hypertension and intense anticoagulation are at high risk for an anticoagulant-related ICH [1,19–21]. Although many cases with warfarin-related ICH are due to excessive anticoagulation, most ICH occurs at INR \( < 3.0 \) [20,22]. Most of our patients were within or below the therapeutic INR range. Consistent with previous reports [1,20,21], we found that warfarin-related ICH patients were older and had more vascular risk factors than non-warfarin ICH patients. The newer generation oral anticoagulants are associated with substantially lower risk of ICH than warfarin [23–25]. However, warfarin is likely to remain widely used, particularly in lower income and developing countries.

Table 2

<table>
<thead>
<tr>
<th>Location</th>
<th>Total (n = 404)</th>
<th>Non-warfarin (n = 335)</th>
<th>Warfarin (n = 69)</th>
<th>Fisher’s exact P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobar, no. (%)</td>
<td>165 (40.8)</td>
<td>133 (39.7)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td></td>
<td>Deep, no. (%)</td>
<td>169 (41.8)</td>
<td>149 (44.4)</td>
<td>3 (30.0)</td>
</tr>
<tr>
<td></td>
<td>Cerebellum, no. (%)</td>
<td>41 (10.1)</td>
<td>34 (10.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Brainstem, no. (%)</td>
<td>29 (7.2)</td>
<td>19 (5.8)</td>
<td>1 (10.0)</td>
</tr>
</tbody>
</table>

ICH = intracerebral hemorrhage; INR = international normalized ratio.
We confirmed previous findings showing that patients on warfarin have larger volume hemorrhages, usually considered the major determinant of the adverse prognosis [13,26]. The relationship between anticoagulation intensity and hematoma volume has been uncertain, with conflicting results in previous studies. Some studies found no significant correlation between hematoma size and the corresponding intensity of warfarin therapy measured on admission, based on small sample size and varying methodology [11,12,27]. One recent study reported that only INR > 3.0 was associated with larger hematoma volumes [13], but this was limited by many missing INR values, and confounding of evaluation of baseline INR by warfarin reversal. Most previous reports have used the ABC/2 method to estimate hematoma volume. This method has been reported to significantly overestimate volumes, especially when the hematoma shapes are irregular, which is often the case with OAT-related ICH [28]. We therefore used computer-assisted planimetric analysis for hematoma volume calculation. However, we did not confirm a significant association between the intensity of anticoagulation (admission INR) and hematoma volume at presentation, when adjusted by ICH location. The relatively small sample size and a high proportion of infratentorial hemorrhage in the INR > 3.0 group might represent a type 2 error in revealing the association between intensity of INR and hematoma volume.

We investigated the relationship among admission INR values, hemorrhage locations, and hematoma volumes in ICH patients. Our results demonstrate that there was a higher proportion of infratentorial ICH with warfarin overall and that intense anticoagulation with INR > 3.0 was most strongly associated with infratentorial hematomas. However, it is possible that patients on warfarin with posterior fossa hematoma, given the possibility of surgical intervention, are more likely to be transferred to a stroke center, leading to a higher proportion of patients with infratentorial hematoma represented in our sample.

ICH location is well recognized to influence the initial hematoma volume and patient outcome. Previous reports of the location in warfarin-associated ICH have produced conflicting results. A higher proportion of lobar and thalamic hemorrhage has been reported among patients with ICH and anticoagulation [10,17], whereas other studies found an association with cerebellar hemorrhage [14–16], especially in patients on warfarin therapy with an INR > 2.5 [15]. In our cohort, warfarin with INR > 3.0 was an independent predictor of infratentorial hemorrhage, including cerebellar and brainstem location. These data suggest that different mechanisms may be involved in anterior and posterior circulation hemorrhages. Patients with advanced age and hypertension are more likely to have amyloid angiopathy and may be at higher risk of lobar and deep ICH. The infratentorial location predilection in warfarin-related ICH patients with intense anticoagulation is possibly caused by the smaller size of the perforating arteries, with higher arterial branch vulnerability in the posterior circulation [29]. Clarification of the underlying mechanism of different location distributions in warfarin-related ICH requires further investigation.

Our study has several limitations. Its retrospective design, as well as the small number of warfarin patients in the intensive anticoagulant cohort left us with limited power to investigate the underlying effect of INR on initial hematoma volume and hemorrhage location. Time from symptom onset to CT scan may affect ICH volumes, but many of the patients did not have a recorded time of onset. The combined effect of warfarin therapy, hematoma volume and location on mortality will require further investigation. We did not evaluate hematoma growth, previously reported to be greater with warfarin and an important determinant of the worse prognosis [12,26,30].

5. Conclusions

The results from the present study confirmed that warfarin caused larger volume hemorrhages and in addition, showed a disproportionate number of hemorrhages with infratentorial location. This may be another important determinant of the worse outcome in this population.

Sources of funding

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Conflict of interest statement

None.

References

Elevated urea level is associated with poor clinical outcome and increased mortality post intravenous tissue plasminogen activator in stroke patients

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Renal function
Urea
Glomerular filtration rate
Mortality
Outcome

A B S T R A C T

Background: Renal dysfunction is associated with poor outcomes in ischaemic stroke but remains unproven post intravenous thrombolysis. We studied the renal function in stroke patients treated with intravenous tissue plasminogen activator (IV tPA).

Methods: We retrospectively analysed consecutive ischaemic stroke patients treated with IV tPA (0.9 mg/kg) from January 2003 to December 2011. Collected data included demographics, medical histories, stroke severity measured by National Institutes of Health Stroke Scale (NIHSS), serum urea, creatinine, estimated glomerular filtration rate (eGFR), platelet, white cell count and international normalised ratio (INR) at baseline. Poor clinical outcome was defined as modified Rankin Scale (mRS) of 2 to 6 at 3 months. Logistic regression analysis was performed to test the association between renal function and clinical outcomes adjusted for confounders.

Results: In the 378 patients included, the median age was 72 (IQR = 62–81) years, 54.2% were male. Median baseline NIHSS was 12 (IQR = 8–18). There was a statistically significant association between all three renal function markers. After adjustments for confounding factors, baseline urea was significantly associated with poor outcome (OR = 1.100; 95% CI 1.010–1.198 per mmol/L; p = 0.028) and mortality (OR = 1.117; 95% CI 1.027–1.213 per mmol/L; p = 0.009), eGFR was associated with mortality (OR = 0.984; 95% CI 0.970–0.998 per mL/min/1.73 m²; p = 0.026) but not poor outcome (OR = 0.994; 95% CI 0.983–1.004 per mL/min/1.73 m²; p = 0.230), and serum creatinine was not significant for poor outcome (OR = 1.037; 95% CI 0.967–1.113 per 10 μmol/L; p = 0.306) or mortality (OR = 1.032; 95% CI 0.979–1.086 per 10 μmol/L; p = 0.238). No association was observed between ICH and any renal function test.

Conclusions: Elevated serum urea was independently associated with poor clinical outcome and mortality in acute ischaemic stroke patients treated with IV tPA.

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1. Introduction

Intravenous tissue plasminogen activator (IV tPA) is the only intervention shown to be effective in selected acute ischaemic stroke patients [1], but remains grossly underused [2], partially because of uncertainty around patient selection.

Previous studies have confirmed the association between impaired renal function and mortality in stroke patients [3–10]. Patients with end-stage renal disease experience markedly advanced atherosclerotic disease of the cerebral vasculature and an extraordinary high risk of stroke when compared to the general population [11]. In addition, the degree of renal dysfunction present in stroke patients may be a marker of end-organ damage from undetected preexisting untreated diseases or indicate a higher comorbidity burden [5]. These might be the causes that renal dysfunction impedes recovery post stroke.

However, the effects of renal dysfunction on thrombolysis have been only described in small studies of creatinine or estimated glomerular filtration rate (eGFR) with conflicting results [12–14]. Urea is a third biochemical marker of renal function. Previous studies showed that elevated urea predicted poor outcome and increased mortality in patients with myocardial infarction [15–17], acute coronary syndrome [18,19], hypertension [20–22], ischaemic stroke [5,7], and intracerebral haemorrhage [23]. However, serum urea has not been previously investigated in acute ischaemic stroke treated with IV tPA. We hypothesised that impaired renal function, including high serum urea, on admission
was associated with poor clinical outcome and increased mortality in acute stroke patients treated with IV tPA.

2. Methods

2.1. Patient selection

All consecutive ischaemic stroke patients (n = 400) treated with IV tPA (0.9 mg/kg) at Royal Melbourne Hospital from January 2003 to December 2011 were included. Of these patients, 21 were excluded due to missing modified Rankin Scale (mRS) [24] and one was excluded due to missing renal function tests. Therefore, 378 patients formed the study population. The comparison between included patients and excluded patients was conducted. There was no difference of clinical characters between included patients and excluded patients. The Melbourne Health Human Research & Ethics Committee approved the study protocol.

2.2. Clinical assessment and data collection

This was a retrospective analysis of a prospectively collected patient series. The following parameters were recorded in a specific data bank:

1. Demographics (age, gender).
2. Medical histories.
3. Stroke presentation such as baseline National Institutes of Health Stroke Scale (NIHSS) [25] and stroke types according to TOAST classification system [26].
4. Admission laboratory data including serum urea, creatinine, eGFR, platelet, white cell count and international normalised ratio (INR).

Renal function

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 378)</th>
<th>Poor outcomes (n = 128)</th>
<th>p value</th>
<th>Mortality (n = 73)</th>
<th>p value</th>
<th>ICH (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urea (mmol/L), mean (IQR)</td>
<td>7.2 (5.5–9.3)</td>
<td>6.6 (5.0–8.3)</td>
<td>7.7 (5.8–10.0)</td>
<td>0.001</td>
<td>7.0 (5.4–8.9)</td>
<td>8.4 (6.1–11.6)</td>
</tr>
<tr>
<td>Creatinine (μmol/L), mean (IQR)</td>
<td>90 (78–110)</td>
<td>90 (75–100)</td>
<td>90 (79–110)</td>
<td>0.153</td>
<td>90 (76–105)</td>
<td>100 (80–122)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²), median (IQR)</td>
<td>64 (51–78)</td>
<td>69 (58–82)</td>
<td>60 (47–75)</td>
<td>0.002</td>
<td>67 (55–80)</td>
<td>53 (40–64)</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m², n (%)</td>
<td>157 (41.5)</td>
<td>37 (28.9)</td>
<td>120 (48.0)</td>
<td>&lt;0.001</td>
<td>108 (35.4)</td>
<td>49 (67.1)</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 378)</th>
<th>Poor outcomes (n = 128)</th>
<th>p value</th>
<th>Mortality (n = 73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (IQR)</td>
<td>72 (62–81)</td>
<td>66 (58–75)</td>
<td>75 (65–83)</td>
<td>&lt;0.001</td>
<td>71 (59–79)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>205 (54.2)</td>
<td>85 (66.4)</td>
<td>121 (48.0)</td>
<td>0.001</td>
<td>181 (59.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>239 (63.2)</td>
<td>78 (60.9)</td>
<td>161 (64.9)</td>
<td>0.488</td>
<td>189 (62.0)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>94 (24.9)</td>
<td>27 (21.1)</td>
<td>67 (27.0)</td>
<td>0.258</td>
<td>71 (23.3)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>96 (25.4)</td>
<td>24 (18.8)</td>
<td>72 (29.0)</td>
<td>0.034</td>
<td>74 (24.3)</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>195 (51.6)</td>
<td>72 (56.3)</td>
<td>123 (49.6)</td>
<td>0.233</td>
<td>162 (53.1)</td>
</tr>
<tr>
<td>Previous TIA, n (%)</td>
<td>25 (6.6)</td>
<td>10 (7.8)</td>
<td>15 (6.1)</td>
<td>0.520</td>
<td>21 (6.9)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>43 (11.4)</td>
<td>11 (8.6)</td>
<td>32 (12.9)</td>
<td>0.236</td>
<td>33 (10.8)</td>
</tr>
<tr>
<td>NIHSS baseline, median (IQR)</td>
<td>12 (8–18)</td>
<td>9 (6–14)</td>
<td>15 (10–20)</td>
<td>&lt;0.001</td>
<td>11 (7–17)</td>
</tr>
</tbody>
</table>

Baseline laboratory findings

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 378)</th>
<th>Poor outcomes (n = 128)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (×10³/L), median (IQR)</td>
<td>235 (193–287)</td>
<td>229 (194–276)</td>
<td>237 (192–298)</td>
</tr>
<tr>
<td>White blood cell (×10³/L), median (IQR)</td>
<td>7.9 (6.6–9.6)</td>
<td>7.9 (6.5–9.4)</td>
<td>7.9 (6.7–9.7)</td>
</tr>
<tr>
<td>TOAST classification</td>
<td>Large-artery atherosclerosis, n (%)</td>
<td>46 (12.2)</td>
<td>16 (12.5)</td>
</tr>
<tr>
<td>Cardioembolism, n (%)</td>
<td>162 (42.9)</td>
<td>49 (38.3)</td>
<td>113 (45.2)</td>
</tr>
<tr>
<td>Small-artery occlusion, n (%)</td>
<td>3 (0.8)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Other determined cause, n (%)</td>
<td>3 (0.8)</td>
<td>1 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Undetermined cause, n (%)</td>
<td>164 (43.4)</td>
<td>67 (48.4)</td>
<td>102 (40.8)</td>
</tr>
</tbody>
</table>

Poor outcome was defined as mRS of 2–6. ICH = intracerebral haemorrhage; IQR = interquartile range; GFR = glomerular filtration rate; TIA = transient ischaemic attack; NIHSS = National Institutes of Health Stroke Scale.
2.4. Statistical analysis

Statistical analyses were performed with STATA IC version 12 and SPSS version 19.0. Spearman’s rank correlation was used to estimate the association between serum urea, creatinine and eGFR. Group differences in baseline characteristics were assessed with the Mann–Whitney test for continuous variables and Fisher’s exact tests or $\chi^2$ tests for the categorical variables.

Multivariable logistic regression analysis was performed separately for three outcome measures (poor outcome, mortality and ICH) and three renal function markers (serum urea, creatinine and eGFR), adjusting for NIHSS baseline and other outcome-specific confounding factors. The associations between every renal function marker and every outcome adjusted for confounders were estimated using adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI).

3. Results

Patient characteristics, laboratory data, and outcomes are shown in Table 1. Of the 380 patients treated with IV tPA, median age was 72 (interquartile range (IQR) = 62–81) years and 205 (54.2%) were male. Median NIHSS baseline was 12 (IQR = 8–18). At 3 months, 230 (66.1%) patients had poor outcomes and 73 (19.3%) had died. Eighty-eight (23.3%) patients experienced an ICH within 7 days of tPA.

There was a statistically significant association between all three renal function markers (Fig. 1): creatinine versus eGFR (Spearman’s rho = 0.845, p < 0.001); urea versus eGFR (Spearman’s rho = 0.613, p < 0.001); and urea versus creatinine (Spearman’s rho = 0.562, p < 0.001).

3.1. Poor functional outcome

In univariate analysis, age, gender, NIHSS baseline, history of atrial fibrillation, serum urea, and eGFR on admission were associated with 3-month outcome (Table 1). Patients with poor outcome were more likely to have high serum urea and low eGFR than patients with good outcome. In multivariable regression analysis, urea was independently associated with poor outcome adjusted for confounding factors (Table 2 and Fig. 2). For each mmol/L increase in urea, there was 10% increase in odds of achieving poor outcome (OR = 1.100, 95% CI 1.010–1.198, p = 0.028). No statistically significant association between poor outcome and serum creatinine, or poor outcome and eGFR (Table 2) was detected.

3.2. Mortality

In univariate analysis, age, gender, NIHSS baseline, serum urea, creatinine, and eGFR on admission were associated with mortality (Table 1). The deceased patients were more likely to have high serum urea and low eGFR than patients with good outcome. In multivariable regression analysis, urea (Fig. 2) and eGFR were independently associated with mortality (Table 2). For each mmol/L increase in urea, there was 11.7% increase in odds of death (OR = 1.117, 95% CI 1.027–1.213, p = 0.009). Serum creatinine (Table 2) was not independently associated with mortality in a statistically significant way.

3.3. ICH

In univariate analysis, only NIHSS baseline was associated with ICH (Table 1), serum urea (Fig. 2), creatinine and eGFR were not. None of the renal function biomarkers were associated with ICH in multivariable regression analysis (Table 2).

4. Discussion

We found that elevated serum urea level was independently associated with poor clinical outcome and increased mortality in acute ischaemic stroke patients treated with IV-tPA. There was a significant 10% increase in odds of poor outcome and 11.7% increase in odds of...
death with each mmol/L increase in urea. This result is in line with the previous studies that raised serum urea levels had a higher mortality risk in acute stroke [5,21,22]. To our knowledge, this finding has not been reported previously in stroke patients with intravenous thrombolysis therapy. Our study demonstrates that high serum urea could be used to stratify the risk for the treatment of IV tPA.

In this study, univariate analysis showed that patients with poor outcome or death were more likely to have high serum urea and low eGFR than patients with good outcome. Prior studies have demonstrated the association between impaired renal function and mortality in stroke patients without IV tPA treatment [3–10] with follow-up up to 10 years [10]. Yahalom et al. [3] also found that chronic kidney disease, defined as eGFR < 60 mL/min/1.73 m², was a strong independent predictor of poor outcome in patients with acute stroke. Their assessment of functional outcome used the Barthel Index, different to mRS in our study.

However, the impact of renal dysfunction on thrombolysis for stroke has remained unclear (Table 3) [12–14]. Our findings confirmed that eGFR < 60 mL/min/1.73 m² had independent association with mortality. This result is consistent with a multicenter Japanese study, which included 578 patients treated with IV tPA [14]. A meta-analysis of renal function and thrombolysis also suggested an association between reduced eGFR and increased mortality [27]. Traditional stroke risk factors, in particular, hypertension and diabetes, could lead to a similar renal vascular injury and increase the risk of comorbidities. Impaired renal function and severe comorbidity might affect the clinical outcome, as well as induce death. Moreover, renal dysfunction might not only increase plasminogen activator inhibitor-1 activity [28] and levels of lipoprotein(a), von Willebrand factor, fibronectin, fibrin monomers and D-dimer, but also decrease platelet aggregatory responses, fibrinolytic activity, serotonin uptake and its release from platelets [29], and impair endothelial release of tPA [30]. These abnormalities might affect the vascular recanalization and reperfusion and worsen stroke outcome after IV tPA.

High serum urea is not a direct factor in the pathway of systemic dysfunction but rather a surrogate marker of impaired renal function and/or system illness [17,18,31]. So, it could be a strong predictor of poor outcome and mortality, which was confirmed in a few previous studies. An elevated urea was associated with increased mortality in myocardial infarction [15,17], acute coronary syndrome [18,19], heart failure [16,32], hypertension [20–22,33] and heterogeneous critically ill patients [31]. Smith et al. found a 12% relative increase in mortality risk for a 20-U increase in serum urea nitrogen level for myocardial infarction patients and a 33% relative increase for heart failure patients [16]. Bulpitt et al. found that even serum urea concentrations between 5 and 7 mmol/L were associated with an increase in deaths among hypertensive patients [33].

In previous studies, creatinine and eGFR were used as prognostic factors of stroke patients treated with intravenous thrombolysis [12,14]. Furthermore, GFR is considered to be the gold standard for measuring renal function. Nevertheless, in our study, raised serum urea was independently associated with poor clinical outcome and mortality, whereas eGFR was only independently associated with mortality, and serum creatinine was not associated with either. It seems that urea level could provide more information for outcome than creatinine-based measures of renal function. As elevation of urea can occur due to other reasons outside of fall in GFR, other causes may explain the higher prognostic significance of urea [17]. Elevated serum urea is also associated with a state of renal hypoperfusion from hypovolaemia, renovascular disease, sepsis or reduced cardiac output [15], and an increase in protein intake, tubular resorption of urea, or production rate of urea [34].

### Table 2

Multiple logistic regression models including urea, creatinine and eGFR for stroke outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Poor outcome (mRS = 2–6)</th>
<th>Mortality</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI  p value</td>
<td>OR  95% CI  p value</td>
<td>OR  95% CI  p value</td>
</tr>
<tr>
<td>Urea (per mmol/L) a</td>
<td>1.100 1.010–1.198 0.028</td>
<td>1.117 1.027–1.213 0.009</td>
<td>1.036 0.968–1.108 0.306</td>
</tr>
<tr>
<td>Creatinine (per 10 μmol/L) a</td>
<td>1.037 0.967–1.113 0.306</td>
<td>1.032 0.979–1.188 0.238</td>
<td>1.031 0.979–1.0847 0.247</td>
</tr>
<tr>
<td>eGFR (per mL/min/1.73 m²) b</td>
<td>0.954 0.983–1.004 0.230</td>
<td>0.984 0.970–0.998 0.026</td>
<td>1.002 0.992–1.013 0.704</td>
</tr>
<tr>
<td>eGFR (≥60 mL/min/1.73 m²)</td>
<td>1.403 0.813–2.361 0.203</td>
<td>2.570 1.329–4.969 0.005</td>
<td>22.87 0.495–1.382 0.468</td>
</tr>
</tbody>
</table>

ICH = intracerebral haemorrhage; OR = odds ratio; CI = confidence interval. NIHSS = National Institutes of Health Stroke Scale; GFR = glomerular filtration rate. a Due to collinearity, urea, creatinine, eGFR and eGFR <60 mL/min/1.73 m² were each inserted into the model one at a time. All the logistic regression models were adjusted for age, sex, NIHSS and atrial fibrillation (poor outcome); age, sex and NIHSS (mortality) and NIHSS (ICH) are based on univariate analyses.

Fig. 2. Box plot of urea level by good outcome (mRS = 0–1) and poor outcome (mRS = 2–6), survival and death, and no ICH and ICH.
In addition, the high intensity of catabolic processes that accelerate with age is another source of increased urea in elderly patients. It is well known that increased age is an independent risk factor for poor outcome and death in patients treated with IV-tPA [35,36]. As shown in a number of studies, it was the level of urea rather than of creatinine that increases with age in healthy individuals, whereas the level of protein (albumin, haemoglobin, ferritin) decreases [18,37]. Moreover, serum urea level is particularly relevant in the elderly population as the ability of creatinine to reflect changes in GFR weakens as muscle mass decreases [16].

Our results showed that the levels of serum urea, creatinine, and eGFR were not significantly different between patients with ICH and without ICH after treatment with IV-tPA. Patients treated with IV-tPA were previously found to have a higher incidence of ICH within 36 h (27.4% vs. 16.6%) if they had renal dysfunction (eGFR < 60 mL/min/1.73 m²) [14]. Lyer et al. reported that an impaired eGFR, defined as < 90 mL/min/1.73 m², tended to be associated with symptomatic ICH [12]. The meta-analysis of the 3 studies of renal dysfunction on the effect of rt-PA showed increased incidence of symptomatic intracranial haemorrhage in patients with chronic renal disease (OR = 3.38, 95% CI 1.60–7.15) [27]. Impaired kidney function (even preclinical) might increase the risk of hemorrhagic microangiopathy, which may eventually lead to cerebral haemorrhage [38]. However, our findings were not consistent with the above results, but rather supported a previous study that renal dysfunction in patients receiving thrombolytic therapy was not associated with increased ICH [13]. So the poor outcomes in correlation with increased urea may be not due to ICH after thrombolysis. Some limitations of the present study should be noted. First, this is an observational retrospective study. Therefore, it is unavoidable that both identified and unidentified confounders may have influenced the outcomes despite attempts to control these factors through multivariable analyses. Second, we only concentrated on renal function on the admission without consideration of later evolution of the three markers post the treatment with IV-tPA. Unlike at baseline, these laboratory parameters were not systematically evaluated after tPA administration at our hospital. Third, our numbers of patients were small and we evaluated several outcomes and several blood biomarkers, so the results could be simply due to play of chance. However, our results are in line with the existing literature in other conditions and can be logically explained, so may well be true.

Elevated serum urea on admission was independently associated with poor clinical outcomes and increased mortality in acute ischaemic stroke patients treated with IV-tPA. Further prospective studies are necessary to understand the mechanism of this association.

**Conflict of interest**

The authors declare that they have no competing interests.

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**References**


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**Table 3**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>eGFR and poor clinical outcome</th>
<th>eGFR and mortality</th>
<th>eGFR and ICH</th>
<th>Creatinine and poor clinical outcome</th>
<th>Additional finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyer et al. [12]</td>
<td>2008</td>
<td>196</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.127 (1.002–1.265)</td>
<td>1.285 (1.049–1.583)</td>
<td>eGFR was also associated with symptomatic ICH (OR = 2.64; 1.10–6.56)</td>
</tr>
<tr>
<td>Agrawal et al. [13]</td>
<td>2010</td>
<td>74</td>
<td>2.356 (0.540–10.271)</td>
<td>2.94 (1.38–6.42)</td>
<td>Not reported</td>
<td>1.307 (0.967–1.113)</td>
<td>Urea was associated with poor outcome (OR = 1.100; 95% CI 1.01–1.198 per mmol/L) and mortality (OR = 1.117; 95% CI 1.027–1.213 per mmol/L)</td>
</tr>
<tr>
<td>Naganuma et al. [14]</td>
<td>2011</td>
<td>578</td>
<td>1.55 (1.01–2.38)</td>
<td>1.55 (0.229–10.527)</td>
<td>1.985 (0.439–8.983)</td>
<td>Not reported</td>
<td>1.81 (1.16–2.84)</td>
</tr>
<tr>
<td>Zhang et al. (present)</td>
<td>2013</td>
<td>378</td>
<td>1.403 (0.833–2.361)</td>
<td>2.570 (1.329–4.969)</td>
<td>0.827 (0.495–1.382)</td>
<td>Not reported</td>
<td>1.123 (0.967–1.113)</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; ICH = intracranial haemorrhage; OR = odds ratios; CI = confidence intervals.

* a OR with 95% CI for eGFR < 60 mL/min/1.73 m² [13,14] (present), poor clinical outcome is mRS of 4–6 [14] or mRS of 2–6 [13] (present), and outcomes evaluated at discharge [13] or 3 months [14] (present).

* b OR and 95% CI per 10 mmol/L [12] (present), mRS of 3–6 [12] or mRS of 2–6 (present).

* c Univariate results were 2% (eGFR < 60 mL/min/1.73 m²) vs. 8% (eGFR < 60 mL/min/1.73 m²)
Clopidogrel Hyper-Response and Bleeding Risk in Neurointerventional Procedures
C. Goh, L. Churilov, P. Mitchell, R. Dowling, and B. Yan

ABSTRACT
BACKGROUND AND PURPOSE: Antiplatelet therapy is associated with decreased ischemic events after neurointerventional procedures. Antiplatelet resistance negates the protective effects of antiplatelet medication, leading to a higher incidence of ischemic events. A possible link between antiplatelet hyper-response and increased hemorrhagic complications has been inadequately investigated. We aimed to examine the correlation between antiplatelet hyper-response and the risk of hemorrhagic complications.

MATERIALS AND METHODS: Patients who were treated with antiplatelet medications and underwent neurointerventional procedures were prospectively recruited. We collected the following data: demographics, vascular risk factors, antiplatelet and anticoagulation treatment, antiplatelet responsiveness, coagulation profile, and hemorrhagic complications. P2Y12 receptor–mediated platelet inhibition was tested by using the VerifyNow assay device. The primary end points were postprocedural major and minor hemorrhagic complications. Receiver operator characteristic analysis was used to evaluate the percentage of platelet inhibition as a diagnostic tool for bleeding events. The association between hemorrhage and percentage of platelet inhibition was investigated by using logistic regression modeling.

RESULTS: Forty-seven patients were enrolled. The mean age was 56 ± 12 years, and 28% were men. Ten patients (21.3%) developed hemorrhagic complications. Clopidogrel response was higher in patients with a major bleeding complication compared with those with minor or no bleeding (median, 94% versus 24% platelet inhibition; P = .0084). Of the 7 patients (14.9%) defined as hyper-responders with ≥72% platelet inhibition, 42.8% had a major bleeding complication.

CONCLUSIONS: Hyper-response to clopidogrel is associated with increased risk of hemorrhagic complications. Larger studies are urgently needed to validate a clinically useful threshold to define clopidogrel hyper-response and to examine the clinical effects of antiplatelet dosage adjustment.

ABBREVIATIONS: ACT = activated clotting time; aPTT = activated partial thromboplastin time; CI = confidence interval; IQR = interquartile range; ROC = receiver operating characteristic
Patients undergoing endovascular neurointervention may differ from the percutaneous coronary intervention population in terms of demographics and cardiovascular risk factors, particularly those being treated for cerebral aneurysm. This difference has the potential to alter the balance of risk between ischemic complications of the procedure and hemorrhagic complications of antiplatelet treatment.

This study aimed to describe the incidence of hyper-response to clopidogrel in the population of patients undergoing neurointervention and to investigate the association between clopidogrel hyper-response and the risk of hemorrhagic complications.

**MATERIALS AND METHODS**

Patients were recruited from those undergoing endovascular neurointervention during the weekly elective session at the Royal Melbourne Hospital between May 2010 and May 2011 (Fig 1). Patients were excluded if they refused consent, were younger than 18 years of age, or had a history of an acute event (transient ischemic attack, ischemic infarct, or acute intracranial hemorrhage) within the 24 hours before the procedure. Demographic and clinical data collected included age, sex, and cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking history, and history of previous cerebrovascular ischemic events). The study protocol received ethics committee approval.

The standard antiplatelet regimen at our institution is dual therapy with clopidogrel, 75 mg, and aspirin, 100 mg, for the 3 days before an endovascular neurointerventional procedure.

All procedures were performed by 1 of 3 experienced neurointerventionalists. Arterial access was via a 6F femoral sheath, with hemostasis obtained postprocedure by use of an Anglo-Seal device (St. Jude Medical, Minnetonka, Minnesota). Systemic anticoagulation with intravenous heparin during the procedure was titrated to an ACT twice normal. The postprocedural unfractionated heparin during the procedure was

Some procedure

Whole blood was obtained for testing at the time of the initial femoral puncture; following discard of the first 5 mL, citrated Vacette tubes (VWR, Arlington Heights, Illinois) were filled and inverted 5 times with blood analyzed by using the VerifyNow assay device (Accumetrics, San Diego, California).

The VerifyNow assay is a point-of-care device using a 2-channel disposable cartridge, with platelet aggregation measured by increasing light absorbance through the sample. The first chamber contains a strong agonist for platelet activation independent of aspirin or clopidogrel therapy, providing a baseline platelet function measurement (BASE). The second chamber gives a measurement expressed as P2Y12 reaction units (PRU), representing platelet activation by the adenosine diphosphate-P2Y12 pathway. Percentage of inhibition is calculated from the formula \( \frac{1 - (PRU/BASE)}{100} \). The VerifyNow assay has been shown to correlate well with the current criterion standard light transmittance aggregometry and with other point-of-care assay devices, and it has been validated in a head-to-head comparison of assay methods based on outcome measures.

Outcomes were measured by clinical assessment during the hospital admission and at the 6-week review appointment. The primary end point was Thrombolysis in Myocardial Infarction major or minor periprocedural bleeding events. The need for investigation with Doppler sonography or CT or MR imaging of the brain was guided by clinical assessment.

Statistical analysis was performed by using the commercial statistical software STATA, Version 11IC (StataCorp, College Station, Texas). Platelet inhibition is reported as median IQR due to non-normal distribution as assessed by the Shapiro-Wilk test. The Wilcoxon–Mann-Whitney test was used to compare the percentage of platelet inhibition by clopidogrel between bleeding and nonbleeding groups with the corresponding effect size estimated by using median regression. The receiver operator characteristic analysis curve was used to evaluate the percentage of platelet inhibition measured by the VerifyNow assay device as a diagnostic tool for bleeding events. Association between the presence of periprocedural bleeding and the percentage of platelet inhibition was investigated by using logistic regression modeling (both unadjusted and adjusted for mean aPTT and intraprocedural ACT). The statistical significance threshold for all the tests performed was set as \( P = .05 \).

**RESULTS**

**Study Population**

Forty-seven patients were enrolled in the study, 34 women and 13 men, with a mean age of 56 ± 12 years (range, 30–78 years). There was a history of hypertension in 46.8%, dyslipidemia in 25.5%, and diabetes mellitus in 4.3% of patients, and 29.8% were current smokers. Previous TIA or ischemic stroke was documented in only 0.9%.

**Procedure**

All endovascular procedures were performed by 1 of 3 neurointerventionists. All except 1 in the study population received treatment for an intracranial aneurysm, by coil embolization alone (23.4%), with balloon remodelling (21.3%) or stent assistance (19.1%) or by use of a flow-diverting stent (34%). The other patient underwent stent placement for a vertebral artery stenosis. All except 9 patients received ongoing systemic anticoagulation with
intravenous heparin following the procedure: 21 patients for up to 24 hours and 17 patients for 48 hours. One patient who had a Factor V Leiden deficiency received 10 hours of intravenous unfractionated heparin postprocedure and then low-molecular-weight heparin until therapeutic anticoagulation with warfarin had been achieved.

Treatment of 3 patients deviated from the standard antiplatelet regimen. Two received a single loading dose of 450 mg of clopidogrel at 3 hours or at 5 hours before the procedure. The other had a history of Factor V Leiden deficiency and had been receiving subcutaneous low-molecular-weight heparin due to cessation of his usual long-term anticoagulation with warfarin. The decision was made to give him 3 days of clopidogrel loading at 75 mg daily, rather than dual antiplatelet therapy.

**Clopidogrel Response and Bleeding Events**

Response to the antiplatelet effects of clopidogrel varied widely, with the percentage of platelet inhibition ranging between 0% and 99% (median, 30%; IQR, 12%– 61%). Figures 2 and 3 illustrate the distribution of platelet inhibition and bleeding events among the study population.

Eleven patients had a bleeding event during the procedure or in the 24 hours postprocedure. Thrombolysis in Myocardial Infarction major bleeding events occurred in 3 patients (6.4%). Two of these had documented periprocedural intracranial hemorrhages. A 5-mm left temporal intracerebral bleed occurred in a patient with 99% platelet inhibition and PRU 5, whose right posterior communicating artery aneurysm was treated by placement of a flow-diverting stent. MR imaging of the brain showed no evidence of an underlying cavernoma, mass, or infarct. A tiny subarachnoid bleed within a sulcus at the right vertex occurred in a patient with 94% platelet inhibition and PRU 21, who had a right supraclinoid carotid aneurysm treated by placement of a flow-diverting stent. The other patient had a large retroperitoneal hemorrhage in a patient with 99% platelet inhibition and PRU 21, who had a right supraclinoid carotid aneurysm treated by placement of a flow-diverting stent. The patient had a large retroperitoneal hemorrhage, with levels of platelet inhibition measured at 72% and PRU 83 at the time of the procedure. Because this patient received premedication as a single 450-mg dose of clopidogrel 5 hours before the procedure, this may actually be an underestimation of the achieved platelet inhibition. A large subarachnoid hemorrhage in 1 patient was related to on-table aneurysm perforation, so it was not included in the bleeding group for statistical analysis. Minor bleeding events in 7 (15%) patients were small groin hematomas of little clinical significance.

Clopidogrel response was greater in the 10 patients with a bleed of any size (median platelet inhibition, 63.5%; IQR, 36%–75%) compared with those with no bleeding complication (median platelet inhibition, 19%; IQR, 11%–47%), resulting in a median difference between the degree of platelet inhibition in bleeding and nonbleeding groups of 38% (95% CI, 10.6%–65.4%; P = .015).

Comparison between clopidogrel response in the 3 patients with a major bleed and those with minor or no bleeding demonstrated a more pronounced difference, with median platelet inhibition of 94% (IQR, 72%–99%) versus 24% (IQR, 11.5%–55.5%), resulting in a median difference between percentage platelet inhibition in these 2 groups of 69% (95% CI, 23%–100%; P = .008).

ROC analysis was undertaken to identify an optimal threshold to define hyper-response to clopidogrel. Using 72% or greater platelet inhibition as the criterion, 7 patients (14.9%) were defined as clopidogrel hyper-responders; 42.8% of these patients had a major bleeding complication, while all non-hyper-responders were major bleeding complication-free. If we used a threshold of ≥72% inhibition to define hyper-response, the percentage of platelet inhibition by clopidogrel as a diagnostic tool for clinically significant bleeding events demonstrated high diagnostic capacity (ROC area = 0.96; 95% CI, 0.89–1), resulting in sensitivity of 100% and specificity of 90.9%. Due to the small sample size and low number of events, caution is required in the extrapolation of these results into clinical practice; larger studies would be required to define and validate a robust threshold for clinical use.

Including minor with major bleeding in the ROC analysis results in a lower diagnostic capacity (ROC area = 0.75; 95% CI, 0.58–0.93), with a threshold of ≥53% inhibition corresponding to a sensitivity of 70% and a specificity of 75.7%, and is of limited clinical utility. The incidents of minor bleeding in our study were all small groin hematomas, a complication that may be influenced by puncture technique and by achieving inadequate hemostasis at the end of the procedure. Also, because the cutoff below which patients are deemed to be low responders has variably been nominated as anywhere between 23% and 40% platelet inhibition, use of this lower threshold would necessarily result in a narrow therapeutic window.

**Systemic Anticoagulation with Intravenous Heparin and Bleeding Events**

When divided by bleeding outcome, mean ACT was similar among all groups with 392.2 (95% CI, 354.32–430.15) in those with no bleeding complication, 373.3 (95% CI, 315.67–431) in those with any bleed, and 375 (95% CI, 207.9–542.1) in those with clinically significant bleed.
In the patients whose intravenous heparin was continued in the ward, the mean aPTT was also similar between each of the bleeding outcomes: the postprocedure aPTT was 63.3 (95% CI, 51.09–75.57) in those with no bleeding complications, 60.4 (95% CI, 49.38–71.38) in those with any bleed, and 60.6 (95% CI, 54.66–66.47) in those with a clinically significant bleed.

DISCUSSION

To our knowledge, no previous studies have investigated clopidogrel hyper-response and bleeding risk in the neurointervention population, though a few studies have examined variation in clopidogrel response in this population without describing how the rate of bleeding complications correlated with platelet function test results.18–21

Two previously published studies in the cardiac population that specifically address bleeding complications in the context of antiplatelet medication showed a strong correlation between clopidogrel hyper-response and bleeding risk. Sibbing et al11 found that 38% of patients undergoing percutaneous coronary intervention were hyper-responders, who had a higher incidence of major bleeding (2.2%) compared with the remainder of the population (0.8%). Cuisset et al12 assessed bleeding risk in the first month after discharge of patients with acute coronary syndrome on dual antiplatelet therapy, finding that the risk of major or minor bleeding was 6.6% for those in the first quartile of clopidogrel response compared with 1.4% in the remainder.

This study showed that a strong correlation between the degree of platelet inhibition by clopidogrel and the incidence of periprocedural bleeding complications also exists in patients undergoing elective neurointerventional procedures.

Systemic anticoagulation with heparin remains a potential confounding factor linking clopidogrel hyper-response with an increased risk of perioperative bleeding in this population. The mean intraoperative ACT for the study population was at the upper end of the acceptable range, which could increase the risk of bleeding events regardless of the individual antiplatelet response to clopidogrel. However, because all patients received a similar dose of intraprocedural heparin and there were no differences in ACT measurements between bleeding and nonbleeding groups, the relatively high intraprocedural anticoagulation achieved does not unduly alter the validity of our hypothesis.

Of potential concern is the influence of postprocedural heparin on our results, given that the 2 intracranial hemorrhages occurred in patients who received intravenous heparin following the procedure. However, when the patients who received heparin infusions were divided into groups based on bleeding outcome, there were no differences in the mean aPTT achieved by each group, in contrast to the large difference in clopidogrel effect between the groups.

While the relatively high intraoperative ACT and the use of heparin anticoagulation in the postprocedural period may well potentiate the effects of antiplatelet medication on bleeding risk, they do not account for the preponderance of bleeding events among the patients with a high level of response to the antiplatelet effects of clopidogrel.

The possibility that the type of intervention performed may impact bleeding risk is another consideration. The 2 small intracranial hemorrhages in this study group occurred in patients who had undergone placement of a flow-diverting stent. However, it is difficult to implicate traction on arteries or altered flow dynamics related to stent placement in the etiology of these events, given that the bleeding site was distant from the treated vessel in both cases. The early experience of this method of aneurysm treatment emphasizes the potential thrombotic complications of parent vessel occlusion, small artery occlusion, and in-stent thrombosis. A multicenter study of 70 patients treated with the Silk flow-diverting stent (Balt Extrusion, Montmorency, France) reported 3 extracranial hemorrhages but no intracranial hemorrhage.22 A multicenter study of 31 patients treated with the Pipeline flow-diverting device (Covidien, Irvine, California) reported no hemorrhagic complications.23

A more likely mechanism by which flow-diverting stents could affect perioperative bleeding risk is in their requirement for postprocedural anticoagulation with intravenous heparin, which accounts for the high number of such patients in our study. In addition, these patients continue to receive at least 6 months of antiplatelet medication, usually with clopidogrel. While the administration of heparin did not significantly affect the results of this study, the need for ongoing clopidogrel administration highlights the potential for clopidogrel hyper-response to increase the cumulative risk of adverse bleeding events.

Differences between patients undergoing neurointerventional procedures and the cardiac patients who have been studied in greater numbers may influence the clinical impact of interindividually
vidual variability in the clopidogrel response. In concentrating on elective patients and excluding those with a recent ischemic or hemorrhagic event, our study population is strongly weighted toward patients undergoing treatment for a cerebral aneurysm. These patients tend to be younger with fewer cardiovascular risk factors than those undergoing cerebrovascular or coronary revascularization, so the background risk of thromboembolic events may be reduced. Whether this is offset, or perhaps overshadowed, in the periprocedural period by the need for catheterization of intracranial arteries is uncertain, but regardless, it may have implications for clopidogrel hyper-responders during the 6–12 months postprocedure when patients with intracranial stents will receive maintenance dual antiplatelet therapy. It is possible that a given antiplatelet dose in a neurointervention patient will be associated with an increased bleeding risk compared with patients undergoing cardiac percutaneous coronary intervention or cerebrovascular stent placement.

Authors of future research into the identification and management of clopidogrel hyper-response should bear in mind the lessons from previous research into hypo-response. Despite the large body of evidence available linking low clopidogrel response to an increased risk of adverse cardiovascular outcomes, differences in assay devices and the choice of statistical methods to define “hyporesponse” mean that researchers have struggled to achieve consensus on the optimal cutoff defining low response.

A different approach to understanding the impact of variability in the clopidogrel response relies on identifying genetic polymorphisms in the CYP2C19 allele that are associated with high or low response. The CYP2C19*2 variant is the most common of several loss-of-function alleles. Conversely, the CYP2C19*17 variant allele causes increased metabolism and function of clopidogrel and has been shown to reduce the incidence of major adverse cardiovascular events in patients with acute coronary syndrome.

A target of future research would be a prospective study comparing genetic testing with measures of platelet aggregation to determine which is best able to predict the risk of an adverse bleeding outcome. The high specificity of genetic testing may prove to be a drawback, given the multifactorial etiology of clopidogrel response variability, and the time required to perform genetic testing may reduce its clinical utility in comparison with point-of-care assay devices. In addition, genetic testing will need to include the full panel of CYP2C19 alleles because there is evidence that the combination of high- and low-function variants will result in a low-to-normal function phenotype.

CONCLUSIONS

Hyper-response to the antiplatelet effects of clopidogrel is associated with a significant increase in bleeding risk in the setting of endovascular neurointervention. Any proposed threshold value for a clinically significant increased risk of major bleeding will require validation with a larger study population. Testing for genetic polymorphisms associated with increased platelet inhibition by clopidogrel is a promising avenue of further research. However, point-of-care assay devices retain the advantage of speed and simplicity of use and will include the effects of nongenetic determinants of platelet function. Standardization of study methodological in future research protocols is of critical importance to provide statistically robust and clinically useful thresholds defining high and low response to clopidogrel.

Disclosures: Peter Mitchell—UNRELATED: Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: ev3, Comments: Neuro Exchange scientific meeting attendance, Other: Boston Scientific, Comments: unrestricted clinical research nurse support.

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Rapid Neurological Recovery after Intravenous Tissue Plasminogen Activator in Stroke: Prognostic Factors and Outcome

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Key Words
Stroke · Tissue plasminogen activator · Recovery

Abstract
Background: Treatment with tissue plasminogen activator (tPA) is associated with improved outcome in acute ischemic stroke. Of note, a proportion of patients demonstrate rapid and significant neurological recovery within 24 h. This has previously not been systematically studied. We aimed to examine its incidence, predictive factors and correlation with clinical outcomes. Methods: We included 161 patients with acute ischemic stroke who received intravenous tPA within 4.5 h. Patient demographics and clinical data were collected. Rapid neurological recovery was defined as an improvement of at least 50% within 24 h as measured by the National Institute of Health Stroke Scale (NIHSS) score, and long-term outcomes were assessed by 3-month modified Rankin Scale. The incidence of rapid neurological recovery and its correlation with outcomes were studied. The predictors of the phenomenon were examined by univariate analysis. Results: Rapid neurological recovery was present in 44 of the 161 patients (27.3%). This correlated with favorable outcomes at 3 months (p < 0.0005). Lower baseline NIHSS score (p = 0.006), mild (NIHSS score < 12) versus severe stroke (NIHSS score ≥ 12; p = 0.002), normal serum glucose levels on admission (3.3–7.7 mmol/l; p = 0.009) and younger age (p = 0.043) predicted rapid neurological recovery. However, there was no association with time to treatment (p = 0.3). Conclusion: Rapid neurological recovery defines a rapid responder population and was demonstrated in a quarter of patients treated with intravenous tPA. It strongly predicts a good clinical outcome.

Introduction

Ischemic stroke is a major cause of morbidity and mortality [1–3]. Treatment with intravenous tissue plasminogen activator (IV tPA) has been shown to reduce mortality and improve long-term clinical outcomes [4–7]. However, trials have demonstrated variability in neurological improvement as well as the timing of the recovery, without clear prognostic predictors identified [8, 9].

The rapid neurological recovery in ischemic stroke refers to the dramatic improvement in neurological function, defined as ≥50% improvement in the National Institute of Health Stroke Scale (NIHSS) score [10] within 24 h of treatment with thrombolysis [11]. This phenomenon was first described in patients treated with intraarterial (IA) thrombolysis [11], but has not previously been studied in the acute stroke population treated with IV tPA.

We aimed to study the incidence of rapid neurological recovery among ischemic stroke patients treated with IV tPA and to correlate this with long-term functional outcomes. We hypothesized that baseline clinical severity and time to treatment are predictive of this phenomenon.
Methods

Patients
We screened 166 consecutive ischemic stroke patients treated with IV tPA at the Royal Melbourne Hospital (RMH) between January 2003 and January 2009. There was no departure from the RMH stroke protocol, which stipulated thrombolysis (IV tPA at 0.9 mg/kg) for all acute ischemic stroke patients with NIHSS scores greater or equal to 4 and presenting within 4.5 h of symptom onset, without contraindications. Exclusion criteria were stroke mimics, and subsequent endoluminal therapies such as IA thrombolysis or clot retrieval. Stroke mimics were defined as the absence of acute ischemic stroke on posttreatment CT imaging (at 24–48 h) and the presence of an alternative diagnosis on discharge. Of the 166 patients, 5 were excluded due to missing records; therefore, 161 patients formed the study population.

Data Collection
Patient data were collected retrospectively for patients admitted prior to ethics approval and prospectively thereafter. Midway through the prospective arm of data collection, a change in RMH stroke protocol extended the treatment time window for IV thrombolysis from 3 to 4.5 h after the results of the ECASS (European Cooperative Acute Stroke Study) III trial had been published [12]. Therefore, some patients included after this change (November 2008) had a longer time to treatment.

The following parameters were recorded in a specific data bank: (1) demographics (age, sex); (2) medical history and risk factors such as hypertension (previous clinical diagnosis or regular treatment with antihypertensive medication), diabetes mellitus (previous diagnosis or current treatment with insulin or oral hypoglycemic medication), smoking history (current or ex-smoker), ischemic heart disease, hypercholesterolemia (previous diagnosis or current treatment with lipid-lowering medication), atrial fibrillation (previous diagnosis or evident on admission), previous stroke, previous transient ischemic attack, premorbid modified Rankin Scale (mRS) score [13]; (3) admission variables such as serum glucose (random blood glucose on admission), admitting blood pressure, coagulation profile (platelets, international normalized ratio, activated partial thromboplastin time); (4) stroke characteristics such as hemisphere, time to treatment (symptom onset to administration of tPA bolus); (5) stroke severity variables such as baseline NIHSS score [10] and Oxfordshire stroke syndrome classification (OSSC) [14]; (6) hemorrhagic transformation [15]; (7) outcome variables such as absolute clinical recovery in NIHSS score at 24 h, rapid neurological recovery (defined as ≥50% decrease in NIHSS score at 24 h), 30-day mortality, 3-month mRS score [13]. NIHSS and mRS assessments were performed by neurologists or neurology trainees who had previously completed the NIHSS and mRS accreditation.

Statistics
Independent sample t testing and χ² testing was used to test the null hypothesis that rapid neurological recovery was not predictive of a good outcome at 3 months. Mean mRS scores were compared using t testing, and the mRS outcome score was dichotomized into favorable (mRS score 0–1) and unfavorable (mRS score 2–6) for χ² testing (using continuity correction). Univariate logistic regression analysis was used to analyze all potential predictors while adjusting for age. Statistical analysis was performed using the SPSS 16.0 (SPSS Inc.) statistics package, with assistance of a medical statistician.

Results
Of the 161 patients with acute ischemic stroke, 78 (48.4%) were female and 83 (51.6%) were male, with a mean age of 70.9 years (range: 24–96 years). The mean baseline NIHSS score was 14.2, and the mean time to treatment was 156 min. Postthrombolysis 24-hour follow-up and 3-month functional outcome data were obtained for 132 patients (81.9%). The mean population characteristics including demographics, risk factors and admitting clinical findings are compared with those found in the phase IV SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) [16] in table 1.

Fifty patients (31.1%) had a favorable functional outcome at 3 months (mRS scores 0–1), while 82 (50.9%) ranged between minor disability and dependent (mRS scores 2–5). The remaining 29 patients (18%) were deceased at 3 months, either directly as a result of infarct or due to subsequent complications. Twenty-eight patients (17.4%) experienced hemorrhagic transformation, 13 (8.1%) symptomatic, of which 6 (3.7%) subsequently died. Rapid neurological recovery was observed in 44 patients (27.3%) of the total population.

Significant differences in outcomes were observed between patients with rapid neurological recovery and patients without rapid neurological recovery when analyzed by χ² testing. Patients with rapid neurological recovery had reduced 30-day mortality (p = 0.001), and improved 3-month functional outcomes (p < 0.0005). Figure 1 illustrates this disparity in outcomes. It depicts the relatively even spread in the non-rapid neurological recovery group, whereas the rapid neurological recovery group appears heavily skewed, with the majority achieving a favorable outcome and also no deaths or severe disability. Furthermore, independent sample t tests also showed a statistically significant difference of 2.305 (p < 0.0005) between the mean mRS scores of the 2 groups at 3 months.

Univariate logistic regression analysis was used to identify prognostic predictors of rapid neurological recovery (table 2). These included younger age (p = 0.043) and age <72 years (p = 0.01), as well as low baseline NIHSS score (p = 0.006) and NIHSS score <12 (p = 0.002). Lower serum glucose on admission (p = 0.015) and nor-
mal admitting glucose (3.3–7.7 mmol/l; 59–139 mg/dl; p = 0.009) were also significant predictors of rapid neurological recovery. The OSSC as a whole was a significant predictor (p = 0.08): patients with a total anterior circulation infarct (TACI) were less likely to experience rapid neurological recovery when compared to patients with a partial anterior circulation infarct (p = 0.001), lacunar infarct (p = 0.059) and posterior circulation infarct (p = 0.068). Time to treatment was found to be unrelated to incidence of rapid neurological recovery (p = 0.300) (fig. 2). The odds ratios of all meaningful predictors are shown relative to unity in figure 2.

Discussion

The incidence of rapid neurological recovery in a population of ischemic stroke patients treated with IV tPA has not previously been reported. Recently, the study by Christoforidis et al. [11] reported a 24.5% rate of rapid neurological recovery (which the authors referred to as the 'Lazarus phenomenon') among patients treated with IA thrombolysis. Our own study assessed 161 patients and found the incidence of rapid neurological recovery to be 27.3% (44 patients) in patients treated intravenously with tPA. Interestingly, this result is comparable to that found in the Christoforidis study [11] despite the different route of administration.

The results from our study confirm that rapid neurological recovery is a powerful predictor of favorable outcome at 3 months, with 85% of patients in this group achieving an mRS score of 0 or 1 and none suffering severe disability or death (fig. 1). In contrast, just over 10% of patients without rapid neurological recovery achieved a favorable outcome, with a similar proportion suffering severe disability or death (fig. 1).

The present study identified multiple predictors of rapid neurological recovery. First, a low baseline NIHSS score was shown to be highly predictive. Patients presenting with a baseline NIHSS score of less than 12 were significantly more likely to experience rapid neurological recovery than those with baseline NIHSS scores of 12 or

| Table 1. Baseline characteristics of patients in our study and in the phase IV tPA trial SITS-MOST |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| | Our study (n = 161) | Patients with rapid neurological recovery (n = 44) | Patients without rapid neurological recovery (n = 117) | SITS-MOST (n = 6,483) |
| Age, years | 71 ± 14 | 67 ± 15 | 72 ± 14 | 68 ± 7 |
| Gender (female) | 78 (48.4%) | 60 (51.3%) | 18 (40.9%) | 2,581 (39.8%) |
| Premorbid independence (mRS score <2), n | 136 (84.5%) | 39 (88.6%) | 97 (82.9%) | 5,899/6,337 (93%) |
| Hypertension, n | 127 (78.9%) | 34 (77.3%) | 93 (79.5%) | 3,710/6,318 (58.7%) |
| Smoking (current or previous), n | 50 (31.1%) | 16 (36.4%) | 34 (29.1%) | 2,643/6,114 (43.2%) |
| Diabetes mellitus, n | 35 (21.7%) | 7 (15.9%) | 28 (23.9%) | 1,020/6,374 (16%) |
| Hypercholesterolemia, n | 79 (49.1%) | 19 (43.2%) | 60 (51.3%) | 1,967/5,661 (34.8%) |
| Ischemic heart disease, n | 61 (38.9%) | 13 (29.5%) | 48 (41.0%) | NA |
| Atrial fibrillation, n | 61 (37.9%) | 17 (38.6%) | 44 (37.6%) | 1,507/6,306 (23.9%) |
| Time to treatment, min | 156 ± 32 | 152 ± 35 | 158 ± 32 | 140 ± 25 |
| Admitting glucose, mmol/l | 7.7 ± 3.4 | 6.6 ± 1.5 | 8.1 ± 3.1 | 6.4 ± 1.3 |
| Systolic pressure, mm Hg | 150 ± 31 | 148 ± 28 | 151 ± 33 | 150 ± 16 |
| Diastolic pressure, mm Hg | 84 ± 14 | 84 ± 12 | 84 ± 15 | 81 ± 9 |
| Degree of neurological severity, NIHSS score | 14 ± 6 | 12 ± 5 | 15 ± 6 | 12 ± 5 |
| Low NIHSS score (<12), n | 62 (38.5%) | 26 (59.1%) | 36 (30.8%) | NA |
| High NIHSS score (≥12), n | 99 (61.5%) | 18 (40.9%) | 81 (69.2%) | NA |
| OSSC | | | | |
| PACI | 83 (51.6%) | 31 (70.5%) | 52 (44.4%) | NA |
| TACI | 68 (42.2%) | 8 (18.2%) | 60 (51.3%) | NA |
| LACI | 4 (2.5%) | 2 (4.5%) | 2 (1.7%) | NA |
| POCI | 6 (3.7%) | 3 (6.8%) | 3 (2.6%) | NA |

Values denote either means ± SD or numbers with percentages in parentheses. PACI = Partial anterior circulation infarct; TACI = total anterior circulation infarct; LACI = lacunar infarct; POCI = posterior circulation infarct.
more (table 2). These findings support the view that the NIHSS score is also a surrogate marker of clot burden [17]. Fischer et al. [17] showed that the NIHSS score was highly predictive of clot burden and location shown on angiography. It follows that a great clot burden would be less susceptible to thrombolysis in patients presenting with a high NIHSS score. This is consistent with our results as a significantly greater proportion of these patients experienced poor acute recovery. Second, the OSSC was also found to be an important prognostic predictor. Patients presenting with a TACI had a lower incidence of rapid neurological recovery than patients presenting with a partial anterior circulation infarct, a lacunar infarct or a posterior circulation infarct (table 2). These findings also suggest a relationship between the OSSC and clot burden as patients with a TACI are likely to have a greater clot burden than other patients, and correspondingly experience worse acute recovery. Although this relationship seems theoretically plausible, it has yet to be appropriately investigated.

Table 2. Univariate logistic regression analysis of potential predictors of rapid neurological recovery (age adjusted)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>p</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – increasing[1]</td>
<td>0.043</td>
<td>0.976</td>
</tr>
<tr>
<td>Age &lt;72 years[1]</td>
<td>0.01</td>
<td>2.533</td>
</tr>
<tr>
<td>Gender – female</td>
<td>0.417</td>
<td>0.742</td>
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<tr>
<td>Pre-mRS</td>
<td>0.879</td>
<td>1.029</td>
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<tr>
<td>Hypertension</td>
<td>0.555</td>
<td>0.750</td>
</tr>
<tr>
<td>Smoking history</td>
<td>0.700</td>
<td>0.861</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.323</td>
<td>1.591</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>0.420</td>
<td>1.338</td>
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<tr>
<td>Ischemic heart disease</td>
<td>0.440</td>
<td>1.362</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.380</td>
<td>0.705</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>0.295</td>
<td>1.997</td>
</tr>
<tr>
<td>Previous transient ischemic attack</td>
<td>0.330</td>
<td>2.159</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.653</td>
<td>1.001</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>0.946</td>
<td>1.157</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>0.884</td>
<td>1.011</td>
</tr>
<tr>
<td>Baseline serum glucose – increasing</td>
<td>0.015</td>
<td>0.781</td>
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<tr>
<td>Normal baseline serum glucose</td>
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<tr>
<td>(3.3–7.7 mmol/l)</td>
<td>0.009</td>
<td>2.810</td>
</tr>
<tr>
<td>NIHSS score – increasing</td>
<td>0.006</td>
<td>0.912</td>
</tr>
<tr>
<td>NIHSS score &lt;12</td>
<td>0.002</td>
<td>3.133</td>
</tr>
<tr>
<td>OSSC[2]</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>PACI vs. TACI</td>
<td>0.001</td>
<td>4.189</td>
</tr>
<tr>
<td>LACI vs. TACI</td>
<td>0.059</td>
<td>7.613</td>
</tr>
<tr>
<td>POCI vs. TACI</td>
<td>0.068</td>
<td>5.476</td>
</tr>
<tr>
<td>PACI vs. LACI</td>
<td>0.563</td>
<td>1.817</td>
</tr>
<tr>
<td>PACI vs. POCI</td>
<td>0.760</td>
<td>1.307</td>
</tr>
<tr>
<td>LACI vs. POCI</td>
<td>0.803</td>
<td>0.719</td>
</tr>
<tr>
<td>Time to treatment</td>
<td>0.300</td>
<td>0.994</td>
</tr>
</tbody>
</table>

OR = Odds ratio; PACI = partial anterior circulation infarct; TACI = total anterior circulation infarct; LACI = lacunar infarct; POCI = posterior circulation infarct.


[2] Odds of rapid neurological recovery in patients with the first syndrome, as compared to the second.

Our study found no relationship between time to treatment and incidence of rapid neurological recovery (fig. 2). This was unexpected as previous studies have shown that time to treatment is a significant predictor of long-term outcomes [18, 19]. As rapid neurological recovery is predictive of long-term outcomes, we anticipated an association between time to treatment and rapid neurological recovery. Furthermore, the Christoforidis study [11] found that time to treatment was predictive of rapid neurological recovery in their IA thrombolysis trial. Their apparent discrepancy with our own study prompted us to subsequently test for an association between time to treatment and 3-month functional mRS...
outcomes. We found no relation between the two variables in our study population \[p = 0.868; \text{Exp}(B) = 1.001\]. We acknowledge that past metaanalyses have shown that time to treatment is associated with good recovery, whereas our own study was not consistent with this relationship [18]. We can partly attribute this finding to the disparity in patient numbers among discrete time blocks. We modified our time to treatment variable from a continuous to an ordinal variable in 90-min blocks (as in the metaanalysis by Hacke et al. [18]). Although there was still no association between time to treatment and rapid neurological recovery \(p = 0.625\), it did show that of the 161 patients, 123 underwent thrombolysis within 91–180 min, while only 6 did so between 0 and 90 min and 23 between 181 and 270 min, and 3 patients had no time to treatment data. This overrepresentation of one group may explain why time to treatment was not associated with good recovery. Nonetheless, we acknowledge this is a curious finding.

Serum glucose level on admission was also a strong predictor of rapid neurological recovery. Patients in this study presenting with hyperglycemia were less likely to experience a dramatic recovery after thrombolysis (fig. 2).

This is consistent with previous studies, which show that patients presenting with hyperglycemia and diabetics in general have worse clinical outcomes following thrombolysis [20–22]. It is thought that these patients have elevated levels of plasminogen activator inhibitor, which has been shown to be predictive of poor outcome and poor response to thrombolysis [23–26].

The probability of experiencing rapid neurological recovery decreased with advancing age (fig. 2). When the patient group was dichotomized, patients less than 72 years old were more than 2.5 times as likely to experience acute recovery. This is in concordance with other research showing that younger age corresponds to better long-term outcomes after thrombolysis [27].

Our study has several limitations. First, as an observational study, there was no control group to investigate the incidence of rapid neurological recovery among patients not treated with thrombolysis. However, comparison would require patients eligible for thrombolysis to be randomized to treatment and placebo. We do not believe that such a study would be ethically tenable. Second, the clinical assessments were undertaken by single observers. Although this removes interobserver varia-
In conclusion, our study is the first to examine rapid neurological recovery in acute stroke patients treated with IV tPA. We have identified a number of significant prognostic predictors of rapid neurological recovery, and have shown that it correlates with better long-term clinical outcomes. We believe that our results will provide direction for future research, which may further delineate the clinical progression of this subset of acute stroke patients.

References

Clinical Study

Risk of growth in unruptured intracranial aneurysms: A retrospective analysis

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ABSTRACT

This study sought to define the growth of unruptured intracranial aneurysms, in particular the frequency of growth and the characteristic factors predictive of growth. Two hundred and eight patients with 285 unruptured aneurysms were followed. Electronic records and angiographic films were obtained for measurements of aneurysm size. The mean follow-up duration was 21.8 months (range 1.1–137.3 months). Growth was identified in 95 of the 285 aneurysms (33.3%). The cumulative incidence of growth predicted using the Kaplan-Meier method was 22.7% at 1 year, 35.2% at 2 years, and 47.7% at 3 years. Aneurysm growth was significantly associated with a patient history of excessive alcohol consumption ($p = 0.04$).

A high incidence of growth can be seen in conservatively managed aneurysms with time. Consequently, continual follow-up is recommended to monitor for aneurysmal growth.

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1. Introduction

Despite considerable advances in diagnosis, treatment and management, the overall outcomes associated with subarachnoid haemorrhage (SAH) remain poor, with mortality rates of 40–50%, and significant neurological impairment and disability in one-third of patients who survive.1-5 As 85% of SAH is caused by aneurysmal rupture, treatment of unruptured intracranial aneurysms may be a definitive method to reduce the high mortality and morbidity rates.3

Identification of aneurysms that would benefit from treatment requires consideration and recognition of risk factors for aneurysmal rupture. Many studies have considered risk factors such as aneurysm size, location and cigarette smoking,6-12 but few have examined the growth of an intracranial aneurysm.

The growth of an aneurysm has been associated with rupture.10,13,14 however, evidence is limited due to the few clinical studies available. A further in-depth understanding of growth and its characteristics is necessary in investigating risk factors for aneurysm rupture.

This study sought to retrospectively analyze the growth of unruptured intracranial aneurysms in a multicultural Australian population.

2. Materials and methods

2.1. Identification of patients

The records of patients with verified intracranial aneurysms managed at the Royal Melbourne Hospital over the 10 years between January 1997 and December 2006 were reviewed.

Unruptured intracranial aneurysms that had not been treated with any neurosurgical or endovascular intervention were included. Aneurysms with a history suspicious of haemorrhage were excluded if no documentation existed to prove otherwise. All intracranial aneurysms, including extradural, were included. Mycotic, neoplastic or traumatic aneurysms were excluded, as well as aneurysms lacking follow-up angiography.

2.2. Data collection and follow-up

Data were collected for all patients regarding: location of aneurysm in relation to the parent artery, aneurysm size at diagnosis, patient age at diagnosis, patient gender, history of previous or current cigarette smoking, documented hypertension or use of antihypertensive medication, previous history of aneurysmal SAH, family history of verified intracranial aneurysms in first degree relatives, and excessive alcohol consumption.
Aneurysm size was followed up using electronic reports and angiographic films, until subsequent aneurysm rupture, treatment, patient death or until last contact.

2.3. Study population

The study included 208 patients (54 male and 154 female) with 285 unruptured intracranial aneurysms. A total of 150 patients had one unruptured aneurysm, 48 had two aneurysms, five had three aneurysms, two had four aneurysms, two had five aneurysms, and one had six aneurysms. The age of the patients at the beginning of follow-up ranged from 14.0 years to 80.5 years (mean 51.1 years).

2.4. Location and initial size of aneurysms

The unruptured aneurysms were located in the following sites: the cavernous segment internal carotid artery for 24 aneurysms, the distal internal carotid artery and posterior communicating artery for 104 aneurysms, the anterior cerebral artery for 11 aneurysms, the middle cerebral artery for 64 aneurysms, the posterior cerebral artery for 8 aneurysms, the basilar artery and superior cerebellar artery for 24 aneurysms, and the vertebral artery and posterior inferior cerebellar artery for 16 aneurysms.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
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</tr>
<tr>
<td>No. of patients</td>
<td>208</td>
</tr>
<tr>
<td>Total no. of aneurysms</td>
<td>285</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.1</td>
</tr>
<tr>
<td>Range</td>
<td>14.0–80.5</td>
</tr>
<tr>
<td>Sex (No. (%))</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (26.0)</td>
</tr>
<tr>
<td>Female</td>
<td>154 (74.0)</td>
</tr>
<tr>
<td>Cigarette smoking (No. (%))</td>
<td>61 (14.9)</td>
</tr>
<tr>
<td>Hypertension (No. (%))</td>
<td>76 (36.5)</td>
</tr>
<tr>
<td>Prior aneurysmal SAH (No. (%))</td>
<td>63 (30.3)</td>
</tr>
<tr>
<td>Family history of aneurysms (No. (%))</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Excessive alcohol consumption (No. (%))</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td></td>
</tr>
<tr>
<td>Location of aneurysm (No. (%))</td>
<td></td>
</tr>
<tr>
<td>cavernous segment ICA</td>
<td>24 (8.4)</td>
</tr>
<tr>
<td>Distal ICA + PCoA</td>
<td>104 (36.5)</td>
</tr>
<tr>
<td>ACoA</td>
<td>34 (11.9)</td>
</tr>
<tr>
<td>ACA</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>MCA</td>
<td>64 (22.5)</td>
</tr>
<tr>
<td>PCA</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>BA + SCA</td>
<td>24 (8.4)</td>
</tr>
<tr>
<td>VA + PICA</td>
<td>16 (5.6)</td>
</tr>
<tr>
<td>Aneurysm size (mm)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;2.0–24.0</td>
</tr>
</tbody>
</table>

The study included aneurysms with initial diameters ranging from <2.0 mm to 24.0 mm. The median diameter of the 285 aneurysms was 4.0 mm (Table 1).

2.5. Statistical analysis

The incidence of growth was calculated as the number of aneurysms that grew divided by the number of aneurysms in the study. The cumulative incidence of growth was estimated by the Kaplan-Meier product limit method; with censoring of aneurysms that subsequently ruptured, received treatment, or did not exhibit growth at time of last contact. The univariate association of variables was tested by Fisher’s exact two-tailed tests, with p values below 0.05 considered indicative of statistical significance.

3. Results

3.1. Follow-up duration and endpoints

The total follow-up duration was 6228.8 months (519.1 years). The individual follow-up for aneurysms ranged from 1.1 to 137.3 months (mean 21.8 months), with 147 aneurysms (51.6%) followed for 12 months, and 91 (31.9%) followed for 24 months. In 121 aneurysms (42.5%) follow-up terminated due to receiving treatment; 70 aneurysms receiving neurosurgical and 51 endovascular interventions. Three aneurysms ruptured during follow-up, and there were no patient deaths from haemorrhage or other causes.

3.2. Incidence of aneurysm growth

During the follow-up period, 95 of the 285 aneurysms (33.3%) increased in size; nine aneurysms (3.2%) decreased in size. In the 95 aneurysms that increased in size, the mean time between initial imaging and angiographic documentation of growth was 15.9 months (range 0.5–91.0 months). The cumulative incidence of growth estimated using the Kaplan-Meier method was approximately 22.7% at 1 year after initial imaging, 35.2% at 2 years, and 47.7% at 3 years (Fig. 1).

3.3. Magnitude of aneurysm growth

The mean magnitude of growth for aneurysms was 47.7% (range 2.5–300.0%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm</td>
<td></td>
</tr>
<tr>
<td>Location of aneurysm (No. (%))</td>
<td></td>
</tr>
<tr>
<td>cavernous segment ICA</td>
<td>24 (8.4)</td>
</tr>
<tr>
<td>Distal ICA + PCoA</td>
<td>104 (36.5)</td>
</tr>
<tr>
<td>ACoA</td>
<td>34 (11.9)</td>
</tr>
<tr>
<td>ACA</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>MCA</td>
<td>64 (22.5)</td>
</tr>
<tr>
<td>PCA</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>BA + SCA</td>
<td>24 (8.4)</td>
</tr>
<tr>
<td>VA + PICA</td>
<td>16 (5.6)</td>
</tr>
<tr>
<td>Aneurysm size (mm)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;2.0–24.0</td>
</tr>
</tbody>
</table>

ACA = anterior cerebral artery, ACoA = anterior communicating artery, BA = basilar artery, CI = confidence interval, ICA = internal carotid artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, PICA = posterior inferior cerebellar artery, PCoA = posterior communicating artery, SAH = subarachnoid haemorrhage, SCA = superior cerebellar artery, VA = vertebral artery.

Fig. 1. The Kaplan-Meier analysis of growth of unruptured aneurysms.
3.4. Risk factors for aneurysm growth

Univariate analysis revealed excessive alcohol consumption to be a significant risk factor for aneurysm growth ($p = 0.04$). Growth was detected in 71.4% (5 of 7) of aneurysms associated with excessive alcohol consumption, compared to 32.4% (90 of 278) of aneurysms without.

The mean age of patients whose aneurysms enlarged was 49.6 years (range 16.9–76.3 years). These patients tended to be younger than those whose aneurysms did not grow; however, this difference did not reach statistical significance ($p = 0.06$).

The aneurysms that enlarged were located as follows: cavernous segment internal carotid artery for 10 aneurysms, distal internal carotid artery and posterior communicating artery for 35, anterior communicating artery for nine, anterior cerebral artery for three, middle cerebral artery for 19, posterior cerebral artery for three, basilar artery and superior cerebellar artery for 10, and vertebral artery and posterior inferior cerebellar artery for six aneurysms. Statistical analysis revealed that differing location was not associated with aneurysm growth.

Aneurysm growth was not significantly associated with female sex ($p = 0.6$), cigarette smoking ($p = 0.8$), hypertension ($p = 0.2$), prior aneurysmal SAH ($p = 0.5$), family history of intracranial aneurysms ($p = 0.7$), or aneurysm size of 10 mm or greater ($p = 0.4$) (Table 2).

3.5. Subsequent aneurysm rupture

During the 519.1 years of follow-up, 3 of the 285 aneurysms (1.05%) ruptured, resulting in an annual incidence of rupture of about 0.6%. Two of the ruptured aneurysms were located on the anterior communicating artery, and one at the origin of the superior cerebellar artery. These aneurysms were initially 8.0 mm, 1.0 mm, and 5.4 mm in size respectively. Only the 5.4 mm superior cerebellar artery aneurysm had increased in size prior to rupture.

4. Discussion

4.1. Incidence of growth

The study reports an overall incidence of growth of 33.3%, suggesting that a considerable number of aneurysms exhibit growth at some stage in their development. There have been few studies directly addressing the incidence of growth in unruptured intracranial aneurysms. Kamitani et al. previously reported a much higher overall incidence of 95%; however, their study included previously ruptured and/or incompletely operated aneurysms, and it may be difficult to compare growth in these aneurysms to growth in typically unruptured aneurysms, which have not undergone any intervention.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of aneurysms with growth/Total (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 51.1 (mean)</td>
<td>38/137 (27.7)</td>
<td>0.6 (0.4–1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>&lt;51.1</td>
<td>57/148 (38.5)</td>
<td>1.6 (1.0–2.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75/218 (34.4)</td>
<td>1.2 (0.6–2.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Male</td>
<td>20/67 (29.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30/86 (34.9)</td>
<td>1.1 (0.7–1.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>No</td>
<td>65/199 (32.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39/101 (38.6)</td>
<td>1.4 (0.9–2.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>No</td>
<td>56/184 (30.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior aneurysmal SAH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26/87 (29.9)</td>
<td>0.8 (0.5–1.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>No</td>
<td>69/198 (34.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of aneurysms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4/10 (40.0)</td>
<td>1.3 (0.4–4.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>No</td>
<td>91/275 (33.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5/7 (71.4)</td>
<td>5.2 (1.1–23.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>No</td>
<td>90/278 (32.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aneurysm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavernous segment ICA</td>
<td>10/24 (41.7)</td>
<td>1.5 (0.6–3.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Distal ICA + PCoA</td>
<td>35/104 (33.7)</td>
<td>1.0 (0.6–1.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>ACoA</td>
<td>9/34 (26.5)</td>
<td>0.7 (0.3–1.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>ACA</td>
<td>3/11 (27.3)</td>
<td>0.7 (0.2–2.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>MCA</td>
<td>19/64 (29.7)</td>
<td>0.8 (0.4–1.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>PCA</td>
<td>3/8 (37.5)</td>
<td>1.2 (0.3–4.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>BA + SCA</td>
<td>10/24 (41.7)</td>
<td>1.5 (0.6–3.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>VA + PICA</td>
<td>6/16 (37.5)</td>
<td>1.2 (0.4–3.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Aneurysm size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10.0</td>
<td>10/23 (43.5)</td>
<td>1.6 (0.7–3.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>&lt;10.0</td>
<td>85/262 (32.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACA = anterior cerebral artery, ACoA = anterior communicating artery, BA = basilar artery, CI = confidence interval, ICA = internal carotid artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, PICA = posterior inferior cerebellar artery, PCoA = posterior communicating artery, SAH = subarachnoid haemorrhage, SCA = superior cerebellar artery, VA = vertebral artery.

* Within follow-up period of study.
The Kaplan-Meier method predicted a cumulative incidence of growth of 22.7% at 1 year after initial imaging, 35.2% at 2 years, and 47.7% at 3 years, indicating that the timing of growth is variable between aneurysms, possibly related to the presence or absence of risk factors, genetic differences and variable flow dynamics. Koffijberg et al. recently constructed a mathematical model of aneurysm growth.\textsuperscript{19} This model suggests that aneurysm growth may be discontinuous, in which an aneurysm may have irregular episodes of growth, separated by periods of stability.

The importance of continual follow-up is confirmed by aneurysms that continued to show growth at times after 1 year. In this study, the longest interval to growth was 91.0 months after initial imaging, indicating that late changes can occur. Matsubara et al. recommended a follow-up period of at least 3 years for conservatively managed aneurysms.\textsuperscript{10}

4.2. Risk factors for aneurysm growth

In this study univariate analysis identified excessive alcohol consumption to be significant for aneurysm growth. Excessive alcohol consumption may also be an independent risk factor for haemorrhagic stroke and aneurysmal SAH;\textsuperscript{17,18} however, the role of alcohol consumption in aneurysm growth has not been previously recognised,\textsuperscript{14} and the mechanism by which it may increase the risk of growth is unclear. Previous studies have reported an induction of tumour necrosis factor-alpha (TNF-alpha) in response to alcohol consumption.\textsuperscript{19–21} TNF-alpha may contribute to aneurysm growth through activation of signalling pathways, with infiltration of inflammatory cells and mediators into the arterial wall.\textsuperscript{19} Inflammation may progressively weaken the arterial wall, and thus contribute to aneurysm growth.

This present study has shown a trend towards an association between aneurysm growth and younger patient age at the beginning of follow-up. However, excessive alcohol consumption, larger aneurysm size and other factors may have had confounding effects. As in the report of Juvela et al., younger patients have significantly larger aneurysms.\textsuperscript{10}

Other studies have reported various risk factors for aneurysm growth: Juvela et al. reported cigarette smoking and female sex as significant risk factors for growth,\textsuperscript{14} whereas Matsubara et al. found that growth was associated with location at the basilar artery bifurcation or the internal carotid artery, or an aneurysm size of \( \geq 10 \text{ mm} \).\textsuperscript{16} These factors were not found to be significant in the present study. This may be due to differences in the patient population, including racial or genetic characteristics, or differences in geographic location. These studies have been principally based in Japan and Finland; higher incidences of unruptured intracranial aneurysms and higher rates of SAH have been published for the Japanese and Finnish populations, and it is possible that differences in these patient populations may also apply to aneurysm growth when compared to the Australian population used in this study.

4.3. Association between growth and rupture

Aneurysm growth was not associated with rupture in this study. This finding was based on limited univariate analysis; only 3 aneurysms had ruptured in the study. The incidence of rupture in this study, approximately 0.6% per year, may have been lowered due to a relatively large proportion of smaller aneurysms. Wiebers et al. reported in 1981 that typically 80% of unruptured intracranial aneurysms are less than 10.0 mm in size, including 30% of 2.0 mm to 4.9 mm in size.\textsuperscript{8} In comparison, most (91.5%) aneurysms in this study were initially less than 10.0 mm in size, and 53.3% were 2.0 mm to 4.9 mm in size. In addition, this study included no giant aneurysms (greater than 25.0 mm). Giant aneurysms have an exceptionally high rate of rupture and subsequent mortality: 43% to 50%.\textsuperscript{22–24} In practice these aneurysms are frequently lost to follow-up or undergo surgical treatment, thus limiting their availability and potential for study inclusion.

For the three ruptured aneurysms, size measurements may have been underestimated at the time of rupture. An aneurysm may decrease in size at or shortly after the time of rupture, due to collapse or thrombus formation.\textsuperscript{25} Thus, the three ruptured aneurysms might have had additional growth, unmeasurable at the time of rupture.

The surgical examination of aneurysms has revealed that fast-growing aneurysms generally have thinner walls, possibly indicating a predisposition of these aneurysms to rupture.\textsuperscript{13} Clinically, little data are available: Juvela et al.’s study is one of the few clinical studies demonstrating an association between growth and rupture.\textsuperscript{10} Other studies have not shown growth to be associated with rupture, due to rupture rates comparable to or lower than in this study.\textsuperscript{16,26}

4.4. Selection bias

The results of this study may be substantially biased by its patient selection. The study does not represent all unruptured intracranial aneurysms that are encountered in daily practice. Notably, differences in aneurysm size have been observed in the patients, and it is likely that other characteristics – both those measured and those unmeasured in the study – may also be relevant. However, it is highly unlikely that a study will be conducted without selection bias of some kind, due to ethical and practical considerations.

4.5. Measurement bias

Measurements of aneurysm size are subject to interobserver differences when reading angiograms. However, due to standardised procedures established for angiogram measurements, these differences may be negligible. A study by Forbes et al. in 1996, utilizing standardised procedures to measure aneurysms, had reported a high correlation between different angiogram readers, throughout a range of aneurysm sizes.\textsuperscript{27}

4.6. Usefulness of a retrospective study

In order to minimise error, patient records in this study had been reviewed with predefined definitions for key variables and case selection criteria. However, analysis in this study was limited by the data available retrospectively. The completeness of patient data, in particular patient characteristics and risk factors, is unknown and relies solely on recorded information. Scientific accuracy is also weakened by use of electronic records. To further evaluate the growth of aneurysms and the findings proposed by this study, large prospective studies would be ideal.

5. Conclusions

The present study demonstrates a high incidence of growth of unruptured aneurysms over time. The timing of growth varies between aneurysms, and continual follow-up is required for those lesions that have not shown growth in the short term; at a minimum, repeat imaging should be conducted annually. Excessive alcohol consumption may increase the risk of aneurysm growth; however, further studies are required to explore this association.
Acknowledgement

The authors thank Marnie Collins for helpful discussions in statistical analysis, and Tony Petracca for assistance in radiological data retrieval.

References

A pilot study of resistance to aspirin in stroke patients

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Abstract

Aspirin resistance has been shown to be a significant risk factor for recurrent cardiovascular ischaemic events. However, there are a lack of data correlating aspirin resistance and risk of cerebrovascular ischaemic events. This pilot study aimed to determine the prevalence of aspirin resistance in an Australian stroke population and to correlate aspirin resistance with an increased risk of ischaemic stroke. Fifty patients treated with aspirin for 2 years were tested for aspirin resistance using the Ultegra Rapid Platelet Function Assay (Accumetrics, San Diego, CA, USA) on admission to Royal Melbourne Hospital for ischaemic stroke. The 2-year history of ischaemic stroke and transient ischaemic attack (TIA) were assessed. Prevalence of aspirin resistance among our patients was 30%. Univariate analysis suggested a non-significant trend towards increased rate of previous ischaemic stroke or TIA and aspirin resistance (odds ratio, OR = 3.88; 95% confidence interval 0.54–29.87; \( p = 0.18 \)). This study shows that aspirin resistance is prevalent within the Australian ischaemic stroke population.

Keywords: Aspirin resistance; Ischaemic stroke; Transient ischaemic attack

1. Introduction

Aspirin remains the standard first-line therapy in the secondary prevention of vascular events due to underlying atherothrombotic conditions. The Antithrombotic Trialsists’ Collaboration analysed patient data from 21 randomised controlled studies and concluded that the benefit of aspirin reduced the recurrent odds of stroke by 22% compared to placebo.\(^1\) However, the benefits in a stroke population are even more modest, with a relative risk reduction of only 13%.\(^2\) Therefore, a substantial proportion of patients do not derive the expected benefits of stroke prevention.

Between 5% and 60% of patients treated with aspirin may be regarded as aspirin-resistant, on various laboratory measures of platelet function. This has been independently associated with an increased risk of atherothrombotic vascular events in a wide range of cardiovascular patients.\(^3\)–\(^6\) Aspirin resistance has been associated with a 4 times increased hazard risk (HR) of adverse events (HR = 4.1 [1.4–12.1]) among stable cardiovascular patients.\(^3\) The increased risk of clinical events is expected to be similarly linked with aspirin resistance among ischaemic stroke patients, given the common underlying pathology of atherothrombosis. If aspirin resistance predicts an increased risk of stroke recurrence, treatment could be individualised.

Few studies have investigated the role of anti-platelet resistance in stroke. Harrison et al. recruited 100 stroke patients and showed that the incidence of aspirin resistance was 17%, using light transmission aggregometry (LTA).\(^7\) This was comparable to the incidence in studies of myocardial ischaemia.\(^8\) However, this study did not address recurrent stroke. The primary objective of our pilot study was to examine the prevalence of aspirin resistance in Australian patients who present with acute ischaemic stroke. The secondary objective was to test the hypothesis that aspirin resistance was more common in those with previous cerebrovascular events.
2. Materials and methods

2.1. Patients and study design

This study was approved by the Human Research and Ethics Committee (HREC) at the Royal Melbourne Hospital (Melbourne, Victoria) and all subjects provided written informed consent. Over a 7 month period patients presenting consecutively to Royal Melbourne Hospital Comprehensive Stroke Centre with acute ischaemic stroke were screened for enrolment. Inclusion criteria were consenting age \( \geq 18 \) and patients who had been taking aspirin for at least 2 years and had presented with an acute ischaemic stroke (excluding transient ischaemic attack, TIA). Patients were excluded if they had an intracerebral haemorrhage on CT scan, significant diseases or abnormalities (terminal cancer, life threatening infection) that might compromise participation. Patients treated with clopidogrel in combination with aspirin were also excluded.

All patients received standard treatment according to Royal Melbourne Hospital Comprehensive Stroke Centre protocol. After a single screening visit to establish eligibility, qualified patients were enrolled in the study. Demographic information (age, gender, race, vascular risk factors) and clinical data which included National Institutes of Health Stroke Scale (NIHSS), Trial of Org 10172 (TOAST) scale\(^9\) and Oxfordshire Community Stroke Project Classification\(^10\) were obtained within 48 hours of admission. Any history of prior ischaemic events was analysed retrospectively for the previous 2 years while taking aspirin and included ischaemic stroke, TIA, myocardial infarction and unstable angina. A single blood sample was obtained per recruited patient to establish the presence of aspirin resistance.

2.2. Blood sampling

Whole blood was obtained via venepuncture into a 2 mL partial fill 3.2% sodium citrate vacuum collection tube using a 21-gauge needle. A tourniquet was used while performing venepuncture. For patients with an in-dwelling cannula, blood was collected after sufficient discard (about 5 mL) had been drawn to clear the line. The tubes were then gently inverted 3–5 times and incubated at room temperature for at least 30 min after collection before testing but for no longer than 4 hours. Blood was taken no less then 2 hours after aspirin ingestion as documented on ward charts.

2.3. Measuring aspirin resistance

Aspirin-induced platelet inhibition was measured using the point-of-care device, the Ultegra Rapid Platelet Function Assay (RPFA) developed by Accumetrics (San Diego, CA, USA). This turbidimetric-based optical detection system measures platelet induced aggregation proportional to changes in light transmission. Modified disposable cartridges containing fibrinogen-coated beads and platelet agonist are inserted into the Ultegra RPFA device to test specifically for aspirin responsiveness. A citrate anti-coagulated blood sample is then gently inverted 4–5 times and placed onto the cartridge. The device automatically dispenses blood, mixing it with the cartridge reagents, thereby no blood handling is required. Fibrinogen-coated beads agglutinate in proportion to the number of activated platelets expressing glycoprotein GP IIb/IIIa receptors, subsequently increasing light transmission through the sample. The result is expressed in Aspirin Reaction Units (ARU), taking about 5 min to test one sample of blood. An ARU value \( \geq 550 \) is consistent with no platelet dysfunction whereas values \( <550 \) are consistent with platelet dysfunction. Aspirin resistance based on the Ultegra RPFA is defined as an ARU \( \geq 550 \) in a patient taking aspirin. The threshold value of 550 ARU was determined by correlation with adrenaline-induced light transmission aggregometry in aspirin-naive patients tested before and then between 2 hours and 30 hours after aspirin ingestion.\(^11\)

Patients received 100 mg aspirin dose as is standard management in the Royal Melbourne Hospital Comprehensive Stroke Centre. Aspirin resistance was recorded as a dichotomous variable, all patients with ARU value \( <550 \) and known to be taking aspirin were regarded as aspirin sensitive.

2.4. Analyses

All statistical analyses were performed using STATA 9 (StataCorp LP., College Station, TX, USA). Continuous variables are expressed as median and range. Dichotomous variables are presented as percentages. The relative frequency of dichotomous baseline and clinical variables among aspirin-resistant, compared to aspirin-sensitive, patients was analysed using odds ratios (OR) and their 95% confidence intervals (CIs) with the Fisher’s exact test calculated. Logistic regression was used for the continuous variable of age to assess association with aspirin resistance. Statistical significance was defined as \( p < 0.05 \). However, this pilot study does not have sufficient power to provide statistically significant results because it was designed to provide indications for future research.

3. Results

We studied 50 ischaemic stroke patients admitted to the Royal Melbourne Hospital Comprehensive Stroke Centre during the recruitment period (Table 1). The median age of patients was 77 [51.4–93.6], 74% were male and 98% were Caucasian.

3.1. Prevalence of aspirin resistance

Fifteen out of 50 patients (30%) were found to be aspirin resistant. The distribution of ARU values is shown in
Our patients had a median ARU of 509 (range 385–626). All patients enrolled in the study had been taking aspirin for at least 2 years prior to admission with the median duration of aspirin therapy 5 years (range 2–31). Fig. 2 shows ARU values in patients who had a history of ischaemic stroke or TIA compared to those who did not. Patients with previous events had a higher median ARU of 550 (range 471–573) compared to those without events, median ARU of 496 (range 385–626).

### 3.2. Aspirin resistance and recurrent ischaemic stroke

Three patients had a history of stroke and 5 had a history of TIA with 1 patient having both, giving a rate of recurrent ischaemic stroke or TIA of 7/50 (14%) over the previous 2 years. Of these 7 patients, 4/7 were aspirin resistant. Of the 43 patients without a history of ischaemic events, 11/43 were aspirin resistant. In this sample, the odds of having a past history of either TIA or ischaemic stroke was about 4 times higher in patients with aspirin resistance compared to those without, but the difference was not significant (odds ratio, OR = 3.88; 95% confidence interval, 0.54–29.87; \( p = 0.18 \)).

### Table 1
Comparison of patient characteristics between aspirin-resistant and aspirin-sensitive patients (\( n = 50 \))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (( n = 50 ))</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>77 (51, 93)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>37 (74%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>49 (98%)</td>
</tr>
<tr>
<td>ARU</td>
<td>509 (385, 626)</td>
</tr>
<tr>
<td>Duration of aspirin therapy (yrs)</td>
<td>5 (2, 31)</td>
</tr>
</tbody>
</table>

#### History of ischaemic events

| Past history of TIA | 5 (10%) | 3 (20.0%) | 2 (5.7%) |
| Past history of stroke | 3 (6%) | 1 (6.7%) | 2 (5.7%) |
| Past history of combined stroke + TIA | 7 (14%) | 4 (26.7%) | 3 (8.6%) |
| Past history of MI | 6 (12%) | 2 (13.3%) | 4 (11.4%) |
| Past history of MI + unstable angina | 4 (8%) | 0 (0.0%) | 4 (11.4%) |

#### TOAST classification of strokes

| Large artery atherosclerosis | 13 (26%) | 2 (13.3%) | 11 (31.4%) |
| Cardiogenic embolic | 7 (14%) | 3 (20.0%) | 4 (11.4%) |
| Lacunar infarcts | 9 (18%) | 3 (20.0%) | 6 (17.1%) |
| Strokes of undetermined aetiology | 21 (42%) | 7 (46.7%) | 14 (40.0%) |

#### Clinical syndrome of stroke

| NIHSS | 4.5 (2, 20) | 7 (2, 14) | 4 (2, 20) |
| TACI | 4 (8%) | 1 (6.7%) | 3 (8.6%) |
| PACI | 24 (48%) | 9 (60.0%) | 15 (42.9%) |
| POCI | 8 (16%) | 2 (13.3%) | 6 (17.1%) |
| LACI | 14 (28%) | 3 (20.0%) | 11 (31.4%) |

#### Vascular risk factors

| Atrial fibrillation\( ^a \) | 15 (30%) | 6 (40.0%) | 9 (25.7%) |
| Smoking\( ^b \) | 36 (72%) | 11 (73.3%) | 25 (71.4%) |
| Hypercholesterolemia\( ^c \) | 39 (78%) | 9 (60.0%) | 30 (85.7%) |
| Previous carotid endarterectomy\( ^d \) | 3 (6%) | 0 (0.0%) | 3 (8.6%) |
| Carotid stenosis\( ^e \) | 12 (24%) | 2 (13.3%) | 10 (28.6%) |
| Hypertension | 48 (96%) | 14 (93.3%) | 34 (97.1%) |
| Diabetes\( ^f \) | 21 (42%) | 4 (26.7%) | 17 (48.6%) |

ARU = aspirin reaction unit, LACI = lacunar infarct, MI = myocardial infarction, NIHSS = National Institutes of Health Stroke Scale, PACI = partial anterior circulation infarct, POCI = posterior circulation infarct, TACI = total anterior circulation infarct, TIA = transient ischaemic attack, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

\( ^a \) Known atrial fibrillation on admission or known paroxysmal atrial fibrillation.

\( ^b \) History of smoking or current smoker.

\( ^c \) Hypercholesterolemia defined as previous treatment with cholesterol lowering agent on admission or fasting lipids of \( >5.5 \) mmol/L cholesterol on admission.

\( ^d \) Previous endarterectomy of at least one internal carotid artery.

\( ^e \) Defined as at least one carotid artery with measurement \( \geq 50\% \) on Ultrasound by Doppler or North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria in patients receiving an angiogram.

\( ^f \) Previous diagnosis of diabetes on admission. All patients with diabetes in this study had non insulin dependent diabetes mellitus.
classification (Table 1). However, there was a trend towards lower rates of diabetes, carotid stenosis and hypercholesterolemia among resistant patients (Table 2). Male gender also suggested an increased risk of being aspirin resistant (OR = 7.3; 95% confidence interval, 0.87–334.10; p = 0.08). No statistically significant differences between the 2 groups were demonstrated for any of the variables we assessed using univariate analysis (Table 2).

4. Discussion

Prospective clinical studies have shown that aspirin resistance as measured by laboratory tests is associated with an increased risk of atherothrombotic events. These studies, however, have not analysed ischaemic stroke patients in particular and have not asked whether aspirin resistance increases the risk of recurrent ischaemic stroke. Our study is the first to determine the prevalence of aspirin resistance in an Australian stroke population and to determine if this was more common in patients with a prior history of vascular events. This would suggest that aspirin-resistant patients are at higher risk of recurrent events, which would require testing in a prospective design.

This study suggests that aspirin resistance is prevalent in patients presenting with acute ischaemic stroke. Aspirin resistance tended to be more common among males but did not show a statistically significant correlation with any clinical variable. Aspirin resistance in our patients suggests increased risk of ischaemic stroke and TIA but not of cardiovascular events among our population of ischaemic stroke patients.

The prevalence of aspirin resistance at 30% in our study is comparable to results of cardiology and stroke studies using the Ultegra RPFA. Previous studies reported rates of aspirin resistance of 19%, 23% and 17% respectively using the Ultegra RPFA in varying patient populations. The limited number of studies examining aspirin resistance in a stroke population indicate that aspirin resistance prevalence is 12% to 34%.

It is difficult to compare our results in terms of increased risk of ischaemic stroke associated with aspirin resistance due to the lack of literature analysing this hypothesis. Two studies have attempted to correlate aspirin resistance with recurrent ischaemic stroke. Grundman et al. conducted a retrospective study in 53 patients taking aspirin for secondary prevention of ischaemic stroke or TIA. The rate of aspirin resistance was 34% among patients with a recent recurrent ischaemic event compared to 0% of patients with no recent events. Grundman’s inclusion criteria consisted of history of previous cerebrovascular or cardiovascular events, which indicated that the population was not exclusively stroke. This open criterion also suggests that asymptomatic and symptomatic groups may have been insufficiently comparable in terms of ischaemic stroke events.

Grotemeyer et al. followed up 180 post ischaemic stroke patients over 2 years. This study found 33% of the population to be aspirin resistant with a 10-fold increase in clinical events among resistant patients. The major study endpoints were not specific to recurrent stroke constituting MI, vas-
cular death and stroke. The ability to generalise the results of this study was reduced as all patients had ischaemic stroke in the internal carotid artery territory excluding those with posterior circulation infarcts. These two studies used alternative methods of measuring aspirin resistance compared to our study.

The cause of aspirin resistance is uncertain and is probably multifactorial. Biological, genetic and environmental factors are likely candidates. Our study provides no statistically significant clinical predictors of aspirin resistance on univariate analysis. Diabetes, hypercholesterolemia, smoking, age, and female gender have been associated with aspirin resistance. Hypercholesterolemia appeared to be lower among resistant patients in our study population. These findings are not expected as numerous studies suggest that diabetes and hypercholesterolemia predict increased risk of aspirin resistance.

Gum et al. provided the first evidence of a clinical association between aspirin resistance and increased cardiovascular events. Aspirin resistance predicted increased events independent of age and conventional vascular risk factors. The suggestion of lower rates of diabetes, cholesterol and increased incidence of male gender among our resistant population may be due to small sample size and chance. Further studies are needed to analyse clinical predictors of aspirin resistance.

Our study has strengths. Because patients were tested only after 100 mg aspirin had been given as documented on the ward drug charts, measuring aspirin resistance on admission was not confounded by compliance, a simple mechanism of laboratory and clinical aspirin resistance often overlooked. Some previous studies have relied on patient compliance when measuring aspirin resistance and thus potentially overestimated the numbers of aspirin-resistant patients. The use of a point-of-care (POC) test to measure aspirin resistance adds clinical relevance to our results. A quick and easy method of testing aspirin resistance is necessary if it is to become a part of standard management in secondary prevention of stroke. POC tests overcome problems encountered by earlier studies in which aspirin resistance had been measured using the traditional gold standard of LTA.

Our study has limitations. First, our sample may have underestimated the true prevalence of aspirin resistance and rate of recurrent ischaemic stroke. Patients who had been treated with antiplatelet agents other then aspirin (e.g. clopidogrel) were excluded. Second, assessment of the patient’s history of ischaemic events was carried out retrospectively. This was a particular limitation for history of TIA and unstable angina for which patients are not always admitted to hospital and therefore rely on history and records kept by their general practitioner. Third, compliance with aspirin therapy over the previous 2 years could be assessed only on patient history or the history from the primary carer.

The issue still remains that if aspirin resistance does correlate with increased cerebral ischaemic events in a stroke population, the mechanism of aspirin resistance is not clarified, nor is the appropriate management of these patients. Further studies need to be conducted to assess the most appropriate management of aspirin-resistant patients. Eventually aspirin resistance may become routinely screened and managed in much the same way as blood pressure or hypercholesterolemia as one of multiple risk factors that optimise secondary prevention of ischaemic stroke.

Our data suggests that aspirin resistance is prevalent within the ischaemic stroke population and is similar to that demonstrated in the cardiology literature. Furthermore aspirin resistance tended to be more prevalent in patients at an increased risk of cerebral ischaemic events. Further evaluation of the clinical consequences of aspirin resistance using the Ultegra RPFA in a larger prospective study is required.

References


When to Measure Lipid Profile after Stroke?

A Prospective Serial Study

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Key Words
Brain ischemia · Lipids · Statin

Abstract

\textbf{Background:} Although acute decreases in total cholesterol (TC) are well documented in myocardial infarction, previous stroke studies have produced conflicting results. The timing of lipid estimation in ischemic stroke is becoming important with recent trial results indicating the benefits of statins. We therefore aimed to determine the optimal time for lipid measurements after stroke. We hypothesized that TC would acutely decrease after stroke and return to baseline by 12 weeks.

\textbf{Methods and Results:} We performed a prospective, observational study of 50 patients (age 68.5 ± 11.2 years) who presented with acute ischemic stroke. Of these, 22 (44\%) were HMG-CoA reductase (statin) naïve, 15 (30\%) had already been on statins and 13 (26\%) were commenced on statins. Of the 50 patients, 38 (76\%) completed 12 weeks of follow-up, 5 died, and 7 were lost to follow-up. Fasting lipid profile (TC, low-density lipoprotein, high-density lipoprotein, triglyceride) was measured \(\leq 48\) h, 4 weeks and 12 weeks following ictus. In patients who were statin naïve, there was a significant increase in TC at the week 12 evaluation.

\textbf{Conclusions:} Cholesterol levels in acute stroke are an unreliable measure of lipid status. Initiation of statins should ideally be based on measurements taken 12 weeks after stroke.
atorvastatin versus placebo. For these reasons, stroke clinicians are now considering the use of statins in secondary prevention. Clearly, the accurate measurement of the lipid profile after stroke is becoming an important issue.

However, data concerning the fluctuations of the lipid profile after acute stroke are scarce. To date, the few studies have reported conflicting results [14–17]. All but one study had methodological problems in that few acute patients were studied and patients with intracerebral hemorrhage were included as well as those with ischemic stroke.

Given this uncertainty, we aimed to investigate the lipid profile alterations after ischemic strokes, using serial measurements. The lipid measurements in the first 48 h after ictus were compared with those at week 4 and after a 12-week period. We tested the null hypothesis that the lipid profile at 48 h after stroke was not significantly different from the baseline lipid profile obtained at 12 weeks following stroke. If the lipid profile obtained in the acute stage of stroke does not reflect the baseline lipid profile, this could have important implications for decisions concerning initiation of statin therapy.

Materials and Methods

A prospective observational study was undertaken to investigate the serial fluctuation in the lipid profile between the first 48 h following acute ischemic stroke and week 12 after ictus. All eligible and consenting patients were recruited from the RMH (Royal Melbourne Hospital, Melbourne, Australia) Emergency Department. Patients were eligible if they had an acute ischemic stroke syndrome following acute ischemic stroke and week 12 after ictus. All eligible patients were enrolled in the study. Patients were examined by a neurologist and underwent CT scanning of the brain. The exclusion criteria were: an unclear time of onset of stroke, transient ischemic attack, intracerebral hemorrhage or a significant life-threatening condition or history of cerebrovascular disease, when treated with simvastatin, had a significant reduction in further nonstroke vascular events although not in further strokes [20]. However, at the time that this study was performed, statin drugs were not usually initiated because of the lack of evidence of benefit in secondary stroke prevention. Furthermore, a proportion of patients had statins commenced by their primary care physicians, using established cardiology guidelines. If statins were initiated during the period after stroke following discharge, this information was recorded. Measurements of these lipid parameters were performed at the central laboratory at the RMH. Prehospital admission cholesterol levels were not considered appropriate in this setting. All our patients had had their lipid measurements done by different laboratories outside of the hospital and we believed that these measurements would be at variance to measurements performed at our hospital laboratory.

We had performed power calculations and estimated that 37 pairs of subjects would be required in order to have 80% power to detect a 10% difference in the TC levels obtained within 48 h of the onset of ictus and week 12 after onset of ictus, at the 5% significance level. Results are presented as mean and standard deviation for normally distributed data. Paired-sample t tests were performed for comparisons between time points. Given that multiple consecutive comparisons were performed, the Bonferroni procedure for adjustment was applied at each step of analysis. Statistical analysis was undertaken using the STATA statistical software package, version 5.0 (Stata Corporation, College Station, Tex., USA, 1997).

Results

Of the 50 patients (mean age 68.5 ± 11.2 years) recruited for the study, 38 (76%) completed the 12-week follow-up, 5 died and 7 were lost to follow-up. Their clinical characteristics are presented in table 1.

Of note, 15 patients (30%) had already been on statins and a further 13 patients (26%) were commenced on statins after stroke by their primary care physician. There were 22 patients (44%) who were statin naïve (i.e. had never been on statins prior to recruitment and remained statin-free during the course of the study). Consequently, we analyzed the results for the patients who were statin naïve throughout the study period in order to draw more meaningful results. Of the 22 statin naïve patients, 13 were available for follow-up. The comparison of their lipid profile is presented in figure 1 and table 2.

In the statin naïve group of patients (n = 22), there was a rise of 18% in TC between the first 48 h and week 12. This rise was greater than that which had been used for...
the sample size calculations and was statistically significant (p < 0.01). There was no significant difference between the TC measured in the first 48 h and week 4. Similarly, the LDL also increased by 17% between the first 48 h and 12 weeks (p < 0.01). No statistically significant differences in the triglyceride and HDL levels were observed between baseline (48 h following stroke) and 12 weeks.

There was no statistically significant correlation (Pearson correlation coefficient r = 0.13) between stroke severity and the alteration in the lipid profile in the statin-naïve group of patients.

**Table 1.** Clinical characteristics of the stroke patients on admission

<table>
<thead>
<tr>
<th></th>
<th>On admission (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD), years</td>
<td>68.5 ± 11.2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (44)</td>
</tr>
<tr>
<td>NIHSS score (mean ± SD)</td>
<td>10.02 ± 7.67</td>
</tr>
<tr>
<td>Oxfordshire classification [16]</td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>11 (22)</td>
</tr>
<tr>
<td>PACI</td>
<td>24 (48)</td>
</tr>
<tr>
<td>LACI</td>
<td>11 (22)</td>
</tr>
<tr>
<td>POCI</td>
<td>4 (8)</td>
</tr>
<tr>
<td>TOAST classification [17]</td>
<td></td>
</tr>
<tr>
<td>Large artery</td>
<td>27 (54)</td>
</tr>
<tr>
<td>Small artery</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Time to blood sample after stroke (mean ± SD), h</td>
<td>25.22 ± 14.6</td>
</tr>
<tr>
<td>Statin naïve</td>
<td>22 (44)</td>
</tr>
<tr>
<td>On statin prior to recruitment</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Commenced on statin after recruitment</td>
<td>13 (26)</td>
</tr>
</tbody>
</table>

TACI = Total anterior circulation infarct; PACI = partial anterior circulation infarct; LACI = lacunar infarct; POCI = posterior circulation infarct. Figures in parentheses indicate percentages.

**Table 2.** Mean lipid levels ± SEM (mmol/l) of statin-naïve patients at different time points after onset of stroke ictus

<table>
<thead>
<tr>
<th></th>
<th>48 h</th>
<th>4 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>4.48 ± 0.21</td>
<td>4.73 ± 0.83</td>
<td>5.31 ± 0.43</td>
</tr>
<tr>
<td>LDL</td>
<td>2.84 ± 0.41</td>
<td>2.76 ± 0.72</td>
<td>3.36 ± 0.37</td>
</tr>
</tbody>
</table>

**Discussion**

In measuring the lipid profile after ischemic stroke of the 22 serially studied patients who were statin naïve, it was observed that TC and LDL levels increased by about 18 and 17%, respectively, between the acute ictus and 3 months after stroke (fig. 1). We therefore conclude that acute measurements of the lipid profile are prone to falsely low lipid measures, as in acute myocardial infarction, and that the decision to initiate lipid-lowering agents after stroke should ideally be based on lipid measurements at least 3 months after stroke.

Lipid disturbance has recently been emerging as an important contributor to the pathogenesis of stroke [11]. In the recent Prospective Pravastatin Pooling Project [12], which studied primary stroke prevention in patients with and without a history of prior ischemic heart disease, treatment with pravastatin was associated with a 23% reduction in stroke incidence. A recent meta-analysis [21] of randomized trials of lipid-lowering therapies reported the data from patients with various preexisting vascular conditions. The occurrence of stroke as an endpoint was analyzed and it was concluded that patients randomized to statin therapy had a relative risk reduction of stroke by 26%.

The Stroke Prevention by Aggressive Reduction of Cholesterol Levels Study [13], the largest study of the utility of statins in secondary stroke prevention, is currently under way. These studies underline the importance of accurate measurements of the lipid profile in order to iden-
tify patients who would benefit more from lipid-lowering agents.

Acute alterations in lipid and lipoprotein concentration have been well reported after acute myocardial infarction [1–4]. The pathophysiology underlying lipid alterations after myocardial infarction is not entirely unclear [22]. There are several theories. First, lipoprotein synthesis in the liver may be affected after acute physiological stress such as ischemia. Ischemia is usually followed by an inflammatory process, which alters the hepatic production of plasma proteins. Shifts in the synthesis and secretion of proteins lead to a shift in synthesis of lipoproteins such as LDL and very-low-density lipoprotein. Secondly, C-reactive protein is shown to increase after acute myocardial infarction and stroke [5, 23]. C-reactive protein binds with lipoproteins in in vitro experiments. This may facilitate the removal of lipoproteins from the circulation by the reticuloendothelial system. It follows that lipid alterations would be expected in other acute ischemic injuries such as stroke.

However, very few studies have been undertaken to investigate the alterations in lipid measurements after acute stroke and the findings are contradictory. In an early study by Hollanders et al. [14], TC decreased in the first week after acute stroke and thereafter TC increased slowly and returned to baseline after 3 months. This study was conducted prior to the era of CT brain scanning and the diagnosis of stroke was based on clinical assessment alone.

Mendez et al. [15] studied 24 patients and included patients with stroke and transient ischemic attacks. In this study, there were only 12 patients who fulfilled the clinical criteria for stroke. Patients who presented with stroke showed a significant increase in TC and LDL between day 7 and day 90. The late accrual of patients in this study may have confounded the results. In contrast, all of our patients were enrolled and had their baseline lipid studies within 48 h of the ictus.

Woo et al. [16] studied 83 patients with stroke, but included patients with intracerebral hemorrhage, which may have confounded the data analysis. It is possible that hemorrhagic injury may induce a different acute inflammatory reaction and consequently, a different alteration in the lipid profile, as compared with ischemic injury. In contrast to the studies by Hollanders et al. [14] and Mendez et al. [15], TC was significantly lower in the 3-month follow-up compared with TC in the first 48 h [16].

A shortcoming of our study was that it was observational and noninterventional in that we were unable to influence the prescription habits of medical practitioners who assumed the care of the stroke patients out of hospital. Consequently, a proportion of patients were given lipid-lowering agents (statins) which potentially confounded the initial analysis of lipid alterations. Therefore, the most useful information was obtained in those patients who were never treated with statins (i.e. statin naïve). Although our numbers were relatively small, the results were statistically significant and consistent with studies in acute myocardial infarction.

We have identified several possible confounding factors in our results. The different nutritional intake and physical activities of stroke patients may also influence lipid levels. All patients in our stroke unit received the same level of nutritional care and encouragement in physical activity. However, it was not possible for us to alter the above once the patients were discharged from the hospital. We were also unable to measure the exact alteration in lipids before the onset of stroke and then immediately after. This was due to the lack of reliable lipid data prior to the stroke.

Our results in figure 1 show the upward trend of cholesterol levels (both LDL and TC) from within 48 h of stroke onset to week 12 after ictus in patients who were statin naïve. The data support our conclusion that cholesterol level within the acute phase of stroke is an unreliable measurement. Our results also mirror the findings from studies of the time course of alterations in lipid profiles after acute myocardial infarction [1–3]. In one study, TC significantly decreased after myocardial infarction and the maximal decrease was observed between days 4 and 12 [5]. There was also a positive correlation between infarct size and the degree of TC reduction [4]. We could not find a correlation between stroke severity measured by the NIHSS and acute reduction of TC. We consider our results in statin-naïve patients to be in agreement with Mendez et al. [15] and Hollanders et al. [14]. Moreover, we have excluded patients with intracerebral hemorrhage, where lipid measurements are not clinically relevant and may exhibit a different temporal profile.

We conclude that lipid measurements taken during the acute stages of stroke are falsely low and hence unreliable. It might be argued that precise measures of lipid status are not clinically important, given that recent studies using statins have included patients in the cholesterol range considered normal. For example, the Heart Protection Study [20], the first study to involve a significant stroke cohort, included patients with LDL cholesterol less than 3.0 mmol/l. On the other hand, the Heart Protection Study [20] only showed benefit in the reduction of non-stroke vascular events in patients with a past history of
stroke. The question whether stroke patients with differing levels of cholesterol may benefit from future stroke reduction after statin therapy remains open. In addition, government pharmaceutical guidelines are still likely to specify cholesterol thresholds for the use of statins and hence reliable measurements are required. Furthermore, the value or otherwise of acute statin therapy for ischemic stroke, unlike acute myocardial infarction which has been demonstrated in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study [24], has not been clearly established. For these reasons, we recommend that an acute lipid profile, if high levels of TC were shown, is not necessarily an argument against commencing statins, given that our results have shown that cholesterol levels increase in the following months. On the other hand, if normal levels of acute TC were found, we recommend that a repeat lipid profile be performed in 12 weeks on which ideally the decision to commence treatment should be based.

Acknowledgment

The study was funded by the Royal Melbourne Hospital Neuroscience Foundation.

References

Section 2 Specific risk factors: pharmacogenetics and ageing

This section deals with newly acclaimed methods of investigation of the possible and identifiable risk factors not previously recognized as fundamental such as genetic factors but these as well as aging processes may represent an important avenue of showing an individual's exposure to risk factors other than those commonly recognized such as diabetes mellitus, hypertension, smoking and atrial fibrillation.

List of my publications submitted in full


Association between CYP2C19 Polymorphisms and Outcomes in Cerebral Endovascular Therapy


ABSTRACT

BACKGROUND AND PURPOSE: Differing responses to clopidogrel following endovascular treatment of cerebrovascular diseases may increase the risk of vascular complications. CYP2C19 gene polymorphisms influence clopidogrel activity. We aimed to study the clinical impact of CYP2C19 gene polymorphisms in patients undergoing endovascular treatment.

MATERIALS AND METHODS: This was a prospective, longitudinal, observational study. Information on demographics and cerebrovascular status was collected as baseline. Clopidogrel response was tested by the VerifyNow P2Y12 assay. CYP2C19 genotyping was undertaken by polymerase chain reaction–restriction fragment length polymorphism. Three-month follow-up data included vascular complications, mortality, and modified Rankin Scale score. Associations were investigated among CYP2C19 genotypes, clopidogrel responsiveness, and clinical outcomes.

RESULTS: One hundred and eight participants were included. Median age was 56 years (interquartile range, 48.8–65.0 years), and 35 (32.4%) were male. Forty-four participants were classified into group 1 (homozygous CYP2C19*1/*1); 31, into group 2 (25 with CYP2C19*1/*2, two with CYP2C19*1/*3, three with CYP2C19*3/*3, one with CYP2C19*2/*3); 28, into group 3 (24 with CYP2C19*1/*17, four with CYP2C19*17/*17); and 5, into group 4 (CYP2C19*2/*17). A significantly higher proportion of participants in group 3 experienced ischemic events (9 of 28, 32.1%) compared with group 1 (5 of 44, 11.4%; \( P = 0.04 \); odds ratio, 3.7; 95% confidence interval, 1.1–12.6). There was no significant difference in clopidogrel response among the 4 genotype groups.

CONCLUSIONS: Individuals with CYP2C19*17 may have increased risk of ischemic events following endovascular treatment, independent of clopidogrel responsiveness. Larger studies are required to confirm the influence of CYP2C19*17 on clinical outcomes and to understand the mechanisms for increased ischemic events.

ABBREVIATIONS: IQR = interquartile range; PRU = platelet reactivity unit

Endovascular treatment of cerebrovascular diseases, for example intracranial aneurysms and large artery stenosis, involves the placement of metallic coils or stents. These procedures are followed by increased thrombotic activity and platelet aggregation, resulting in ischemic complications. Clopidogrel is a commonly used antiplatelet drug to reduce the rate of procedure-related thrombosis.

Clopidogrel is a prodrug and requires hepatic metabolism mediated by the cytochrome P450 2C19 (CYP2C19) enzyme to produce the active R-130964 constituents. Active R-130964 permanently binds to P2Y12 G-protein-coupled platelet surface receptors to block the effects of adenosine diphosphate, leading to inhibition of platelet aggregation.

The response to clopidogrel varies widely among individuals. Up to 66% of patients with cerebrovascular disease have a reduced response to clopidogrel, placing them at higher risk of thrombosis, while 14.9%–38% of patients are hyper-responsive to
clopidogrel. Differing responses to clopidogrel may be related to CYP2C19 gene polymorphisms. Of particular clinical importance are the CYP2C19*2 and CYP2C19*3 alleles, more common in Asian descent than African and Caucasian descent, which reduce enzyme activity and have been associated with an increased incidence of stent thrombosis in coronary intervention studies. In contrast, CYP2C19*17 may increase hemorrhagic complications, but its impact on ischemic events and clinical outcome has not been definitively clarified.

The influence of CYP2C19 polymorphisms on outcomes to clopidogrel treatment has been poorly studied in patients with cerebrovascular disease compared with cardiovascular disease. Results from studies in coronary artery disease cannot be readily extrapolated to cerebrovascular disease owing to their different pathophysiology. Coronary artery studies focus mainly on clopidogrel hyporesponsiveness and ischemia as phenotypic outcomes because hemorrhagic complications are rare. However, both ischemia and hemorrhage are considerable risks for patients undergoing endovascular neurointervention.

We prospectively investigated the relationship among common CYP2C19 variants, clopidogrel response, and clinical outcomes in patients following neurointerventional procedures. We hypothesized that CYP2C19 variants were associated with clinical outcomes.

**MATERIALS AND METHODS**

**Subjects**

This was a prospective cohort study. Consecutive patients who underwent elective neurointervention for intracranial aneurysms or intracranial stenosis were prospectively recruited from The Royal Melbourne Hospital. The neurointervention procedures included simple coiling, balloon-assisted coiling, stent-assisted coiling, balloon and stent-assisted coiling, and Pipeline Embolization Device (Covidien, Irvine, California) flow-diversion stent placement of intracranial aneurysms and intracranial stenosis.

Inclusion criteria were the following: age older than 18 years, imaging evidence of intracranial aneurysms or intracranial stenosis intended for neurointervention, and ongoing use of clopidogrel on recruitment. Participants were excluded if there was significant coagulopathy, such as hemophilia, or other terminal medical comorbidities. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Royal Melbourne Hospital Human Research and Ethics Committee (HREC 2006.155).

Baseline demographic information for each participant included the following: age, sex, ethnicity (African, Asian, Caucasian), cerebrovascular risk factors (smoking history, diabetes, hypertension, hypercholesterolemia, atrial fibrillation, and peripheral vascular disease), size and location of the aneurysms, and indication for the procedure (stent placement or coiling of aneurysm or stenosis). All participants were prescribed clopidogrel, 75 mg/day, and aspirin, 150 mg/day, for at least 3 days before the procedures. Concomitant use of heparin, warfarin, and proton-pump inhibitors was noted.

**Ex Vivo Clopidogrel Response Testing**

Arterial blood samples were collected perioperatively through the angiographic puncture site of the femoral artery. Samples collected in sodium citrate tubes were rested at room temperature (25°C) for 30 minutes to 4 hours. After resting, the samples were tested for clopidogrel responsiveness by using the VerifyNow P2Y12 assay (Accutronics, San Diego, California) in accordance with the manufacturer’s instructions. The assay produces a value for inhibition of platelet activity in a percentage (percentage inhibition). This value indicates the level of active clopidogrel metabolite–P2Y12 receptor interaction, which inhibits platelet aggregation. According to the manufacturer’s manual, percentage inhibition is derived by the VerifyNow P2Y12 assay from the platelet reactivity unit (PRU) and baseline platelet thrombosis activity (BASE). The formula used to calculate percentage inhibition is Percentage Inhibition = (BASE − PRU) × 100/BASE.

**CYP2C19 Genotyping**

For each patient, a second blood sample was collected, from which genomic DNA was extracted by using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) and suspended in DNA Hydration Solution (Qiagen).

Genotyping for CYP2C19*2, *3, and *17 was performed by using polymerase chain reaction–restriction fragment length polymorphism as previously described (Genotyping). Each polymerase chain reaction contained GoTaq Hot Start Mastermix (Promega, Madison, Wisconsin; 400-μmol/L deoxyadenosine triphosphate, 400-μmol/L deoxyguanosine triphosphate, 400-μmol/L deoxyctydine triphosphate, 400-μmol/L deoxythymidine triphosphate, and 4-mmol/L magnesium chloride), 20-μM forward and reverse primers, nuclease-free water, and 50-ng DNA for *2 and *17 and 100-ng DNA for *3.

For CYP2C19*2, the 169-bp polymerase chain reaction product was digested by 200-U Smal (New England Biolabs, Ipswich, Massachusetts) at 25°C overnight. The CYP2C19*1 (wild type) yields a 120- and 49-bp product, whereas the CYP2C19*2 (681 G>A) variant is resistant to digestion.

The 636 G>A region for CYP2C19*3 identification was analyzed by digesting the 329-bp polymerase chain reaction product with 16-U BamHI (New England Biolabs) at 37°C for 2 hours. The CYP2C19*1 yields a 233- and 96-bp product, while the CYP2C19*3 variant was resistant to digestion.

The 470-bp polymerase chain reaction product (containing the 806 C>T region) was digested with 40-U SfaNI (New England Biolabs) at 37°C for 3 hours followed by enzyme inactivation at 65°C for 20 minutes. CYP2C19*1 yielded 3 products of 183, 142, and 113 bp. The CYP2C19*17 variant yielded 3 products of 217, 142, and 113 bp after digestion. The digested patterns for each genotype were separated on a 3% gel by electrophoresis.

To investigate the potential effect of different types of CYP2C19 polymorphisms, we classified the participants into 4 mutually exclusive genotype groups based on their expected phenotypic behavior.

**Clinical Outcomes**

A neurologist (B.Y.) specializing in cerebrovascular disease assessed the participants at 3 months after the procedure. Participants who were unable to attend clinics were contacted by telephone.

Clinical end points included cerebral ischemic events and intracerebral hemorrhage periprocedurally and at 3 months postprocedural, and 3-month postprocedural modified Rankin Scale score and mortality. Periprocedural complications included intraoperative clot formations. Three-month ischemic end points included transient ischemic attack (TIA) and symptomatic and asymptomatic (without symptoms but evident on repeat imaging) ischemic stroke. TIA was defined by an acute neurologic deficit that resolved within 1 hour without evidence of ischemia on neuroimaging. Ischemic stroke was defined by an acute neurologic deficit with evidence of ischemia on neuroimaging, without hemorrhage. Hemorrhagic complications included intracranial hemorrhages and any hemorrhage outside the cranium. Major hemorrhagic complications were defined if the participant required surgical intervention. Brain CT and angiography were performed as clinically indicated to identify vascular events.

The modified Rankin Scale score is a 6-scale score used to describe functional status. mRS 0–1 is generally regarded as good functional outcome, and mRS 2–6, poor functional outcome.21

**Statistical Analysis**

Group 1 comprised wild type carriers (CYP2C19*1/*1), who also acted as the control group. Group 2 comprised participants who carried CYP2C19*2 or CYP2C19*3 (presumed hypofunctioning alleles) in the absence of CYP2C19*17 (presumed hyperfunctioning allele). Group 3 comprised participants with CYP2C19*17 in the absence of CYP2C19*2 and CYP2C19*3. Group 4 comprised CYP2C19*2/*17 individuals (combination of hypo- and hyperfunctioning alleles). Group 1 was used as a reference group (because CYP2C19*1 is known to be the wild type variant) to facilitate the estimation of the effect of the inheritance of other polymorphisms on individual clopidogrel response and clinical outcome compared with the wild type.

Distribution of age and clopidogrel response among the 4 genotype groups was examined by using the Kruskal-Wallis test equality-of-population rank test. Imbalances in the proportion of vascular risk factors in the 4 genotype groups were tested by the Fisher exact test. Logistic regression analysis was used to investigate the association between the group membership and the categorical outcomes (ischemia, hemorrhage, good functional outcome [mRS 0–1]). The effect sizes for each outcome were estimated as odds ratios by using group 1 as a reference.

The statistical analyses were conducted by using STATA, Version 13 IC (StataCorp, College Station, Texas) and SPSS, Version 19 software (IBM, Armonk, New York). Due to the exploratory nature of this study, no adjustment for multiplicity of comparisons was made, and the value of \( P = .05 \) was the threshold for statistical significance for all the comparisons.

**RESULTS**

**Baseline Characteristics**

A total of 108 participants recruited from 2010 to 2013 were included in this study. Among them, 93 (86.1%) underwent endovascular treatment for unruptured aneurysms; 13, (12.0%) for intracranial stenosis; and 2 (1.9%), for venous sinus stenosis. Eleven (10.2%) participants underwent coiling alone, 26 (24.1%) underwent balloon-assisted coiling, and 13 (12.0%) underwent concurrent stent placement and coiling, while 7 (6.5%) required balloon-assisted stent placement and coiling. The median age was 56 years (interquartile range [IQR], 48.8–65.0), and 35 participants (32.4%) were men. Most (91.7%) were of white descent.

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There was no significant difference in the distribution of sex among the 4 groups (Kruskal-Wallis, \( P = .93 \)). There was also no significant difference in the distribution of sex in the genotype groups (Fisher exact test, \( P = .06 \)). No significant difference was found among the 4 genotype groups for cerebrovascular risk factors, such as history of cerebrovascular disease (transient ischemic attack, ischemic and hemorrhagic stroke), cigarette smoking, diabetes, hypertension, hypercholesterolemia, and atrial fibrillation or peripheral vascular disease (Fisher exact test \( P = .13, \) \( P = .73, \) \( P = .72, \) \( P = .61, \) \( P = .96, \) \( P = .91, \) \( P = .12, \) respectively).

**CYP2C19 Genotypes**

On the basis of the CYP2C19 genotypes, 44 participants were classified into group 1 (homozygous CYP2C19*1/*1); 31, into group 2 (25 with CYP2C19*1/*2, two with CYP2C19*1/*3, three with CYP2C19*3/*3, one with CYP2C19*2/*3; none had CYP2C19*2/*2). Twenty-eight were classified into group 3 (24 with CYP2C19*1/*17, four with CYP2C19*17/*17) and 5, into group 4 (CYP2C19*2/*17; none had CYP2C19*3/*17). There was no significant difference in the distribution of age, sex, and other cerebrovascular risk factors among the 4 CYP2C19 genotype groups.

**CYP2C19 Genotypes and Outcomes**

At 3 months postprocedural, 18 of 108 (16.7%) participants had experienced ischemic events, 16 (14.8%) had hemorrhagic complications (5 major and 11 minor), and 4 (3.7%) had complications of both a hemorrhagic and ischemic nature. Two of the ischemic complications occurred in the periprocedural period. Ninety-nine of 108 (91.7%) participants had good functional outcome at 3 months. One participant, who carried CYP2C19*1/*1, died (Tables 1 and 2).

A significantly higher proportion of participants in group 3 (CYP2C19*1/*17 or *17/*17) experienced ischemic events (9 of 28, 32.1%) compared with group 1 (CYP2C19*1/*1) individuals (5 of 44, 11.4%; \( P = .04; \) odds ratio, 3.7; 95% confidence interval, 1.1–12.6). The difference remained significant after adjustment for age (\( P = .03; \) OR, 4.0; 95% CI, 1.1–14.3) and ex vivo clopidogrel response (\( P = .04; \) OR, 4.5; 95% CI, 1.1–17.9). No significant differences between group 1 (5 of 44, 11.4%) and the other genotype groups, groups 2 (3 of 25, 9.7%) and 4 (1 of 5, 20%), were identified in the incidence of ischemia. Other adjustments for sex, history of cerebrovascular disease, and peripheral vascular disease did not have a significant influence on the results.

**Table 1: Clopidogrel response by genotype groups**

<table>
<thead>
<tr>
<th>Genotype Group</th>
<th>n</th>
<th>Percentage Inhibition (% in Group 1)</th>
<th>Fisher Exact Test, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=38)</td>
<td></td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=25)</td>
<td></td>
<td>17.0</td>
<td>.05</td>
</tr>
<tr>
<td>Group 2 (n=25)</td>
<td></td>
<td>30.0</td>
<td>.93</td>
</tr>
<tr>
<td>Group 3 (n=5)</td>
<td></td>
<td>30.0</td>
<td>.12</td>
</tr>
<tr>
<td>Group 4 (n=5)</td>
<td></td>
<td>32.0</td>
<td>.03</td>
</tr>
</tbody>
</table>

\(^a\) Group 1: CYP2C19*1/*1, Group 2: CYP2C19*1/*2/*3, Group 3: CYP2C19*1/*17/*17, Group 4: CYP2C19*2/*17.

\(^b\) Percentage inhibition = (BASE – PRU) × 100/BASE.
No significant differences between group 1 and the other genotypic groups were identified in the incidence of hemorrhage. Age is a known influencing factor on mRS. However, there was no significant difference in age-adjusted mRS between group 1 and the other genotypic groups.

**CYP2C19 Genotypes and Ex Vivo Clopidogrel Response**

Clopidogrel response was available in 93 participants. Of these participants, 38 of 44 (86.4%) were from group 1; 25 of 31 (80.1%), from group 2; 25 of 28 (89.3%), from group 3; and 5 of 5 (100%), from group 4. The median clopidogrel response was 37.5% inhibition (IQR, 12.0%–70.0%) for group 1, 17.0% (IQR, 6.0%–47.0%) for group 2, 30.0% (IQR, 12.0%–47.0%) for group 3, and 30.0% (IQR, 24.0%–54.0%) for group 4. Overall, there was no significant difference in clopidogrel response in terms of percentage inhibition among the 4 genotype groups (Kruskal-Wallis, P = .5). There was no significant difference in percentage inhibition among patients with no complications (26.0%; IQR, 1.0%–53.0%) compared with ischemic events (30.6%; IQR, 2.75%–51.0%; P = .5) and hemorrhagic events (47.9%; IQR, 31.5%–70.8%; P = .9).

PRU values were also compared between the genotype groups 2, 3, and 4 and group 1. The median PRU between group 1 and group 2 was not significant (237; IQR, 105–291 versus 261; IQR, 184–316; P = .78). Similarly, no significance was found between group 1 and group 4 (237; IQR, 105–291 versus 246; IQR, 195–281; P = .88). There appeared to be a significant difference between the median PRUs of group 1 and group 3 (237; IQR, 105–291 versus 232; IQR, 209–245; P = .03).

**Ex Vivo Clopidogrel Response and Clinical Outcomes**

Among the 93 participants with clopidogrel-response testing, 16 (17.2%) experienced ischemic events. There was no significant difference between the median clopidogrel response of participants who developed ischemic events ([n = 16] 15.5%; IQR, 2.5%–55.0%) compared with participants without ischemic events ([n = 77] 30.0%; IQR, 13.0%–65.0%) (P = .3).

Of the 93 participants with clopidogrel-response results, 14 (15.1%) experienced hemorrhagic events. The median clopidogrel response of participants who experienced hemorrhagic events was significantly higher ([n = 14] 46.0%; IQR, 30.0%–72.0%) compared with those who did not experience hemorrhages ([n = 22] 22.0%; IQR, 1.0%–53.0%) (P = .03).

There was no significance between the median PRU values for the ischemic-versus-nonischemic participants (253; IQR, 151.75–313.75 versus 244; IQR, 172–295; P = .44). Similarly, the median PRU evaluation was made for hemorrhagic-versus-nonhemorrhagic participants (211; IQR, 100–242 versus 249; IQR, 172.5–306.5; P = .60). These results showed no statistical significance.

**DISCUSSION**

Clopidogrel is a common antiplatelet prescribed to prevent secondary ischemia for patients with cerebrovascular conditions treated by endovascular techniques. However, variations in clopidogrel response associated with CYP2C19 polymorphisms may have a negative impact on treatment results.

Our investigation suggests increased risk of ischemic events in individuals carrying the CYP2C19*17 allele (group 3) compared with homozygous CYP2C19*1/*1 wild type carriers (group 1). CYP2C19*17 is generally thought to be hyperfunctioning; this feature should suggest an increased risk of hemorrhage. However, our study shows CYP2C19*17 to be significantly associated with ischemic events, despite no significant association with platelet activity. This novel finding is unexpected and leads us to suspect involvement of other pathways in the association between the CYP2C19 gene and clinical outcomes. Our study did not obtain data from imaging sources to interpret clinical outcomes but, instead, defined ischemic events evidenced by stroke or transient ischemic attacks in clinical follow-up only.

Correlation between CYP2C19*17 and secondary ischemic events following endovascular treatment of cerebrovascular disease has not been reported previously, to our knowledge. However, studies investigating the phenotypic effects of CYP2C19*17 are limited, and the influence of this polymorphism on the activity of clopidogrel, and hence clinical outcomes, remains controversial. Although a recent study in patients with myocardial infarction has suggested a significantly increased incidence of bleeding events and 1-year mortality rate among CYP2C19*17 carriers, others have found that CYP2C19*17 has minimal influence on clopidogrel response. The lack of association between CYP2C19*17 and the ex vivo clopidogrel response in the present study, along with conflicting findings in previous studies, suggests that the polymorphism may influence clinical outcomes via mechanisms independent of measured clopidogrel response in this patient population. This influence has not been previously investigated and deserves further exploration in future studies.

Compared with CYP2C19*17, CYP2C19*2 and CYP2C19*3 are well-documented as hypofunctioning alleles in healthy subjects and patients with coronary artery and cerebrovascular diseases. These alleles have also been reported to be significantly associated with subacute stent thrombosis and myocardial infarction following percutaneous coronary intervention. This correlation is understood to be a leading cause for increased risk of ischemic complications. Our results did not find CYP2C19*2 or CYP2C19*3 to be significantly associated with clinical outcome and clopidogrel response. However, the trends indicated in our results are reflective of those in previous literature.

In this study, CYP2C19 polymorphism was not associated significantly with mRS, a commonly used functional outcome in interventional studies of cerebrovascular disease. The inclusion of primarily participants undergoing elective procedures may explain the small number of poor functional outcomes recorded, with mRS ≥2 recorded in only 8.5% (7 of 106). This low incidence

Table 2: Postprocedural clinical outcomes by genotype groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 44)</th>
<th>Group 2 (n = 31)</th>
<th>Group 3 (n = 28)</th>
<th>Group 4 (n = 5)</th>
<th>Fisher Exact Test, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic complication (No.) (%)</td>
<td>5 (11.4)</td>
<td>3 (9.7)</td>
<td>9 (32.1)</td>
<td>1 (20.0)</td>
<td>.08</td>
</tr>
<tr>
<td>Hemorrhagic complication (No.) (%)</td>
<td>8 (18.2)</td>
<td>1 (3.2)</td>
<td>5 (17.9)</td>
<td>2 (40.0)</td>
<td>.06</td>
</tr>
<tr>
<td>mRS = 2 (No.) (%)</td>
<td>5 (11.4)</td>
<td>1 (3.2)</td>
<td>2 (7.1)</td>
<td>1 (20.0)</td>
<td>.35</td>
</tr>
</tbody>
</table>

*Group 1: CYP2C19*1/*1, Group 2: CYP2C19*2/*2, */3, */2/*3, Group 3: CYP2C19*/17, */17, Group 4: CYP2C19*/17."
of poor clinical outcome limited our ability to draw conclusions concerning the influence of CYP2C19 genotypes on functional outcomes. Further studies to validate the association between CYP2C19 polymorphisms and functional outcomes are needed because cerebrovascular complications (ischemia and hemorrhage) are major contributors of morbidity.

Our results did not show a significant association between clopidogrel response and CYP2C19 polymorphisms and clinical outcome. Point-of-care clopidogrel response testing platforms such as the VerifyNow P2Y12 assay could add clinical benefits for patients receiving endovascular neurointervention, provided that standardized values predicting response (ischemia and hemorrhage) can be defined. However, there is currently no standard definition for VerifyNow P2Y12 assay values. Values assigned to define clopidogrel hyporesponsiveness in previous studies vary widely between 15%16 and 40%,27 though the cutoff value of 20% is commonly used.10,28 Likewise, there is no standard VerifyNow between the PRU values in CYP2C19**17 comes of our study, ischemia and hemorrhage, compared to no complications. Similarly, no significance was found in PRU values of clopidogrel hyperresponsiveness. However, the PRU values were not found to be statistically significant for the clinical outcomes of our study, ischemia and hemorrhage, compared to no complications. Similarly, no significance was found in PRU values of CYP2C19**17 compared with the wild type. However, the PRU values in CYP2C19**17 carriers were significantly lower compared with the wild type. The influence of CYP2C19**17 on platelet reactivity is an area that requires more research.

The findings in our study were novel. However, the mechanism by which CYP2C19*17 influenced clinical outcomes remains undefined because we did not find a significant correlation between the CYP2C19*17 genotype and platelet activity. The main limitation of the present study was the small sample size, and the elective nature of the endovascular treatments was likely a contributing factor to low rates of poor functional outcomes.

CONCLUSIONS

Our results suggest an increased risk of ischemic events in carriers of CYP2C19*17 who undergo neurointervention. Further research to validate the association and to understand the underlying biologic mechanisms is warranted.

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REFERENCES


Large-Vessel Occlusion Is Associated with Poor Outcome in Stroke Patients Aged 80 Years or Older Who Underwent Intravenous Thrombolysis

Wusheng Zhu, MD, PhD,*† Lulu Xiao, MD,* Monica Lin, BSc,† Xinfeng Liu, MD, PhD,* and Bernard Yan, FRACP†

Objective: We aimed to investigate the association between large-vessel occlusion (LVO) and functional outcome in elderly stroke patients treated with intravenous (IV) tissue plasminogen activator (tPA). Methods: This was a retrospective study of acute ischemic stroke patients who received IV tPA within 4.5 hours after stroke onset between 2007 and 2013. Patients were categorized into 2 groups based on age (≥80 or <80 years). LVO was evaluated by computed tomography angiography (CTA) before thrombolysis. Favorable outcome was defined as a modified Rankin Scale (mRS) score of 2 or lower at 3 months, or equal to the prestroke mRS score. Results: Of 359 thrombolysis patients, 175 patients with CTA before a standard dose of IV tPA therapy (0.9 mg/kg body weight; maximum 90 mg) were included. Sixty-five patients were in the group aged 80 years or above with a median age of 84 (interquartile range: 82.5, 86) years. LVO was observed more often in the group with unfavorable outcome compared with the group with favorable outcome in older stroke patients (60.6% versus 21.9%, \( P = .002 \)). The baseline National Institutes of Health Stroke Scale (NIHSS) score (odds ratio .864; 95% confidence interval [CI], .779-.959; \( P = .006 \)) and LVO (odds ratio .233; 95% CI, .059-.930; \( P = .039 \)) were independent associative factors for the unfavorable outcome in older patients treated with IV tPA after adjustment for patient characteristics. Conclusions: The baseline NIHSS score and LVO were independent predictors for functional outcome in elderly stroke patients received IV tPA. Key Words: Stroke—elderly—intravenous thrombolysis—CT angiography—modified Rankin scale. © 2016 National Stroke Association. Published by Elsevier Inc. All rights reserved.

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**Introduction**

A recent meta-analysis of individual patient data from randomized trials showed that alteplase significantly improves the overall good outcome when stroke patients received alteplase within 4.5 hours of stroke onset. Elderly patients have been accounted for 30% of all acute ischemic stroke patients. However, there is no consensus regarding thrombolysis for stroke patients over 80 years. Although some large-scale randomized controlled clinical trials exclude acute stroke patients aged 80 years or older from intravenous (IV) thrombolysis for its under-representation, there has been an increase in the proportion of elderly patients who underwent IV thrombolysis in recent years. Moreover, it is becoming clear that a proportion of stroke patients aged 80 years or older derive significant benefit from IV thrombolysis, even in patients aged 90 years or older. It is critical to clarify outcome predictors for this group of patients.

The baseline National Institutes of Health Stroke Scale (NIHSS) score has been validated as the predictor of mortality and unfavorable outcome in stroke patients aged 80 years or older who underwent thrombolysis, but vascular imaging predictors remain uncertain. Large-vessel occlusion (LVO) is a predictor of poor outcome in acute ischemic stroke. Computed tomography angiography (CTA) is an accurate tool for the assessment of LVO; however, CTA may be more risky in patients aged 80 years or older because of higher prevalence of renal failure. Therefore, it is important to establish the utility of CTA prior to recommending its routine use in 80-year-old patients.

The aim of the present study was to investigate the association between LVO and outcome in acute ischemic stroke patients aged 80 years or older who underwent IV tissue plasminogen activator (tPA) therapy, to test the hypothesis that LVO is associated with poor outcomes in these patients.

**Methods**

**Patients**

We analyzed the medical records of 359 acute ischemic stroke patients admitted to the Royal Melbourne Hospital who were treated with IV tPA within 4.5 hours of stroke onset, between December 2007 and February 2013. Eligibility criteria included patients with computed tomography (CT)-confirmed acute ischemic stroke who were administered .9 mg/kg of IV tPA within 4.5 hours of onset of symptoms. The following characteristics were included: age, sex, prestroke modified Rankin Scale (mRS) score, onset-to-treatment time, vascular risk factors (hypertension, diabetes, hypercholesterolemia, atrial fibrillation, smoking, ischemic heart disease, and previous stroke), baseline NIHSS score, CTA before IV tPA, CT or magnetic resonance imaging after IV tPA, and 3-month mRS score. The patients were divided into 2 groups by age: older group (aged ≥80 years) and younger group (aged <80 years). Patients diagnosed with stroke mimics or patients who received IV tPA plus intra-arterial (IA) therapy were excluded from our study.

**Imaging**

CTA was routinely performed in acute ischemic stroke patients before thrombolysis at the Royal Melbourne Hospital from December 2007, unless contraindicated (e.g., known contrast allergy or renal impairment). LVO was identified as proximal vessel occlusion as follows: internal carotid artery, middle cerebral artery (M1 and M2 segments), anterior cerebral artery (A1 segment), V4 segment of vertebral artery, basilar artery, and posterior cerebral artery (P1 segment). CT or magnetic resonance imaging scans were performed approximately within 24 hours of IV tPA to identify the hemorrhagic transformation and the extent of infarction. Symptomatic intracerebral hemorrhage was defined as blood at any site in the brain associated with a worsening of the NIHSS score by 4 points or higher within 24 hours. The presence of LVO was assessed on CTA image by 2 independent experienced stroke neurologists (W.Z. and B.Y.). The symptoms of the acute ischemic stroke patients were consistent with LVO.

**Outcome**

The primary outcome was the 3-month mRS score. Favorable outcome was defined as an mRS score of 2 or lower at 3 months, or equal to the prestroke mRS score. Secondary outcomes were symptomatic intracerebral hemorrhage after IV tPA and mortality at 3 months post stroke.

**Statistical Analysis**

Statistical analysis was performed using the SPSS (version 19; SPSS Inc., Chicago, IL). Between-group differences were made using the Student t-test or the Mann–Whitney U-test for continuous variables, chi-square test, or the Fisher exact test for categorical variables. Logistic regression was used to test predictors of unfavorable outcome in elderly stroke patients (aged ≥80 years) who received IV tPA. The model was adjusted for patient characteristics (diabetes, hypertension, smoking, atrial fibrillation, prior stroke history, hypercholesterolemia, LVO, and NIHSS score on admission). All statistical tests were 2-sided, and P values less than .05 were considered to be statistically significant.

**Results**

**Baseline Characteristics**

In our tPA database, 243 acute ischemic stroke patients who underwent CTA before IV tPA therapy were screened (243 of 359 thrombolysis patients, 67.7%).
Sixty-eight patients were excluded from the study: 40 patients underwent bridging therapy (IV tPA plus IA), 17 patients were lost to follow-up, 6 patients did not have baseline NIHSS scores, and 5 patients were stroke mimics. We finally included 175 patients who had the following characteristics: 104 male patients (59.4%), 126 patients with pre-mRS score of 0, 3 patients with a pre-mRS score of 1, 13 patients with a pre-mRS score of 2, 19 patients with pre-mRS score of 3, and 14 patients with pre-mRS score of 4. The median age was 74 years (interquartile range [IQR]: 64-83), and the median baseline NIHSS score was 9 (IQR: 5-16).

Comparison of Baseline Characteristics and Outcome between Older and Younger Patients

Of the 175 patients, 65 (37.1%) were 80 years old or older with a median age of 84 years (IQR: 82.5-86.0). Of the 65 patients, 32 (49.2%) were male and the mean baseline NIHSS score was 11 (IQR: 5-17). As for younger patients (aged <80 years), the mean age was 68 (IQR: 58-73) years and the median baseline NIHSS score was 8 (IQR: 5-14).

Older stroke patients were more likely to have arterial hypertension (75.4% versus 59.1%, \( P = .029 \)), history of atrial fibrillation (41.5% versus 25.5%, \( P = .027 \)), previous stroke history (18.5% versus 9.1%, \( P = .071 \)), high prestroke mRS score (\( P < .001 \)), and high mortality rate (23.1% versus 8.2%, \( P = .006 \)). The patients were less likely to be a male (49.2% versus 65.5%, \( P = .035 \)) or current smokers (9.2% versus 28.2%, \( P = .003 \)) or have favorable outcome. There was no difference in the prevalence of LVO between older and younger patients (41.5% versus 39.1%, \( P = .749 \)). A comparison of baseline characteristic and outcome between older and younger groups is shown in Table 1.

Factors Associated with Functional Outcome in Older Patients

The factors associated with functional outcome in older stroke patients treated with IV tPA are given in Table 2. High baseline NIHSS score (14.9 ± 6.9 versus 8.7 ± 6.0, \( P < .001 \)) and LVO (60.6% versus 21.9%, \( P = .002 \)) occurred more frequently in the unfavorable outcome group than in the favorable outcome group. After adjustment for patient characteristics, logistic regression showed that baseline NIHSS score (odds ratio .864; 95% confidence interval, .779-.959; \( P = .006 \)) and LVO (odds ratio .233; 95% confidence interval, .059-.930; \( P = .039 \)) remained the significant predictors for unfavorable outcome in older patients treated with tPA (Table 3).

| Table 1. Baseline characteristics and outcome of older (age ≥ 80) and younger (age < 80) stroke patients who underwent thrombolysis |
|---|---|---|
| Characteristics | Age 80 years or older (n = 65) | Age younger than 80 (n = 110) | \( P \) value |
| Male, n (%) | 32 (49.2) | 72 (65.5) | .035* |
| Age (years), median (IQR) | 84 (82.5-86.0) | 68 (58-73) | <.001* |
| Prestroke mRS score of 0-2, n (%) | 44 (67.7) | 98 (89.1) | <.001* |
| Onset to treat time (min), mean (SD) | 159.8 ± 50.1 | 160.1 ± 58.4 | .967 |
| Baseline NIHSS score, median (IQR) | 11 (5-17) | 8 (5-14) | .194 |
| Hypertension, n (%) | 49 (75.4) | 65 (59.1) | .029* |
| Diabetes, n (%) | 11 (16.9) | 31 (28.2) | .092 |
| Hypercholesterolemia, n (%) | 37 (56.9) | 53 (48.2) | .264 |
| Atrial fibrillation, n (%) | 27 (41.5) | 28 (25.5) | .027* |
| Previous stroke history, n (%) | 12 (18.5) | 10 (9.1) | .071 |
| Current smoker, n (%) | 6 (9.2) | 31 (28.2) | .003* |
| Ischemic heart disease, n (%) | 18 (27.7) | 22 (20.0) | .242 |
| Peripheral vascular disease, n (%) | 1 (1.5) | 6 (5.5) | .261 |
| Large-vessel occlusion, n (%) | 27 (41.5) | 43 (39.1) | .749 |
| Internal carotid artery, n (%) | 7 (10.8) | 10 (9.1) | .749 |
| Middle cerebral artery, n (%) | 18 (27.7) | 32 (29.1) | .749 |
| Posterior cerebral artery, n (%) | 2 (3.1) | 1 (9.1) | .749 |
| Favorable outcome, n (%) | 32 (49.2) | 77 (70) | .006* |
| Symptomatic ICH, n (%) | 4 (6.2) | 3 (2.7) | .426 |
| Mortality, n (%) | 15 (23.1) | 9 (8.2) | .006* |

Abbreviations: ICH, intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

*\( P < .05 \).
The major result of our study demonstrated that LVO was significantly related to unfavorable outcome in elderly stroke patients aged \( \geq 80 \) years who received IV tPA. Age has been shown to be associated with unfavorable collateral circulation.\(^{18,19}\) Based on our results, we suggest that elderly stroke patients with LVO be selected to undergo IA therapy. Compared with elderly stroke patients receiving IV tPA alone, the risk of in-hospital mortality for patients undergoing IA therapy plus IV tPA has not increased.\(^{20}\) IA therapy has been shown to have an equal recanalization rate and hemorrhage rate between elderly patients and younger patients.\(^{21,22}\) Elderly stroke patients may achieve favorable outcomes after recanalization by endovascular treatment.\(^{22,23}\) However, the study of Chandra et al showed that elderly patients had poor clinical outcome and higher mortality at 90 days, compared with nonelderly patients after IA therapy.\(^{24,25}\) A meta-analysis showed that elderly patients had higher rates of mortality and intracerebral hemorrhage at 3 months than younger patients after IA therapy.\(^{24,25}\) Results of the meta-analysis have shown that ASPECTS and NIHSS scores were independent predictors of favorable outcome in elderly patients for anterior circulation LVO after mechanical thrombectomy.\(^{26}\) The risks and benefits of IA therapy needed to be assessed before performance of the treatment.\(^{25}\)

The baseline NIHSS score was the important independent predictor of unfavorable outcome in elderly stroke patients treated with tPA in our study, which was consistent with previous findings.\(^{13}\) Besides, the mortality rate at 3 months was higher in older patients than in younger patients in our study, which is now well acknowledged. Each patient underwent emergency CTA before IV tPA therapy in our study. CTA is an accurate and safe tool for evaluating intracranial vessel stenosis or occlusion.\(^{27,28}\) CTA detects LVO with 100% sensitivity and specificity compared to digital subtraction angiography.\(^{29}\) In our study, CTA was routinely performed in stroke patients before thrombolysis, unless contraindicated (e.g., known contrast allergy or renal impairment). Results have shown that the safety of elderly patients who underwent CTA may be acceptable if the patients were selected. Several limitations of our study have to be addressed. First, our study was a relatively small single-center cohort study and longitudinal studies are required to confirm our findings. Second, 40 patients who received bridging therapy (IV tPA plus IA) were excluded in our study. The exclusion of these patients introduced select bias in the proportion of LVO in our study. Third,

### Table 2. Factors associated with 3-month functional outcome in older (age \( \geq 80 \)) stroke patients received IV tPA

<table>
<thead>
<tr>
<th>Factors</th>
<th>Favorable outcome (n = 32)</th>
<th>Unfavorable outcome (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>16 (50.0)</td>
<td>16 (48.5)</td>
<td>.903</td>
</tr>
<tr>
<td>Onset to treat time (min), mean (SD)</td>
<td>158.8 ± 52.3</td>
<td>160.8 ± 48.6</td>
<td>.869</td>
</tr>
<tr>
<td>Baseline NIHSS score, mean (SD)</td>
<td>8.7 ± 6.0</td>
<td>14.9 ± 6.9</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>25 (78.1)</td>
<td>24 (72.7)</td>
<td>.614</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>5 (15.6)</td>
<td>6 (18.2)</td>
<td>.783</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>20 (62.5)</td>
<td>17 (51.5)</td>
<td>.371</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>13 (40.6)</td>
<td>14 (42.4)</td>
<td>.883</td>
</tr>
<tr>
<td>Previous stroke history, n (%)</td>
<td>5 (15.6)</td>
<td>7 (21.2)</td>
<td>.562</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>3 (9.4)</td>
<td>3 (9.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>8 (25.0)</td>
<td>10 (30.3)</td>
<td>.633</td>
</tr>
<tr>
<td>Large-artery occlusion, n (%)</td>
<td>7 (21.9)</td>
<td>20 (60.6)</td>
<td>.002*</td>
</tr>
<tr>
<td>Internal carotid artery, n (%)</td>
<td>1 (3.1)</td>
<td>6 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery, n (%)</td>
<td>6 (18.8)</td>
<td>12 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral artery, n (%)</td>
<td>0 (0)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic ICH, n (%)</td>
<td>0 (0)</td>
<td>4 (12.1)</td>
<td>.114</td>
</tr>
<tr>
<td>ICH, n (%)</td>
<td>3 (9.4%)</td>
<td>9 (27.2%)</td>
<td>.063</td>
</tr>
</tbody>
</table>

Abbreviations: ICH, intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

*P < .05.

### Table 3. Multivariate analysis for favorable outcomes at 3 months in older (age \( \geq 80 \)) stroke patients treated with IV tPA

<table>
<thead>
<tr>
<th>Factors</th>
<th>Favorable outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-vessel occlusion</td>
<td>.233</td>
<td>.059-.930</td>
<td>.039*</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>.864</td>
<td>.779-.959</td>
<td>.006*</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

*P < .05.

### Discussion

The major result of our study demonstrated that LVO was significantly related to unfavorable outcome in elderly stroke patients aged 280 years who received IV tPA. Age has been shown to be associated with unfavorable collateral circulation.\(^{18,19}\) Based on our results, we suggest that elderly stroke patients with LVO be selected to undergo IA therapy. Compared with elderly stroke patients receiving IV tPA alone, the risk of in-hospital mortality for patients undergoing IA therapy plus IV tPA has not increased.\(^{20}\) IA therapy has been shown to have an equal recanalization rate and hemorrhage rate between elderly patients and younger patients.\(^{21,22}\) Elderly stroke patients may achieve favorable outcomes after recanalization by endovascular treatment.\(^{22,23}\) However, the study of Chandra et al showed that elderly patients had poor clinical outcome and higher mortality at 90 days, compared with nonelderly patients after IA therapy.\(^{24,25}\) A meta-analysis showed that elderly patients had higher rates of mortality and intracerebral hemorrhage at 3 months than younger patients after IA therapy.\(^{24,25}\) Results of the meta-analysis have shown that ASPECTS and NIHSS scores were independent predictors of favorable outcome in elderly patients for anterior circulation LVO after mechanical thrombectomy.\(^{26}\) The risks and benefits of IA therapy needed to be assessed before performance of the treatment.\(^{25}\)

The baseline NIHSS score was the important independent predictor of unfavorable outcome in elderly stroke patients treated with tPA in our study, which was consistent with previous findings.\(^{13}\) Besides, the mortality rate at 3 months was higher in older patients than in younger patients in our study, which is now well acknowledged. Each patient underwent emergency CTA before IV tPA therapy in our study. CTA is an accurate and safe tool for evaluating intracranial vessel stenosis or occlusion.\(^{27,28}\) CTA detects LVO with 100% sensitivity and specificity compared to digital subtraction angiography.\(^{29}\) In our study, CTA was routinely performed in stroke patients before thrombolysis, unless contraindicated (e.g., known contrast allergy or renal impairment). Results have shown that the safety of elderly patients who underwent CTA may be acceptable if the patients were selected. Several limitations of our study have to be addressed. First, our study was a relatively small single-center cohort study and longitudinal studies are required to confirm our findings. Second, 40 patients who received bridging therapy (IV tPA plus IA) were excluded in our study. The exclusion of these patients introduced select bias in the proportion of LVO in our study. Third,
underwent IV tPA therapy.

Conclusions
LVO and baseline NIHSS score are the independent predictors of outcome in elderly stroke patients who underwent IV tPA therapy.

References
Review

Suboptimal response to clopidogrel: A genetic risk factor for recurrent ischaemic stroke

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A B S T R A C T

Anti-platelet agents (APA) are widely used in the secondary prevention of ischaemic stroke but about 30% of patients derive suboptimal platelet inhibition from APA. An underlying cause for suboptimal platelet inhibition is varying response to clopidogrel, which is linked to polymorphisms in the CYP2C19 gene responsible for the metabolism and activation of clopidogrel. CYP2C19 polymorphism influences clinical outcomes in patients with coronary artery disease, particularly among those treated with percutaneous transluminal coronary artery stenting. Randomized controlled trials have shown that high doses of clopidogrel can overcome suboptimal platelet response in carriers of the CYP2C19*2 allele. The United States Food and Drug Administration has issued a boxed warning advising clinicians to consider genotyping patients prior to prescribing clopidogrel. There are ongoing studies investigating the clinical utility of genotyping to inform management decisions in stroke prevention.

1. Introduction

Stroke is Australia’s second most common cause of death after coronary heart disease and a leading cause of disability.1 In 2011, Australians suffered an estimated 60 000 new and recurrent strokes, equivalent to one stroke every 10 minutes.1 Stroke costs Australia an estimated $2.14 billion per year.1 Australia’s ageing population will see the incidence and burden of disease caused by stroke continue to increase annually. In recent years studies have highlighted the importance of suboptimal response to clopidogrel and increased risk of major cardiovascular events.2 It follows that suboptimal response to clopidogrel places patients with ischaemic stroke at increased risk of recurrent events, given the common underlying pathophysiology between cardiovascular and cerebrovascular ischaemia. This review aims to highlight the current understanding of variable response to clopidogrel and its implications for stroke prevention.

2. Anti-platelets and ischaemic stroke

Anti-platelet agents (APA) have proven benefits in secondary prevention of ischaemic stroke.3 Acetylsalicylic acid is the traditional first line agent in prevention of ischaemic stroke with a 22% reduction in the odds of a recurrent stroke.4 Clopidogrel first came to the fore as an alternative APA in stroke prevention following landmark trials in the late 1990s.5 The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial demonstrated an 8.7% reduction in relative risk (RR) in favour of clopidogrel over acetylsalicylic acid for prevention of ischaemic stroke, myocardial infarction (MI) or vascular death among high risk patients. It followed that dual anti-platelet therapy with acetylsalicylic acid plus clopidogrel has become the standard of care for treatment of acute coronary syndrome (ACS), ST segment elevation MI and following percutaneous coronary intervention (PCI).5 The combination of acetylsalicylic acid plus clopidogrel in patients with stroke, however, increases the risk of haemorrhagic complications with no significant increase in protection from recurrent ischaemic stroke.6

3. Recurrent stroke: a possible expression of suboptimal platelet inhibition

Despite widespread use of APA, the rate of recurrent stroke remains a significant concern at approximately 6–9% per year after a first-ever stroke.7 Studies investigating acetylsalicylic acid resistance in the ischaemic stroke population have shown the incidence of acetylsalicylic acid resistance to be up to 30%.8 Acetylsalicylic acid resistance increases the risk of adverse vascular events among patients with stable cardiovascular and cerebrovascular disease (hazard ratio [HR] 4.1 95% confidence interval [CI] 1.42–12.06, \( p = 0.009 \)).9 There is ongoing interest in optimising APA therapy in ischaemic stroke. The Platelet-Orientated Inhibition in New TIA or Minor Ischaemic Stroke (POINT) study is recruiting study participants.
subjects and aims to investigate the effect of early clopidogrel plus acetylsalicylic acid compared to acetylsalicylic acid alone in new onset minor cerebrovascular ischaemic events. The rationale for POINT is that clopidogrel may provide additional benefit to patients by acting via an independent biochemical pathway.

4. Clopidogrel metabolism

Clopidogrel is a pro-drug that, once metabolized to its active form, irreversibly inhibits platelet aggregation by blocking the platelet P2Y_{12} adenosine diphosphate (ADP) receptor (Fig. 1). The pharmacodynamic and pharmacokinetic effect of clopidogrel demonstrates significant interindividual variation. A proposed mechanism for this variation is polymorphism of the genes encoding hepatic cytochrome p450 (CYP) isoenzymes. These enzymes catalyse the oxidation of clopidogrel into its active form through two oxidizing steps. The major enzyme contributing to both steps in the biotransformation of clopidogrel is the CYP2C19 isoform.

5. Genetics and clopidogrel

Several genetic variations of the CYP2C19 gene have been analyzed and are associated with varying levels of the active clopidogrel metabolite. There are numerous alleles of the CYP2C19 gene, labeled according to the accepted star nomenclature (*). The most widely studied alleles are *1, *2 and *3. The CYP2C19*1 allele is fully functional, leading to extensive metabolism of clopidogrel into its active form. The alleles CYP2C19*2 and CYP2C19*3 are non-functional, which results in reduced metabolism.

Mega et al. demonstrated that, in healthy patients who were carriers of at least one reduced-function allele, there is a 32% relative reduction in plasma exposure to the active clopidogrel metabolite compared to non-carriers. The reduced level of active clopidogrel metabolite was correlated with a 25% relative reduction in platelet inhibition as measured by light transmission aggregometry (P < 0.001). Other alleles of the CYP2C19 gene, which include CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7 and CYP2C19*8, may also be associated with reduced or non-functional enzymes, although these alleles occur at low frequency on a population level.

6. CYP2C19 polymorphisms in different racial groups

The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced-function alleles, occurring in 85% of people of Caucasian descent and 99% of Asian descent who are carriers of a loss-of-function allele. Conversely the CYP2C19*17 allele is associated with increased metabolism of clopidogrel and thus increased platelet inhibition, potentially causing increased risk of bleeding, but this has not been shown in large randomized trials.

Overall approximately 30% of Caucasians, 50% of Asians and 40% of Africans are heterozygous for a reduced-function allele. Although several studies have demonstrated the pharmacological effect of CY2C19 polymorphism on response to clopidogrel, the data correlating reduced-function alleles with increased risk of clinical events are limited. There are almost no data for the analysis of the relationship between CYP2C19 alleles and the risk of cerebral ischaemic events.

7. Clinical significance of CYP2C19 polymorphism in ischaemic stroke

The United States Food and Drug Administration (FDA) issued a “boxed warning” for clopidogrel in March 2010. The FDA advised clinicians to be aware that the effect of clopidogrel is reduced among patients with reduced-function CYP2C19 alleles, and that tests are available to determine the CYP2C19 genotype. This announcement was based on results from a study of 40 healthy individuals randomised to treatment with 300 mg followed by 75 mg daily, and 600 mg followed by 150 mg daily for 5 days, in a crossover design. The study determined the CY2C19 genotype of each patient, finding that carriers of reduced-function alleles demonstrated decreased active drug metabolite levels and reduced inhibition of platelets. The warning, however, left the role for genotype testing at the discretion of the physician due to lack of data that correlated these findings with clinical events.

In 2010 Mega et al. published a meta-analysis of nine studies evaluating CYP2C19 genotype and cardiovascular outcomes in 9685 patients. Within the study population 91.3% underwent PCI, of whom 54.5% were patients with ACS, and all were treated with clopidogrel. This meta-analysis showed that the risk of composite outcome of cardiovascular death, MI or stroke was increased among patients with one reduced-function allele (HR 1.55, 95% CI 1.11–2.17, P = 0.01) and a greater risk was found for those with two reduced-function alleles (HR 1.76, 95% CI 1.24–2.50, P = 0.02) compared to non-carriers. There was a trend towards increased risk of non-fatal ischaemic stroke associated with carriers of at least one reduced-function allele (HR 1.73 95% CI 0.68–4.38, P = 0.25); however, due to the low rate of stroke in the study cohort, this was not statistically significant.

The Pare et al. study had contrasting results to those of the Mega et al. meta-analysis. Pare et al. genotyped patients from two large randomized controlled trials. These trials were the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, which included 5059 patients with ACS, and the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) study, which included 1156 patients with atrial fibrillation. In both trials all patients were randomized to receive...
clopidogrel or placebo in addition to acetylsalicylic acid. All patients were genotyped for CYP2C19 allele *1, *2, *3 and *17. The study failed to show an increased risk of clinical events associated with CYP2C19 loss-of-function alleles among patients with ACS. This study has issues that limit its application to the ischaemic stroke population.

The magnitude of risk reduction associated with clopidogrel is greatest in patients undergoing PCI. Patients undergoing PCI are therefore at an even greater risk as a result of suboptimal response to clopidogrel. Studies have shown up to 3.6 times the increased risk of adverse events among patients carrying 2 CYP2C19 loss-of-function alleles undergoing PCI compared to non-carriers. This highlights the importance of platelet inhibition in stabilizing atherothrombotic plaques and preventing stent thrombosis. It is not surprising that among patients with atrial fibrillation, the CYP2C19 genotype did not show a significant effect on clopidogrel efficacy. The purpose of acetylsalicylic acid and clopidogrel therapy in the ACTIVE study was to substitute for warfarin to prevent embolic events rather than to specifically prevent atherothrombotic events.

Holmes et al. also conducted a systemic review that looked at CYP2C19 genotype in cardiovascular patients. This meta-analysis of 32 studies confirmed a reduction in platelet inhibition among carriers of CYP2C19 loss-of-function alleles who received standard dose clopidogrel. The investigators found an overall RR of 1.18 (95% CI 1.09-1.28) for cardiovascular events among carriers of CYP2C19 reduced-function alleles compared to non-carriers in a treatment only analysis. When Holmes et al. reported the effect of CYP2C19 genotype on clinical outcomes using an effect modification analysis, they included only four placebo-controlled randomized trials. These four trials included the ACTIVE-A and CURE trials, which comprised the same data set as used by Pare et al. It is, therefore, not surprising that Holmes et al. reported similar findings to Pare et al. in failing to show significant evidence of an association between the CYP2C19 genotype and clinical outcomes.

8. Overcoming suboptimal clopidogrel response in patients with ischaemic stroke

8.1. Alternative maintenance dosing

Mega et al. published a recent study showing that higher doses of clopidogrel can overcome suboptimal platelet inhibition. The randomized double blind controlled trial published late in 2011 included 333 genotyped patients with stable cardiovascular disease taking an acetylsalicylic acid and varying daily maintenance doses of clopidogrel (75 mg, 150 mg, 225 mg and 300 mg). Patients heterozygous for the CYP2C19*2 allele taking an increased maintenance dose of clopidogrel at ≥ 225 mg or greater achieved platelet inhibition equivalent to that among non-carriers taking a standard dose of 75 mg (p < 0.01 for trend). This effect was not demonstrated among patients homozygous for the CYP2C19*2 allele with a failure to optimise platelet inhibition at a maintenance dose up to 300 mg.

The trial included only six patients homozygous for the CYP2C19*2 allele; thus it is poorly powered to detect association in this subgroup. No association between clinical events or bleeding risk with clopidogrel maintenance dose among carriers of the CYP2C19*2 allele was demonstrated. In addition the treatment period of 14 days was not sufficient to observe an effect on clinical outcomes among patients with stable cardiovascular disease. To our knowledge there are no prospective studies showing a clinical benefit to personalising clopidogrel dose based on genotype.

8.2. Novel anti-platelet agents in stroke prevention

Newer APA have been suggested in patients with suboptimal response to clopidogrel. These agents include prasugrel, cilostazol and ticagrelor. Prasugrel is a pro-drug, requiring biotransformation into an active metabolite via CYP450 enzymes. Prasugrel is less reliant on the CYP2C19 isoenzyme than clopidogrel and as such demonstrates less variation in pharmacodynamic and pharmacokinetic response. The analysis of the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON–TIMI 38) study demonstrated reduced ischaemic events in patients with ACS undergoing PCI with prasugrel compared to clopidogrel. This study also showed an increased risk of adverse outcomes and major bleeding associated with prasugrel among patients who had a previous stroke or transient ischaemic attack (HR 1.54; 95% CI, 1.02–2.32, P = 0.04). As such prasugrel should not be considered in ischaemic stroke patients as an alternative to clopidogrel.

Cilostazol is potent inhibitor of phosphodiesterase, reducing platelet aggregation by affecting adenosine reuptake, nitric oxide and prostaglandin production. A Cochrane systematic review published in 2011, and including two randomised controlled trials, showed that among 3477 Asian patients with recent ischaemic stroke, cilostazol was associated with a reduced risk of stroke of all types compared to acetylsalicylic acid (RR 0.67, 95% CI 0.52–0.86). Cilostazol was also associated with a lower risk of haemorrhagic stroke (RR 0.25, 95% CI 0.13–0.55) but an increase in minor adverse events (RR 1.66, 95% CI 1.51–1.83). Further studies are needed to compare cilostazol with clopidogrel among patients with ischaemic stroke.

Ticagrelor is a rapidly acting reversible ADP receptor antagonist which does not require metabolic activation. Analysis of the PLATelet inhibition and patient Outcomes (PLATO) trial found ticagrelor was superior to clopidogrel in reducing cardiovascular events among patients with ACS. Ticagrelor was also associated with increased major bleeding complications compared to clopidogrel (4.5% vs. 3.8% P = 0.03), including fatal intracranial haemorrhage. There are limited data available for use of ticagrelor in ischaemic stroke prevention but, as with many of the novel more potent APA, increased bleeding risk is likely to prevent its widespread use in secondary stroke prevention.

9. Inhibitors of CYP2C19 and clopidogrel efficacy

Inhibitors of the CYP2C19 isoenzyme are a potential cause of suboptimal response to clopidogrel through reducing the metabolism and bioavailability of metabolites required for platelet inhibition. Several drugs have been implicated in the inhibition of the CYP2C19 isoenzyme including statins and calcium channel blockers; however, proton pump inhibitors (PPI), in particular omeprazole, have been most strongly implicated. The effect of PPI on clopidogrel efficacy has been widely studied over the last decade.

Numerous studies indicate that PPI reduce the in vitro activity of clopidogrel. Angiolillo et al. demonstrated a reduction in active clopidogrel metabolites and increased platelet aggregation by approximately 40% and 8% respectively when coadministered with omeprazole compared to clopidogrel alone. There is a lack of data to correlate these findings with an increased risk of clinical events among cardiovascular patients, suggesting that the impact on clopidogrel efficacy may not be clinically relevant.

The issue remains as to whether inhibitors of the CYP2C19 isoenzyme carry an increased risk of ischaemic events among those harbouring loss-of-function alleles. Simon et al. recently analyzed
the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial infarct (FAST-MI), a large observational study of 2353 patients commenced on clopidogrel with or without the addition of a PPI following MI.34 A subgroup analysis of 1579 patients genotyped for the CYP2C19 allele failed to showed an increased risk of vascular events associated with PPI used at 1 year post MI irrespective of loss-of-function allele status.33 This evidence is, however, not conclusive with low numbers of patients carrying two loss-of-function alleles and few clinical events leading to wide CI around the data end points.34

Further large prospective studies are needed analyzing the safety of PPI among patients carrying CYP2C19 loss-of-function alleles, especially those homozygous who are already at greater risk. Supporting the preliminary data is the concept that biologically the effect of a CYP2C19 inhibitor on patients carrying two loss-of-function alleles may be minimal, given these patients have CYP2C19 isoenzymes that are non-functional at baseline.

10. Conclusion

There is increasing concern, supported by recent literature, that a significant proportion of patients demonstrate suboptimal response to clopidogrel which is strongly predicted by polymorphisms in the CYP2C19 allele. The clinical sequelae of suboptimal response to clopidogrel is more pronounced in patients treated with endovascular procedures. High dose clopidogrel appears to overcome suboptimal platelet inhibition but has not definitively demonstrated improved clinical outcomes. Genetic testing for clopidogrel responsiveness should be considered in patients at moderate to high risk for ischemic events (for example, post-endovascular device intervention) but the choice of APA alternatives has not been firmly established. At present the magnitude of the effect of CYP2C19 polymorphism on the risk of recurrent events is unknown within the ischaemic stroke population. Recruitment of patients with ischaemic stroke into prospective studies is recommended for individuals harbouring reduced function CYP2C19 alleles.

Conflicts of interest/disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

Section 3 Intensive monitoring of motor functions post stroke

In order to treat patients afflicted with stroke, it is vital that signs present or in development are immediately recognized. This requires enormous resources not yet fully available. In order to treat strokes effectively, missed signs represent an area of enquiry which in future may be undertaken by devices such as sensors or long term visual monitoring. But at present we are dependent on human labour to do this. If the symptoms develop subsequent to the initial event and remain unrecognized, this could conceivably jeopardize the outlook for the patients’ future.

List of my publications submitted in full

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Wireless Accelerometry is Feasible in Acute Monitoring of Upper Limb Motor Recovery after Ischemic Stroke

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Key Words
Stroke · Acute ischemic stroke · Accelerometry · Monitoring · Acute stroke management

Abstract
Background: Clinical deterioration in the acute stage of ischemic stroke powerfully predicts outcome and may serve as a marker for urgent intervention. However, accurate monitoring of acute stroke patients is hampered by the lack of validated continuous monitoring devices. We sought to assess the use of wireless accelerometry in this setting, hypothesizing that stroke patients would have a greater difference in movement between upper limbs than controls and that the magnitude of correlation between upper limb movements would be negatively associated with the National Institutes of Health Stroke Scale (NIHSS) score.

Methods: In this pilot study, 20 patients with acute ischemic stroke and unilateral upper limb weakness and 10 controls were recruited from a comprehensive stroke centre. All subjects were fitted with two 3-axis accelerometers and underwent 24 h of continuous accelerometry recording of upper limb movements and repeat NIHSS assessments. The intra-class correlation coefficient (ICC), assessing the similarity (or otherwise) of spontaneous movements in each arm, was calculated. The association between NIHSS (total and motor subset scores) and the magnitude of ICC was estimated by Spearman’s rank correlation, receiver-operating characteristic curve analysis was performed and the optimal diagnostic threshold value of ICC was calculated.

Results: The magnitude of the ICC was significantly associated with the baseline NIHSS score ($p = 0.02$) and non-significantly associated with the baseline NIHSS motor score ($p = 0.08$). At the optimal diagnostic threshold of ICC magnitude $= 0.7$, wireless accelerometry distinguished patients from controls with a sensitivity of 0.95, a specificity of 0.6 and a diagnostic odds ratio of 28.5.

Conclusions: The wireless accelerometry system successfully detects a motor deficit in the setting of acute ischemic stroke, accurately differentiating patients from controls, and correlates well with the baseline NIHSS score. Its use is feasible in the acute stroke setting. Overall, it shows promise as a diagnostic tool to continuously monitor acute stroke patients but requires validation in a larger trial.

Drs. C. Le Heron and K. Fang are co-first authors.
Introduction

Since the publication of the landmark NINDS trial in 1995 [1], intravenous thrombolysis with tissue plasminogen activator (IV-tPA) has significantly altered the treatment approach to stroke. IV-tPA improves clinical outcomes after acute ischemic stroke [1, 2], but requires rapid and cohesive management of patients to maximize benefit. It is recognized that the acute clinical course after thrombolysis predicts longer-term functional status [3]. Between 18 and 35% of patients demonstrate rapid motor recovery within 2 h of IV-tPA, leading to a high proportion of good outcomes at 3 months [3–5]. Conversely, those patients who deteriorate or fail to improve in the acute stages after thrombolysis have a poor prognosis; this group may require urgent investigation and intervention [6–8].

Whilst the trajectory of acute recovery therefore predicts the outcome following stroke, continuous monitoring of this recovery is currently problematic. The National Institutes of Health Stroke Scale (NIHSS) is the most commonly used measure in the acute stroke setting, but it is not ideally suited to intensively monitoring a patient. It is labour intensive, reliant on patient cooperation and subject to significant inter-rater variability [9]. Furthermore, it is a single time point assessment rather than a continuous measure. This is particularly relevant because motor symptoms can fluctuate or change trajectory [7]. The implication is that a single time point assessment may miss the overall trajectory of a patient’s clinical course in this acute period.

Wireless accelerometry-based systems allow objective, continuous, standardized recording of body movement. The utility of accelerometry in measuring movement is well established in the exercise field, where recordings from a triaxial accelerometer system correlate well with the energy expenditure of a limb [10]. The use of accelerometry is increasing in different areas of neurology, including Parkinson’s disease [11], epilepsy [12] and dementia [13]. Within the stroke field, accelerometry has been used to assess long-term functional recovery, to aid rehabilitation and to predict long-term outcomes [14]. However, its use in the acute stages of stroke as an aid to guide management has, to our knowledge, never been reported.

We have developed a wireless accelerometry system [15], and we aimed to investigate the utility of this device for intensively monitoring the motor function of the affected upper limb in the acute period following ischemic stroke. In the first phase of the project, we aimed to demonstrate that accelerometry can accurately differentiate between stroke and control subjects. We therefore hypothesized that the magnitude of the correlation between the left and right arm movements over a period of time is associated with the NIHSS score and could successfully distinguish between stroke and control subjects.

Methods

A total of 20 patients with acute ischemic stroke (confirmed by clinical and radiological assessment) and weakness in at least a single arm were recruited within 48 h of presentation to a comprehensive stroke centre in Melbourne, Australia, between August 2011 and February 2012. Patients who were unable to consent, required intensive care admission or had suffered haemorrhagic stroke were excluded; 10 controls without stroke or underlying upper limb motor impairment were recruited from patients within the same hospital. Subjects were assessed by an NIHSS-accredited neurologist at baseline and at 1, 2, 4 and 24 h, and the corresponding NIHSS total and arm motor score was obtained at these time points. Demographic data were collected, and stroke subtype was classified as per the Oxfordshire stroke classification system criteria [16].

All subjects were fitted with two 3-axis accelerometers (one on each wrist), model Crossbow Imote2 ( fig. 1 ). Accelerometry data were recorded continuously for the first 4 h from baseline, and then for 1 h at 24 h from baseline. The accelerometer output was collected using a wireless sensor node and transmitted to a (remote) base station. Data were collected at a sampling frequency of 100 Hz and transmitted to the base station 3 times per second. At the base station the data were pre-processed using a high-pass filter and aggregated over sequential 10-min intervals using 1,024-point fast Fourier transformation with a maximum power measure [for details, see Gubbi et al. 15]. This maximum power measure represents the highest activity for arm movement recorded during each 10-min interval. For each patient, over the whole data collection period, this resulted in a time-matched series of power readings for both arms.

To quantify the overall difference in arm movements in a given patient over the whole observation period, taking into consideration the longitudinal nature of the data, an intra-class correlation coefficient (ICC) of this time-matched series of power readings for both arms was estimated for every patient, using the ICC calculation ICC(3, k).

The association between baseline NIHSS (both total and motor score) and the magnitude of ICC within the stroke group was assessed by Spearman’s rank correlation using Stata/IC version 12 statistical software.

Receiver-operating characteristic (ROC) curve analysis with the absolute value of subject-specific ICC as a diagnostic variable was utilized to distinguish between stroke and control subjects. Corresponding values for sensitivity, specificity, positive and negative predictive values, and diagnostic odds ratios were calculated. To maximize the correct classification rate, the optimal diagnostic threshold value was calculated using the maximum Youden index (sensitivity plus specificity minus one) and further validated by fitting separate normal distribution curves to patient and control ICC values and choosing the threshold that was 1 standard deviation larger than the midpoint between the means of the resulting distributions. The analysis was performed using MATLAB vR2012b software on a laptop with 4GB RAM and an Intel i7 processor with MySQL database.
The research protocol was approved by the Royal Melbourne Hospital Human Research Ethics Committee (2010.245). Consent was obtained from all subjects.

**Results**

The median age was 77 years in the patient group (interquartile range, IQR, 59–82) and 64 years in the control group (IQR 48–71). The patient group had a higher ratio of males than the control group. Overall stroke severity was mild-to-moderate in the patient group, with a median NIHSS score of 5.5 (IQR 3–9). 75% of patients were recorded within 4 days of symptom onset. Of the 20 ischemic strokes, 19 involved the anterior circulation (with 11 affecting the right hemisphere and 8 the left hemisphere) and 1 involved posterior circulation (table 1); 15 of the anterior circulation strokes involved cortical regions and 4 were lacunar.

There was a significant association between the baseline NIHSS score and the magnitude of ICC (Spearman’s
Rho = −0.53, p = 0.02), with a greater stroke impairment being associated with lower absolute values of ICC (fig. 2). A similar analysis of the association between baseline NIHSS motor score (0–4) and magnitude of ICC did not quite achieve statistical significance (Spearman’s Rho = −0.4, p = 0.08; fig. 2).

The optimal diagnostic threshold for ICC magnitude was 0.7. At this threshold, ROC curve analysis using the ICC magnitude to distinguish stroke patients from controls yielded an AUC of 0.84 (fig. 3). Utilizing this threshold distinguished patients and controls, with a sensitivity of 0.95, a specificity of 0.6, a positive predictive value of 0.83 and a negative predictive value of 0.86. The diagnostic odds ratio at this threshold was 28.5.

**Discussion**

We have shown in this pilot study that a wireless accelerometry system can detect a motor deficit in the setting of acute stroke and can accurately differentiate stroke subjects from controls. We have also found an association between the ICC magnitude (calculated from a 24-hour period of monitoring) and severity of stroke at baseline (measured by the NIHSS), further validating the ICC measure. Finally, we have demonstrated the feasibility of using accelerometry in the acute stroke setting, which is particularly relevant given that wireless accelerometry may be used to monitor these patients and ultimately inform treatment decisions.

The diagnostic use of the ICC to differentiate between stroke patients and controls was our primary outcome measure. This analysis is an important validation step. The magnitude of ICC is derived from a comparison of motor activity in a subject’s upper limbs. An absolute value of ICC = 1 suggests that both limbs show an equal degree of activity, whilst a lower ICC indicates greater asym-
We also examined how the ICC varied depending on stroke severity. We showed a significant association between NIHSS total score and ICC magnitude, with a lower ICC magnitude observed in more severe strokes (fig. 2a). This result is consistent with a previous study which correlated the NIHSS total score with differences in accelerometry (actigraphy) measures during the acute phase of stroke [17] and further validates the use of this technique in the acute setting. We hypothesized that the ICC magnitude would also be associated with the motor severity subsection of the NIHSS. Although this data could be interpreted as showing a trend (fig. 2b), statistical significance was not reached (p = 0.08). Intuitively, it seems logical that asymmetry in movements would be greater with greater unilateral weakness, and we suspect that the failure to reach significance is related to the low power of this pilot study – larger numbers are likely to be needed to demonstrate this association. Additionally, we were comparing the baseline NIHSS motor score to accelerometry data derived over the subsequent 24 h. In some patients there was a change in motor score (improvement or deterioration) which would have influenced the final ICC but was not reflected in their initial NIHSS motor score. However, the small numbers in this study limited our ability to investigate this further. We plan to conduct a larger study that will allow us to analyse how the ICC correlates with a patient’s motor weakness over time, with the goal of validating accelerometry as a continuous measure of limb power in the acute stroke period.

The majority of patients in this study had their wireless accelerometry recorded within 4 days of symptom onset, and generally within 24 h of presentation to hospital. The process of attaching the accelerometers and collecting data was straightforward, taking less than 5 min to set up, and did not interfere with patient care. We initially monitored each patient continuously for 4 h, as this is a realistic ‘window’ during which stroke management decisions may be changed in the acute setting and because current battery life will not extend for a full 24 h (we envisage this will lengthen in subsequent accelerometer models). Stroke severity was mild-to-moderate in this cohort and patients displayed an expected range of stroke territory distribution, given that arm weakness was a criterion for inclusion. One clear limitation of the study is that no patients were monitored within the first 6 h of their stroke, which is likely to be the critical time to identify non-responders to thrombolysis. Although this was beyond the scope of our pilot study and will be the focus of a future project, based on our experience in this study we believe this goal of early monitoring is feasible.

The ability to intensively monitor neurological motor recovery in the acute stroke setting is likely to be critical in guiding management decisions. The trajectory of recovery in the initial hours following stroke correlates with long-term outcome [3]. Rapid recovery is associated with a better outcome at 3 months. The odds of these patients experiencing a good functional outcome is approximately 7 (modified Rankin scale, mRS, 0 or 1) compared to those who do not have a rapid recovery [3, 5]. An analysis of the NINDS tPA data set revealed that only 32.5% of patients without early improvement achieved an mRS of 0 or 1 at 3 months compared to 60.7% of patients who showed early improvement [3]. Felberg et al. [8] found that in patients with middle cerebral artery territory ischemic stroke, those who had not shown a dramatic recovery by the end of their tPA infusion had a median 3-month mRS of 4 compared to an mRS of 1 in those who did show such a recovery. Early identification of the absence of rapid motor recovery will therefore be increasingly important, as it is likely that this is the group who stand to gain the most from early adjunctive therapies, such as endovascular clot retrieval, if this is validated by ongoing phase III trials.

**Fig. 3.** ROC analysis of the ICC magnitude at diagnostic threshold steps of 0.05. The AUC is 0.84. A diagnostic threshold of 0.7 yields a sensitivity of 0.95 and a specificity of 0.6.
Currently, stroke unit care is hampered by a lack of continuous monitoring of function. Accelerometry offers many advantages in monitoring acute stroke recovery. It is an objective, continuous measure, and the data output can be displayed on a screen at the patient’s bedside or a central station, allowing easy tracking of a patient’s progress (or otherwise). The method still has some drawbacks – it will not be effective in unconscious patients, and other conditions (e.g. an arm fracture following a fall) could also confound the analysis. However, these situations are rare. Correlation with NIHSS is not 100% accurate, but in the context of continuous monitoring a single measurement will be less important than a patient’s overall trend – something which current, intermittent measurement will be less important than a patient’s overall rate, but in the context of continuous monitoring a single measurement will be less important than a patient’s overall trend – something which current, intermittent methods of assessing patients may fail to identify.

To conclude, this study has shown that a wireless accelerometry system can accurately distinguish acute stroke patients from controls and that the ICC is significantly associated with a patient’s NIHSS score. It illustrates the feasibility of using this system to continuously monitor patients in the acute stroke setting and opens the way for further trials in this area. Specifically, the system shows significant promise for identifying ‘non-responder’ patients, who may benefit from more aggressive re-intervention, as acute stroke management strategies attempt to emphasize individually tailored approaches.

Acknowledgement

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Disclosure Statement

B.Y., M.P. and J.G. share a provisional patent on the accelerometry device.

No funding was received for this study.

References

A Pilot Study on the use of Accelerometer Sensors for Monitoring Post Acute Stroke Patients

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Abstract—The high incidence of stroke has raised a major concern among health professionals in recent years. Concerted efforts from medical and engineering communities are being exercised to tackle the problem at its early stage. In this direction, a pilot study to analyze and detect the affected arm of the stroke patient based on hand movements is presented. The premise is that the correlation of magnitude of the activities of the two arms vary significantly for stroke patients from controls. Further, the cross-correlation of right and left arms for three axes are differentiable for patients and controls. A total of 22 subjects (15 patients and 7 controls) were included in this study. An overall accuracy of 95.45% was obtained with sensitivity of 1 and specificity of 0.86 using correlation based method.

I. BACKGROUND

Stroke is a major cause of morbidity and mortality in Australia. There is an annual incidence of 48,000 new strokes and the risk of death is 25 to 30% [1]. Acute stroke is caused by a blockage of one of the arteries in the brain resulting in interrupted blood supply. Brain cells deprived of oxygenated blood die rapidly unless blood supply is restored. One of the milestones of modern management of acute stroke is the administration of a thrombolytic (clot-busting medication) in order to unblock the blocked artery [2]. It has been shown in international multi-center studies that patients who receive thrombolytic treatment have better clinical outcomes [2].

The delivery of thrombolytic agents to acute stroke patients require round-the-clock availability of a stroke neurologist to clinically assess the patient. Lack of continuous monitoring translates to missed treatment opportunities in decreasing the morbidity and mortality associated with acute stroke [3]. In addition, the monitoring of motor recovery is critical in the management of stroke patients. Patients who do not exhibit early motor recovery post thrombolysis may benefit from more aggressive treatment. It follows that a portable wireless motion detector would signify a major advance in patient management.

Assessment of the effect of thrombolysis is the core motivation to develop an automated monitoring tool for the assessment of post-stroke individuals' during the 'hot' period after stroke (while the patient is still in the hospital). The National Institute of Health Stroke Scale (NIHSS) is an international initiative to systematically assess stroke and provide a quantitative measure of all stroke related neurological deficit. The NIHSS scale is a 17-item neurological examination to evaluate the levels of consciousness, language, neglect, visual-field loss, extra ocular movement, motor strength, ataxia, dysarthria, and sensory loss. In our work, we are interested in motor strength assessment which is defined as in [4].

Recent technological advances in low-power integrated circuits and wireless communications have made available efficient, low-cost, low-power miniature devices for use in wireless sensing applications. Automated clinical decision making is one of the key research areas in biomedical engineering. A wearable body area network is a viable solution for unhindered monitoring of patient condition [5]. Wireless Body Area Network (WBAN) is one of the key emerging technologies for unobtrusive health monitoring [6]. In order to monitor stroke patients, low-cost hardware platform is necessary. Most major efforts have been in activity monitoring as a fitness aid using smart phones as the base platform. A good summary of the work using these sensors in activity monitoring can be found in [7] including a comparison of commercially available systems. Bouten et. al. [8] developed a basic activity monitoring system using a tri-axis accelerometer and proved the correlation of energy expenditure with the processed accelerometer sensor signal was high on healthy subjects. Often, the areas of focus have been in rehabilitation, which is a reactive response rather than a proactive response. Another area of research in post stroke assessment using accelerometer sensors is the Wolf Motor Function Test (WMFT) [9]. WMFT is a post stroke assessment procedure carried out within days after the onset of stroke. Parnandi et. al. [10], [9] have developed a wireless accelerometer system which replicates WMFT conducted by trained personnel. The assessment is based on 15 tasks rated according to time and quality of motion. They compare the scores obtained from their proposed method with therapist’s scores and report an average error of 0.0667, which is excellent. Once again, researchers [10] are in post stroke assessment spanning days after the onset of stroke and falls under the post stroke rehabilitation category. However, the use of the accelerometer in the ‘hot period’ of stroke is virtually absent in the literature and this is the first attempt to monitor motor activity.

In this project, we propose to develop wireless accelerometer platform in order to monitor the motor recovery in acute-stroke patients. In our previous work [11], we have shown that the accelerometer data obtained from these sensors can be used for monitoring patients. However, the algorithm fails
to differentiate between patients and control. Hence, there is a need to create an efficient algorithm at the first stage to differentiate between patients and controls and then apply stroke index calculation algorithm at the second stage. In this paper, we present a new algorithm for classifying patients and control from the collected accelerometer data.

II. METHOD

A new system for continuously monitoring motor activity of arms based on wireless accelerometer attached to the patient is developed. A wireless sensor is attached to both the arms of the patient. These sensors transmit the accelerometer information to a base station, which is a sensor node capable of receiving the data transmitted from the wireless sensors. The base station is attached to the computer via USB and it receives the activity data at 50Hz. The received data consists of time stamped x, y, and z axes data. The data is then pushed into a MySQL database server for further processing and analysis.

A. A wearable sensor platform

In this pilot study, off-the-shelf iMote2 platform is used. The Imote2.NET can be programmed in Microsoft’s Visual Studio using C#. It is built around the low-power PXA271 XScale CPU. Furthermore, the system integrates an 802.15.4 compliant radio operating at 2.4 GHz bandwidth. The advantage of this platform is its modularity to interface sensors to its existing basic sensor board (ITS400). The ITS400 consists of a three-axis accelerometer (±2g) and a 12-bit, four-channel Analog to Digital (A/D) converter.

B. Data collection Protocol and pre processing

Human Research Ethics Committee approval has been obtained from Royal Melbourne Hospital Human Research Ethics Committee (HREC 2010.245). The data is collected at Melbourne Brain Center. Each data packet included a time stamp and the tri-axis accelerations. A typical plot for a control and patient are shown in Fig. 1. Careful observations of the difference in the muscular activity between the hands indicate reduced activity in the patient (2nd row in Fig. 1). In total, 22 subjects were used to develop the method that included 15 acute stroke patients (8 males, 7 females) and 7 controls (2 males, 5 females). The average age of patients is 69.8 ± 15 years and the average age of controls is 60 ± 16 years. The summary of the patient data is given in Table I.

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III. SIGNAL ANALYSIS AND CLASSIFICATION

Based on the preliminary time and frequency domain analysis of the data collected [11], two new methods are developed for patient/control classification: (a) using cross-correlation of acceleration magnitude between arms over 10 minute window, and (b) using the difference in cross-correlation of the 3 axis of each arm. The methods are explained below:

A. Cross-correlation of magnitude

The hypothesis of this stage is that the correlation of the activities of the two arms varies between patients and controls. In order to prove our hypothesis, the resultant of the accelerometer data is divided into 10 minute windows. For each window, a 1024-point FFT is taken and the power is calculated. The maximum power that represents the highest activity for any frequency (arm movement) is recorded. This results in a time series of power readings for each arm. The correlation coefficient is then calculated between the left and the right arm, which reflects the difference in arm movements. For window size, 1 minute, 5 minutes and 10 minutes were tested before settling with a 10 minute window. A correlation coefficient threshold of 0.7 was empirically chosen for differentiating patients from controls.

B. Cross-correlation between the 3 axis

It is observed that the stroke patients are not comfortable performing rotatory motion from their stroke affected arm, for example, rotating a door knob or rotating their arm around elbow or shoulder joint, whereas healthy persons can do them with ease. This forms the basic motivation of
the developed method and it is based on finding the cross-correlation between acceleration values along x, y and z axes. We consider a 10 minute window as discussed earlier and the following procedure is used: We first take 2 second Hamming window with 50% overlap. Then, correlation of 3 pairs of axes - x and y (eq. 1), y and z (eq. 2), z and x (eq. 3) are calculated to obtain three correlations. The cumulative integral of correlated signals within 10 minutes is calculated to obtain velocity signal. The area under the velocity signal for 10 minute duration gives us $R_{xy}$, $L_{xy}$, $R_{yz}$, $L_{yz}$ and $R_{zx}$ and $L_{zx}$.

$$S_{xy} = \frac{180}{\pi} \tan^{-1} \left( \frac{R_{xy}}{L_{xy}} \right)$$  \hspace{1cm} (1)

$$S_{yz} = \frac{180}{\pi} \tan^{-1} \left( \frac{R_{yz}}{L_{yz}} \right)$$  \hspace{1cm} (2)

$$S_{zx} = \frac{180}{\pi} \tan^{-1} \left( \frac{R_{zx}}{L_{zx}} \right)$$  \hspace{1cm} (3)

![Histogram of $S_{xy}$, $S_{yz}$ and $S_{zx}$ values for controls (top) and patients (bottom)](image)

Values of $S_{xy}$, $S_{yz}$ and $S_{zx}$, near to $45^\circ$ represent less severity whereas away from $45^\circ$ and close to 0$^\circ$ or 90$^\circ$ represent more severity of stroke, with close to 0$^\circ$ represent right arm being affected and close to 90$^\circ$ represent left arm being affected. Fig. 2 shows the histogram of $S_{xy}$, $S_{yz}$ and $S_{zx}$ for controls (top) and patients (bottom) respectively. The histograms also reinforce our belief that value of correlations is close to 45$^\circ$ for controls and close to 0$^\circ$ for patients (based on the side affected by stroke). After obtaining the correlation values, a binary classification based on linear thresholding is performed. An individual is declared as control or patient based on rules presented in Table II.

**TABLE II**

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**Results and Discussion**

The development of diagnostic protocol for monitoring acute stroke, which involves programming the nodes, data collection, analysis and classification of patients and controls is presented. 22 subject data using wireless accelerometer sensor including 15 patients and 7 controls is collected. Table III shows the overall results of patient classification using the two proposed methods. An overall accuracy of 86.36% is obtained with sensitivity of 0.87 and specificity of 0.86 using cross-correlation of magnitudes between arms. Further, the second method is based on difference in correlation between 3 axes is proposed. As it can be seen from Table III, an accuracy of 95.45% is achieved with significant improvement in sensitivity (1) and specificity (0.86). In order to validate our results using the second method, ROC curve (refer Fig. 3) for $S_{xy}$, $S_{yz}$ and $S_{zx}$ are plotted and area under curve of 0.84, 0.85 and 0.82 respectively is obtained.

![ROC curve for $S_{xy}$, $S_{yz}$ and $S_{zx}$](image)

As the methods are implemented on low power nodes, use of non-linear classifiers like Support Vector Machines is deliberately avoided. It is important to note that the threshold values chosen in Table II will have significant effect on the classification. In order to justify this, accuracies obtained for different values of threshold is shown in Fig. 4. For more than 80% of the threshold values, the accuracy is over 90% demonstrating the robustness of the proposed linear classifier. The results in Table III are based on a threshold of $10^\circ$ for $S_{xy}$, $9^\circ$ for $S_{yz}$ and $10^\circ$ for $S_{zx}$.

**Conclusion**

Use of accelerometer sensors for monitoring activity has become one of the key research areas in biomedical research. In this paper, a new algorithm for classifying stroke patients and controls is proposed. There is significant different in arm activity between the stroke affected arm and the normal arm in spite of varying degrees of paralysis. This fact is used to develop two algorithms: using the cross-correlation of activity between arms (resulting in an accuracy of 86%) and
using cross-correlation of activity along three different axes of movement. An overall accuracy of 95.45% is obtained with sensitivity of 1 and specificity of 0.86 using correlation between 3 axes. This study is useful in detecting stroke patients non-invasively and further useful in continuous monitoring.

REFERENCES


Motor recovery monitoring using acceleration measurements in post acute stroke patients

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Abstract

Background: Stroke is one of the major causes of morbidity and mortality. Its recovery and treatment depends on close clinical monitoring by a clinician especially during the first few hours after the onset of stroke. Patients who do not exhibit early motor recovery post thrombolysis may benefit from more aggressive treatment.

Method: A novel approach for monitoring stroke during the first few hours after the onset of stroke using a wireless accelerometer based motor activity monitoring system is developed. It monitors the motor activity by measuring the acceleration of the arms in three axes. In the presented proof of concept study, the measured acceleration data is transferred wirelessly using iMote2 platform to the base station that is equipped with an online algorithm capable of calculating an index equivalent to the National Institute of Health Stroke Score (NIHSS) motor index. The system is developed by collecting data from 15 patients.

Results: We have successfully demonstrated an end-to-end stroke monitoring system reporting an accuracy of calculating stroke index of more than 80%, highest Cohen's overall agreement of 0.91 (with excellent \( \kappa \) coefficient of 0.76).

Conclusion: A wireless accelerometer based 'hot stroke' monitoring system is developed to monitor the motor recovery in acute-stroke patients. It has been shown to monitor stroke patients continuously, which has not been possible so far with high reliability.

Background

Stroke is a major cause of morbidity and mortality in Australia. There is an annual incidence of 48,000 new strokes and the risk of death is 25 to 30% [1]. Of those who survive, stroke contributes to 25% of all chronic disabilities in Australia. Acute stroke is caused by a blockage of one of the arteries in the brain resulting in interrupted blood supply. Brain cells deprived of oxygenated blood die rapidly unless blood supply is restored. One of the milestones of modern management of acute stroke is the administration of a thrombolytic (clot-busting medication) to unblock the blocked artery [2]. This restores blood supply to the brain and arresting the demise of brain cells. International multi-center studies have shown that the patients who receive thrombolytics have better clinical outcomes [2].

The delivery of thrombolytic agents to acute stroke patients requires round-the-clock availability of a stroke neurologist to clinically assess the patient. This is a critical step as there are dangerous mimics of stroke and a wrong diagnosis by a non-specialist will significantly impact upon the correct management decision. A recent survey by the National...
Stroke Foundation reported that 72% of Australian hospitals were unable to provide acute stroke treatment which results in deprivation of evidence-based standard stroke care for a significant proportion of stroke patients in rural Victoria. This translates to missed treatment opportunities in decreasing the morbidity and mortality associated with acute stroke [3]. In addition, the monitoring of motor recovery by clinical observation is critical in the management of stroke patients. Patients who do not exhibit early motor recovery post thrombolysis may benefit from more aggressive treatment. However, the current clinical observation paradigm is time-consuming and subjected to inter-observer bias. It follows that a portable device for continuous monitoring of motor recovery in stroke patients treated with thrombolysis, would signify a major advance in patient management.

Recent technological advances in low power integrated circuits and wireless communications have made available efficient, low cost, low power miniature devices for use in wireless sensing applications. Automated clinical decision making is one of the key research areas in biomedical engineering. A wearable body area network is a viable solution for the unhindered monitoring of patient condition [4]. Automatic patient monitoring systems (PMS) send an alert to the care giver based on the physiological parameters gathered. Wireless Body Area Network (WBAN) is one of the key emerging technologies for unobstructive health monitoring [5]. In an editorial overview about wearable systems by Bonato [6] published in 2003, he emphasizes the impact of technological breakthrough in sensors and sensor networks on biomedical engineering. His observations are indeed true eight years on and we have seen unhindered physiological monitoring using wearable wireless systems.

Assessment of the effect of thrombolysis is the core motivation to develop an automated monitoring tool for the assessment of post-stroke individuals' during the 'hot' period after stroke (while the patient is still in the hospital). The National Institute of Health Stroke Scale (NIHSS) is an international initiative to systematically assess stroke and provide a quantitative measure of all stroke related neurological deficit. It is used as a clinical assessment tool to evaluate acuity in stroke patients, determine appropriate treatment and predict patient outcome. It has been proven to be a very useful tool in treatment planning by Neuro-intervention for acute stroke patients. The scale is a 17-item neurological examination to evaluate the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. The score ranges from 0 to 42. The single patient assessment requires about 10 minutes to complete and is performed every hour by a qualified doctor. In our work, we are interested in motor strength assessment which is defined as in Table 1 [7].

<table>
<thead>
<tr>
<th>Scale</th>
<th>Status</th>
<th>Description</th>
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<tr>
<td>0</td>
<td>No drift</td>
<td>Limb holds 90 degrees for a full 10 seconds</td>
</tr>
<tr>
<td>1</td>
<td>Drift</td>
<td>Limb holds 90 degrees but drifts down before full 10 seconds</td>
</tr>
<tr>
<td>2</td>
<td>Some effort against gravity</td>
<td>Limb cannot get to 90 degrees, but has some effort against gravity</td>
</tr>
<tr>
<td>3</td>
<td>No effort against gravity</td>
<td>No effort against gravity</td>
</tr>
<tr>
<td>4</td>
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<td>-</td>
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<tr>
<td>UN</td>
<td>Amputation</td>
<td>-</td>
</tr>
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</table>
Major efforts involving accelerometer have been in activity monitoring as a fitness aid using smart phones as the base platform. Accelerometer sensors with gyroscope have been used in such fitness products now commercially available. A good summary of the work using these sensors in activity monitoring can be found in [8] including a comparison of commercially available system. Bouten et. al. [9] developed a basic activity monitoring system using triaxial accelerometer and proved the correlation of energy expenditure with processed accelerometer sensor signal was high on healthy subjects. Since then, various application areas where movement monitoring is required has been impacted. Often, the areas of focus have been in rehabilitation which is a reactive response rather than a proactive response. Nevertheless, these technological advances have resulted in the assessments by health care providers becoming more objective. In a detailed study, Yang et. al. [10] have proposed a neural classifier for activity recognition using accelerometer data. Their focus is mainly for signal processing and pattern recognition aspects and they classify eight daily activities on seven subjects with over 95% accuracy. In 2009, Roy et. al. [11] proposed a combined accelerometer-sEMG system for monitoring post stroke patients. They conduct their tests on 10 subjects who had stroke onset between $7 \pm 6$ years before the test. They use 11 tasks for identifying the functional independence with 95% sensitivity using a hybrid neural classifier. It should be noted that the post-stroke in their work refers to period after several years of stroke.

Another area of research in post stroke assessment using accelerometer sensors is conducting Wolf Motor Function Test (WMFT) [12]. WMFT is a post stroke assessment procedure carried out within days after the onset of stroke. It is a time based method to evaluate upper extremity performance in chronic stroke patients. Parnandi et. al. [13,14] have developed a wireless accelerometer system which replicates WMFT conducted by trained personnel. The assessment is based on 15 tasks rated according to time and quality of motion. They compare the scores obtained from their proposed method with therapist’s scores and report an average error of 0.0667 which is excellent. Patel et. al. [15] propose a similar system to quantify the Functional Ability Scale (FAS) score in stroke survivors using three sensors with excellent outcomes. In another interesting work by Lopez-Meyer et. al. [16], assessment of rehabilitation FAS scores using gait is proposed with the sensors embedded in the shoes to monitor the gait. Once again, [13,15,16] are in post stroke assessment spanning days after the onset of stroke and falls under the post stroke rehabilitation category.

Unlike other methods proposed in the literature, our work focuses on post stroke monitoring during 'hot' hours which is usually the first 24 hours after the onset of stroke. In this paper, we propose to develop a wireless accelerometer based system in order to monitor the motor recovery in acute-stroke patients in the hot hour. Accelerometer data obtained from these sensors will be used to develop a new algorithm for stroke monitoring and patient recovery.

**Method**

We develop a new system which when put on patients’ arms will monitor the motor activity continuously. Further, we correlate the scores generated by the developed automated algorithm with an expert score at motor recovery band in NIHSS [7]. The observed indices are retained as in Table 1. However, as per the definition of NIHSS indices 3 and
4, motor activity monitoring is virtually impossible using an accelerometer and hence we have represented 3 and 4 as 3 for all our analysis. The schematic of the proposed method is summarised in Figure 1 and briefly the procedure is as follows. The data is collected using a wireless sensor node attached to a 3-axis accelerometer. The data collected at a predetermined sampling rate is transmitted from both the arms to the base station. On the base station, the data is pre-processed using a basic high pass filter and the activity in a 10 minute window is calculated. The activities of the two arms are compared and visualized in a custom designed graphic user interface.

Wireless accelerometer sensor data acquisition
At this stage of our experimentation, we use Crossbow iMote2 as the sensor platform for collecting the acceleration data. The Imote2.NET is an advanced wireless sensor node platform. It is built around the low-power PXA271 XScale CPU and also integrates an 802.15.4 compliant radio at 2.4 GHz. The design is modular and stackable with interface connectors for expansion boards on both the top and bottom sides. The top connectors provide a standard set of I/O signals for basic expansion boards and we use ITS400 sensor board. It contains a three-axis accelerometer, an advanced temperature/humidity sensor, a light sensor and a 4 channel A/D converter out of which we use tri-axial accelerometer in our experiments. The sensors are mounted on each arm of the patient using an armband and the sensor readings are transferred wirelessly to an iMote2 base station which is connected to a computer via USB connection. This enables the patient to move freely in a given perimeter. Considering the patient is affected by stroke and the measurement is taken within the first 24 hours, movement is usually limited and confined to the wards in any clinical setup. The data is stored using a MySQL server running locally and
MATLAB is used for online analysis and data visualization. The sensitivity of the on board ST accelerometer is ±2g.

Data collection and preprocessing
The movement data was collected in Melbourne Brain Centre, Royal Melbourne Hospital, Australia. The research protocol was approved by Royal Melbourne Hospital Human Research Ethics Committee (2010.245). In total, 25 subjects were used to develop the method which included 15 acute stroke patients (8 males, 7 females) and 10 controls (2 males, 9 females). The average age of patients was 69.8 ± 15 years and the average age of controls was 60 ± 16 years. In the algorithm presented, the data from 10 controls was not utilized. The summary of the patient data including age, sex, diabetes, smoking and hypertension is given in Table 2. The accelerometer data was collected for the first four hours and another one hour after 24 hours. An expert neurologist records the observed NIHSS motor scores and the observed NIHSS overall score at the time of onset (0th hour), 1st hour, 2nd hour, 3rd hour and at 24 hours. For instance, if the patient comes to the hospital at 9 am, the data is collected between 9 am and 1 pm on that day (expert recording at 9 am, 10 am, 11 am, 12 pm) and between 9 am and 10 am on the following day (expert recording at 9 am on the following day). The sampling frequency of the data collected is 100 Hz and three packets of data transfers to the base station every second. Each packet received contained several values of acceleration values along x, y, and z axes. The time stamp was generated at the base station instead of the source node in order to avoid time synchronisation problems in wireless sensor nodes [17]. In total, six acceleration values were received at any given instant (2 arms × 3 axis). This signal was filtered using a Butterworth 6th order high-pass filter with 1 Hz as cutoff frequency. The original raw signal and the filtered output are shown in Figure 2.

Signal analysis and calculation of stroke index
In our experiments, we are interested in relative overall motion of the arms. We derive a score which is equivalent to the NIHSS motor activity and show that it is correlated to the observed NIHSS score. During the calculation of NIHSS score, an NIHSS accredited clinician calculates the score every hour and the test would take approximately 10 minutes. This motivates us to use a 10 minute window for calculating the motor activity. The idea is to calculate the activity of both arms every 10 minutes and compare the calculated activity and arrive at a meaningful index, which correlates with the observed NIHSS motor score. In order to achieve this, three standard acceleration data analysis techniques were employed. Ambrosini et al. [18] propose a new design of a symmetry controller for cycling induced by functional electrical stimulation and test it on post-acute stroke patients (rehabilitation phase). Making use of the cyclical nature of pedalling in their experiment, they design a new algorithm for balancing the electrical stimulation in order to recover motor recovery. Their symmetry index is based on the cyclical activities of the two limbs. However, in the case of ‘hot stroke’, which we are dealing with, continuous activity cannot be ensured and a more generalised method is required for calculating the imbalance. In this paper, we have developed three very basic schemes for calculating such imbalance and the summary of the methods used in the development of the algorithm is given in Table 3.
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Figure 2 Raw accelerometer readings and filtered outputs. Raw accelerometer readings of a patient’s affected hand: Top - Original received from iMote2; Bottom - Filtered signal.

Norm based index
In this method, average activity of each arm is calculated and the Euclidean distance between the activities is used for deriving the index. We first calculate the magnitude of the three dimensions at every instance using equation 1.

\[ A_i = \sqrt{(x_i)^2 + (y_i)^2 + (z_i)^2} \]  

Table 3 Summary of methods employed in signal analysis

<table>
<thead>
<tr>
<th>Domain</th>
<th>Norm based</th>
<th>Signal Magnitude</th>
<th>Area based</th>
<th>Energy based</th>
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<td>Metric</td>
<td>Time</td>
<td>Time</td>
<td>Time</td>
<td>Frequency</td>
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<tr>
<td>Activity measured</td>
<td>Euclidean distance</td>
<td>Manhattan distance</td>
<td>Cumulative velocity of average activity in x, y, and z directions</td>
<td>Energy of activity in a 10 minute window</td>
</tr>
<tr>
<td>Calculation method</td>
<td>Every sample</td>
<td>Average value over 10 minutes</td>
<td>Window of 10 minutes</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Low</td>
<td>High for normal patients and Low for severely disabled patients</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Computational complexity</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td></td>
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</table>


where, $A_i$ is the resultant acceleration magnitude (calculated at every instance) using the accelerations along $x$, $y$ and $z$ axes for both the arms. In the second stage, a 10 minute window is considered and a cumulative integral is calculated to obtain velocities. The area under the velocity curve represented by $R_N$ and $L_N$ are calculated every 10 minutes (results in a scalar quantity for every 10 minute window). The ratio of the velocities indicates the activity of any arm against the other. In order to maintain the ratio comparable and for detecting the defective (paralysed) arm, we use equation 2.

$$S_N = \begin{cases} 
\frac{L_N}{(L_N+R_N)^2} & \text{if } L_N > R_N \\
\frac{R_N}{(L_N+R_N)^2} & \text{if } L_N \leq R_N 
\end{cases}$$

(2)

where, $S_N$ is the norm based stroke index. If $L_N >> R_N$, it implies paralysed right arm and vice versa.

**Signal Magnitude Area (SMA) based index**

Signal Magnitude Area is defined as the sum of acceleration magnitude summations over three axes normalized by the length of the signal. It reflects the activity within a time window instead of at every instance. This has been successfully used in activity recognition by Yang et. al. [10] as a feature and we use it to measure relative activity between the two arms in a time window. It is analogous to the city block distance and is given by the equation 3.

$$SMA_j = \frac{1}{w} \left( \sum_{i=0}^{w} |x_i| + \sum_{i=0}^{w} |y_i| + \sum_{i=0}^{w} |z_i| \right)$$

(3)

where $j$ indicates the window number with length $w$. In our experiments, we have empirically chosen the window length as one second. Similar to norm based method above, a 10 minute window is considered in the second stage and a cumulative integral is calculated. The area under the curve ($L_S$ and $R_S$) is calculated every 10 minutes. The ratio of the integrals is calculated for relative arm activity. In order to maintain the ratio comparable and for detecting the defective (paralyzed) arm, we use equation 4.

$$S_S = \begin{cases} 
\frac{L_S}{(L_S+R_S)^2} & \text{if } L_S > R_S \\
\frac{R_S}{(L_S+R_S)^2} & \text{if } R_S \geq L_S 
\end{cases}$$

(4)

where, $S_S$ is the SMA based stroke index. If $L_S >> R_S$, it implies defective right arm and vice versa. It should be noted that SMA is identical to Manhattan norm of the accelerometer values.

**Average energy comparison based index**

The frequency distribution in the affected and the unaffected arm are compared in this method. Preliminary work on using sensor networks for activity recognition was carried out by Wang et. al. [19] in activity recognition. Very similar to their work, the energy is calculated as the sum of squared FFT magnitude of the signal. The average of the three energy signals over a window of length one second is used in the calculation of the index. Similar to other methods described above, a 10 minute window is considered in the second stage and a cumulative integral is calculated within the window. The area under the curve ($L_E$ and $R_E$) is calculated every 10 minutes. The ratio of energies indicates the
activity of one arm against the other. In order to maintain the ratio comparable and for
detecting the defective (paralysed) arm, we use equation 5.

\[ SE = \begin{cases} 
\frac{L_E}{(L_E + R_E)^2} & \text{if } L_E > R_E \\
\frac{R_E}{(L_E + R_E)^2} & \text{if } R_E \geq L_E 
\end{cases} \] (5)

where, \( SE \) is the Energy in frequency domain based stroke index. If \( L_E \gg R_E \), it implies
defective right arm and \textit{vice versa}.

**Conversion to stroke index**

The \( SN, SS \) and \( SE \) calculated above are the values which correlate with the observed
NIHSS values. However, the values cannot be interpreted by the doctor. Hence we have
devised a conversion method to convert these values to NIHSS scores. Two thresholds
\( Th_1 \) and \( Th_2 \) have to be calculated to convert the indices into discrete values for easy com-
parison with NIHSS index. Neurology assessment by doctors with NIHSS accreditation
has shown fair inter-rater agreement. Hence we define accuracy for the proposed system
as the percentage of agreement between the scores given by a NIHSS accredited doctor
and the proposed solution. For analysis, we have calculated the percentage accuracy of
the system for different values of \( Th_1 \) and \( Th_2 \). The plot of the analysis using the three
techniques is shown in Figure 3. The colour map shows the accuracy contour while x and
y axes represent the two thresholds. As it can be seen, for certain values of calculated
thresholds the accuracy is quite high (in red or maroon colours) particularly for the energy
based method. This chart is obtained using \( T_0, T_1 \) and \( T_2 \) values and is tested using \( T_{24} \).

**Visualisation**

As the system will be used by doctors in a hospital environment, it is important to create
an easily understandable visualisation of the indices as the data is being collected online.
In the initial stage, the problematic arm is not known to the system. As the patient comes
in, two iMote2s will be strapped to the patient’s arms as explained earlier. The online
visualisation we have created for stroke monitoring is shown in Figure 4 for day 2 of data
collection for clarity. The figure is divided into two parts vertically along the midway,
indicating two arms. In the figure, x axis indicates stroke index and y axis indicates the
time of recording. Negative stroke index is for left hand and positive stroke index is for
right hand. As we move away from 0 in either direction, the severity of stroke increases.
The custom colour coding is based on the NIHSS stroke scale given in Table 1. In Figure 4,
the recording started at 11 : 45 am and continued until 12 : 45 pm. The doctor records only
once during this period at the start of the recording (which is onset +24 hours). However,
the system presented here continuously monitors the patient enabling a detailed study
of motor recovery. Recording every 10 minutes has resulted in 7 discrete motor activity
assessment. This is an online (evolving) graph which gets updated every 10 minutes when
the data collection is in progress. In the following section, we present results using the
proposed methods and correlate it with expert’s observation.

**Results and discussion**

The overall results of the developed method for 15 patients is shown in Table 4. Firstly,
we discuss the prediction of the affected arm. Based on continuous arm activity, we keep
track of the overall arm movement in order to predict the stroke affected arm. As it can be
Figure 3 Colormap to help choosing the thresholds. Colour map for choosing appropriate thresholds for converting the accelerometer readings to equivalent motor index: Norm based (top), SMA based (middle), Energy based (bottom). The colormap shows the accuracy contour while x and y axes represent the two thresholds. As it can be seen, for certain values of calculated thresholds the accuracy is quite high (in red or maroon colors) particularly for the energy based method. This chart is obtained using $T_0$, $T_1$ and $T_2$ values and is tested using $T_{24}$. 
Figure 4 Generic visualisation for stroke monitoring. The graph is divided into two sections representing two arms. The colour coding is based on the severity of the stroke - green represents normal activity and red represents severe arm disability. The y axis represents time and x axis represents calculated stroke index. The figure is divided into two parts vertically along midway, indicating two arms. As we move away from 0 in either direction, the severity of stroke increases. The custom colour coding is based on the NIHSS stroke scale given in Table 1. The recording started at 11:45 am and continued until 12:45 pm. The doctor records only once during this period at the start of the recording (which is onset +24 hours) but the system records it continuously. Calculating the index within a 10 minute window has resulted in 7 discrete motor activity assessment. This is an evolving graph which gets updated every 10 minutes when the data collection is in progress.

seen from Table 4, an accuracy of 93.33%, 93.33% and 100% is obtained for norm based, SMA based and energy based methods respectively.

Secondly, the observed NIHSS indices as well as the calculated values using the three proposed methods are presented. Under each category, $T_0$, $T_1$, $T_2$ and $T_{24}$ are given. ‘x’ in the table indicates that the values are not measurable (data unavailable status). During observation, if the patient is moved out of the ward for any reason, the values are not recorded and this is recorded as unavailable. Similarly, as iMote2 is a research prototype, battery and other communication errors lead to errors in the received signal. Based on the received time stamp the program automatically assigns an unavailable status. The accuracies are calculated considering only the available values and an accuracy of 80.77%, 73.08% and 71.15% are obtained using energy based, SMA based and norm based methods respectively. It should also be noted that energy based technique results in over 70% accuracy in $T_{24}$ prediction which are not used in calculation of the thresholds. The energy based method consistently results in standard deviation of 1 among the misclassified output as against the norm based and SMA based approaches.

Although the highest index prediction accuracy using energy based method appears low (80.77%), it should be noted that this implies 4 out of 5 indices are calculated perfectly and one index is varying just by standard deviation of 1. Moreover, the accelerometer based approach results in motor activity index in a much higher resolution of six readings every hour as against one reading every hour. The correlation of variables of calculated indices against the observed values has been assessed by the experts and they are accurate.


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Accuracy: 93.33% 71.15% 93.33% 73.08% 100% 80.77%

The first three columns give basic information about the recording. T₀, T₁ and T₂ are recorded on the first day at the time of onset and every hour subsequent to that. T₂₄ is recorded on the second day at T₀ + 24 hours. The observed values and calculated values using the three methods is given. × means, the recording was unavailable due to either recording technicians fault or fault in the hardware. The errors are highlighted.
Table 5 Confusion matrix showing the misclassification and the results as per three levels of severity- Norm based (left), SMA based (middle) and Energy based (right)

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Rows indicate observed indices.

Although this cannot be verified quantitatively due to resolution mismatch between the data, the experts have closely observed and agreed with the calculated index.

It is important to evaluate the results at varying severities. Table 5 shows the confusion matrix using the three methods. Rows indicate observed values and columns indicate accelerometer based predictions. As it can be seen clearly, energy based method outperforms norm based and the SMA based methods. It results in zero error for higher observed values of severity (2 and 3). However, if the observed value is low (1), the accuracy is only 56% with 27% being classified as medium severity (index 2) and the remaining as high severity (index 3). Non-linear signal processing techniques or more sophisticated features may be required to calculate these indices more accurately when the severity is very low. In order to validate our observations, we calculated Cohen’s statistics and the results are summarised in Table 6. Cohen’s index ($\kappa$) is used as a measure to characterise the reliability of a computer program to match the expert observation and the ability of the method to reproduce the disease classifications [20]. Overall agreement score ($p_o$) and fair-chance corrected agreement ($\kappa$) are calculated for the three proposed methods. Due to multiple levels of stroke index, we have also calculated weighted (linear and quadratic) and unweighted $\kappa$ scores to reduce category bias on $\kappa$. As per our observations, the quadratic $\kappa$ for observer-energy category results in excellent overall agreement ($p_o$) of 0.91 and a fair-chance corrected agreement ($\kappa$) of 0.76 ($\kappa > 0.75$ is considered excellent [21]).

The algorithm was implemented in MATLAB using a laptop with 4GB RAM and Intel i7 processor. The database used as MySQL and Microsoft C# was used for data collection and storing. The algorithm runs almost instantaneously and the first visualisation output occurs a few seconds after the first 10 minutes of data collection (as the analysis window chosen is 10 minutes).

The impact of this work is that it lays the foundation for the development of a device in the monitoring of neurological function post acute stroke. The management of acute stroke is time critical and resource intensive. Particularly important is the window period of 2 to 3 hours after thrombolysis whereby an opportunity exists to re-intervene in patients who fail to respond to the first treatment. Continuous monitoring of neurological recovery in this window period provides valuable insights into the recovery pattern and

Table 6 Cohen’s statistics for the three proposed methods

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Comparison of Unweighted, Linear weighted and quadratic weighted $p_o$ and $\kappa$ calculated for the three methods.
informs the decision to re-intervene which otherwise would not have been impossible. The developed system is not limited to analysis of patients with acute stroke alone. There are many parallel applications that can make use of the technology with the development of new algorithms. There are many similar systems demonstrated for stroke rehabilitation [14]. Similarly, gait analysis and age care devices can utilise the proposed system [16].

In future work, we plan to analyse the accelerometer signal using time frequency analysis in order to improve the classification of the index. As discussed earlier, the variation in the patient’s attitude (whether depressed or not) has considerable effect on the magnitude of hand movement which will impede the effectiveness of the algorithm. This can be addressed by reducing the impact of movement magnitude on the index by calculating better features. The efficiency of data collection also requires improvement by addressing the hardware issues such as power and radio frequency range. This can be done by developing a new hardware prototype dedicated to this objective, which will increase patient movement flexibility as well.

Conclusion
Continuous monitoring of neurological activity is critical in effective stroke monitoring, particularly in the first few hours after the onset of stroke. It provides valuable insight into the recovery pattern and informs the decision to re-intervene with alternate or high dosage drugs. A proof-of-concept wireless accelerometer based motor activity monitoring system is presented in this paper. The architecture and the online algorithm have been presented and shown to work using 15 stroke patients with promising results. Norm based, signal magnitude area and average energy based features are compared for calculating a score equivalent to the NIHSS score and a high correlation is obtained using the energy based method. A new visualisation method is developed which helps the doctors to continuously monitor the recovery pattern. This lays the foundation for the development of a full fledged automated device for acute stroke monitoring.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
JG, BY, MP conceived the study. JG carried out the hardware implementation, development of algorithms and drafted the manuscript. AR participated in the collection and analysis of the data with minor contribution in algorithm development. KF and BY are clinical experts who collected the data, recorded their observations. JG, BY and MP participated in the design and helped to draft the manuscript. All authors read and approved the final manuscript.

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References
Section 4 Relationship with other major disease

This section deals primarily with other major disease and in particular, another very common neurological problem involving over 300,000 persons in Australia. Epilepsy may be a complication of stroke or it may be the result of a common aetiological factor and it is estimated that 40% of persons with epilepsy have concomitant neurological or psychiatric comorbidity. Hence, in my work, I have collaborated with experts in trying to analyse the borderzone between stroke and other neurological diseases especially epilepsy.

List of my publications submitted in full


White Matter Hyperintensities on Brain Magnetic Resonance Imaging in People with Epilepsy: A Hospital-Based Study

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Keywords
Antiepileptic drugs; Epilepsy; Magnetic resonance imaging; Stroke; White matter hyperintensities.

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SUMMARY

Aims: We aim to explore whether people with epilepsy have increased white matter hyperintensities (WMHs). Methods: Eligible patients were categorized into newly diagnosed epilepsy (NE) and chronic epilepsy (CE); the latter were subdivided to those treated with enzyme-inducing antiepileptic drugs (EIAEDs) with or without non-enzyme-inducing antiepileptic drugs (NEIAEDs) and those with NEIAEDs only. WMHs were measured using age-related white matter changes (ARWMC) scale and compared between patients and healthy control group. Higher scores indicate greater WMH changes. The strengths of associations were estimated as incidence rate ratios (IRRs) with 95% confidence interval (CI).

Results: A total of 217 patients were included in the analysis, of whom 67 had NE, 45 had CE treated with NEIAEDs, and 105 had CE treated with EIAEDs. Age was positively associated with ARWMC score (IRR per year, 1.03; 95%CI, 1.03–1.04, P < 0.001). Compared with the healthy control group (n = 23), all patient groups had higher ARWMC score (P < 0.05). The difference was greatest in patients receiving EIAEDs (IRR, 2.13; 95% CI, 1.22–3.70, P = 0.007). Conclusions: WMHs tended to be observed in people with epilepsy, especially in those treated with EIAEDs. People with epilepsy with white matter changes should be evaluated for stroke risk, particularly if they are receiving EIAEDs.

Introduction
Population studies suggest that people with epilepsy are more likely to have subsequent stroke than the healthy population [1,2]. The reasons for this are unclear. The risk appears to be higher in patients on higher doses of antiepileptic drugs (AEDs) [2]. Treatment with AEDs that induce the cytochrome P450 enzyme system (enzyme-inducing AEDs; EIAEDs) is associated with increased risk markers of atherosclerosis. Hyperlipidemia, increased serum homocysteine and C-reactive protein, reduced level of folate, vitamin B12, and increased carotid artery intima media thickness [3–5], all potentially account for the increased stroke risk [6,7]. Conversely, valproate (VPA), an enzyme inhibitor, may decrease adverse vascular events [6,8].

White matter hyperintensities (WMHs), detected on T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) sequence on brain magnetic resonance imaging (MRI), are presumed to be the result of chronic hypoperfusion of the white matter and disruption of the blood–brain barrier, leading to chronic leakage of plasma into the white matter [9,10]. They are more commonly seen in the elderly and in people with hypertension and other vascular risk factors include smoking, diabetes, and a history of vascular disease [9,11]. WMHs are a recognized biomarker of cerebrovascular disease and are associated with 3-fold increase in risk of subsequent stroke and 2-fold increase in mortality [11]. Therefore, WMHs may be used as a surrogate marker for stroke risk.

We examined the burden of WMHs on brain MRI in people with epilepsy. We hypothesized that people with epilepsy have
increased WMHs, and exposure to EIAEDs is associated with more extensive WMHs.

**Materials and Methods**

**Study Population**

This was a retrospective study. The study was approved by the hospital’s Human Research Ethics Committee. Subjects were those patients investigated and treated for epileptic seizures at the Royal Melbourne Hospital (RMH) between 1st August 2009 and 31st July 2013. Eligible patients were consecutively identified from electroencephalography (EEG) laboratory and video EEG monitoring unit. Controls were individuals referred from primary care physicians to the neurology clinics for suspected neurological diseases, but in whom a CNS disorder was excluded after thorough assessment. Individuals with documented psychiatric disorders were also excluded. Both epilepsy group and control group had undergone 3T brain MRI using the same protocol [12].

Eligible subjects were categorized into three groups (Figure 1): (1) people with newly diagnosed epilepsy who had been treated with AEDs for <3 months by the date of the MRI; (2) EIAED group, in whom patients with chronic epilepsy, ever receiving either NEIAEDs or not, were treated with EIAEDs for at least 3 months; and (3) NEIAED group, in whom patients received NEIAEDs for at least 3 months, with EIAEDs for <3 months or without EIAEDs. The duration of 3 months was chosen empirically because shorter exposure has been considered as inadequate trial for AEDs [15].

**MRI Assessment**

Our 3.0 T MRI (Siemens Magnetom Trio, Germany) of epilepsy protocol includes axial FLAIR, T2-weighted, and T1-weighted imaging, where slice thickness is 1 mm [12]. This protocol fulfills recommended standards and parameters for imaging of small vessel disease [9]. WMH was assessed on T2-weighted FLAIR sequence acquired with the following parameters: repetition time, 5000 ms; echo time, 388 ms; inversion time, 1.8 s; matrix, 258 × 256; flip angle, 120°; scan time, 5 min and 52 s. WMH was defined as high signal intensity in the white matter, basal ganglia, and brainstem depicted on FLAIR without cavitation. WMH of nonvascular origin, such as multiple sclerosis, was excluded based on the combination of clinical syndrome and the pattern of WMH. If a patient had undergone more than one MRI, the most recent set of eligible images was assessed.

White matter hyperintensities were rated semiquantitatively using the age-related white matter changes (ARWMC) scale [16]. The validity of this scale has been demonstrated in clinical practice [16,17], providing fast and standardized semiquantitative information [18]. In this visual rating scale, five regions (frontal, parietal–occipital, temporal, basal ganglia, and infratentorial) of the two hemispheres were rated separately (0: no lesions, 1: focal lesion, 2: beginning confluence of lesions, 3: diffuse changes), followed by summation of scores from each region. Examples of rating score are shown in Figure S1. To evaluate the interrater reliability of the ARWMC scale, all MRI images randomly selected for age-stratified patients were rated by BY and PK, who are all experienced board-certified neurologists. The interrater agreement was estimated using interclass correlation coefficients (ICC), with ICC above 0.8 signifying an excellent agreement. All MRI assessment was performed blind to the clinical information.

**Statistical Analysis**

Continuous variables were summarized as medians and interquartile ranges (IQR) and tested by Mann–Whitney U-test or Kruskal–Wallis rank test where applicable. Categorical variables were summarized as percentages and were evaluated using Fisher’s exact test where applicable. ARWMC score was treated as count variable. The relationships between potential factors and ARWMC score were analyzed using the negative binomial regression model [19], which held the best goodness-of-fit in our data among various count models. The strengths of associations were estimated as incidence rate ratios (IRRs) with corresponding 95% confidence interval (CI). For instance, the value of IRRs = 1.5 could be interpreted that per one unit increase in the independent variable, there will be an increase in the ARWMC score by the factor of 1.5. In the multivariate analysis, backwards elimination was used to eliminate variable one by one until all variables achieved a level of conventional significance. Potential factors

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that were significant at $P < 0.20$ in the initial univariate analyses were included as candidates into the multivariate model [20]. Significance level was set at alpha of 0.05, and all tests were 2-tailed. Statistical analysis was performed with the Stata/SE 12.0 statistical package (StataCorp LP, College Station, TX, USA).

**Results**

**Subject Characteristics**

A total of 317 individuals who had undergone 3T brain MRI of epilepsy protocol were eligible for the study. Of 317, 240 (75.7%) were included for analysis and 77 (24.3%) were excluded (Figure 1). The groups were comparable in demographics, seizure history, and vascular risk factors (Table S1). Of 240, 217 had epilepsy (67 with newly diagnosed epilepsy, 45 with chronic epilepsy receiving NEIAEDs, and 105 with chronic epilepsy receiving EIAEDs); 23 were included in the control group. Their clinical characteristics are summarized in Table 1. The epilepsy group and control group were comparable in demographical and vascular risk factors, except for a higher proportion of patients in the epilepsy group being smokers and alcohol abusers compared with the controls (22.1% vs. 0, $P = 0.006$; 30.9% vs. 8.7%, $P = 0.028$, respectively). Not surprisingly higher proportion of patients receiving EIAEDs had focal seizures than generalized seizures compared with other groups, given that CBZ and PHT, both EIAEDs, are first-line treatments for focal seizures.

Of 150 patients in chronic epilepsy group, CBZ and VPA were the most frequently used EIAED and NEIAED, in 88 (58.7%) and 69 (46.0%) patients, respectively (Table S2); 99 (72.3%) received more than one drug till the time of MRIs. Time from index seizure to MRI and duration of AED treatment were both longer in EIAED group than that in NEIAED group (median time: 146.6 vs. 75.9 months, $P = 0.02$; median duration: 109.2 vs. 46.7 months, $P = 0.009$, respectively). Of 67 patients with newly diagnosed epilepsy, 38 (56.7%) had not been commenced on AED therapy and 29 (43.3%) had been treated for <3 months by the time of MRI (median 1.6 [IQR, 1.1–2.2] months).

**ARWMC Score**

An excellent interrater agreement of the ARWMC score was observed (ICC, 0.94; 95% CI, 0.93–0.95). The median ARWMC score in the chronic epilepsy group was 1 (IQR: 0–3), which was higher than that in control group (0, IQR: 0–2, $P = 0.029$). Table S3 shows the regional ARWMC scores in the patient subgroups. Compared to the control group, WMHs (ARWMC ≥1) were detected in significantly higher proportions of patients in the chronic epilepsy group (43.5% vs. 66.4%, $P = 0.039$). Figure 2 shows the distribution of ARWMC scores among the four groups. Univariate analysis showed that age, diabetes, hypertension, dyslipidemia, and atrial fibrillation were associated with ARWMC score (Table 2). Among these covariates, only age remained significant in the multivariate model (IRR per year, 1.03; 95%CI, 1.03–1.04, $P < 0.001$). There was no significant association between ARWMC score and seizure type, duration of treatment, or time from first seizure.

After adjusting for age, patients with epilepsy remained to have significantly higher ARWMC score compared to the control group (IRR, 1.93; 95%CI, 1.13–3.30, $P = 0.016$; Figure 3). Compared to control group, the score was higher in those with chronic epilepsy receiving EIAEDs (IRR, 2.13; 95%CI, 1.22–3.70, $P = 0.007$) and in NE patients (IRR, 1.79; 95%CI, 1.01–3.16, $P = 0.046$), and trended higher in those who had received NEIAEDs only (IRR, 1.65; 95%CI, 0.88–3.10, $P = 0.12$).

**Discussion**

We found significant increase in WMHs among people with epilepsy, especially in those treated with EIAEDs. To our best
knowledge, this is the first study demonstrating an association between EIAEDs and WMHs on MRI brain in people with epilepsy. This finding is consistent with the accumulating evidence suggesting that EIAEDs may pose deleterious effects on arterial vasculature [27]. Several studies demonstrated elevated levels of total cholesterol, low-density lipoprotein cholesterol and triglycerides among patients treated with EIAEDs [5,21,22]. It has been proposed that CYP induction may reduce the levels of oxysterol intermediates, leading to reduced feedback inhibition of hydroxymethylglutaryl-coenzyme A reductase on cholesterol production [14,23]. In addition, elevation of lipoprotein(a) [24], C-reactive protein [23] and homocysteine [4], and increased intima media thickness (IMT) of the common carotid artery (CCA) have been observed in EIAEDs users [5,25]. Conversion of carbamazepine or phenytoin (both EIAEDs) to NEIAEDs, such as lamotrigine and levetiracetam, has been shown to reduce homocysteine levels [3]. The risk of stroke associated with exposure to valproic acid (an enzyme inhibitor) remains controversial. While valproic acid may inhibit atherosclerosis by increasing resistance of the endoplasmic reticulum [26,27], it also increases insulin resistance and the risk

![Figure 2](image)

**Figure 2** Distribution of ARWMC scores in patient groups. Each column represents the percentage of patients with the specified total ARWMC score, which ranges from 0 to 12. The number above each column indicates the number of patients with the specific ARWMC score. ARWMC, age-related white matter changes scale; NE, patients with newly diagnosed epilepsy; AED, antiepileptic drug; EIAED, patients with enzyme-inducing AEDs; NEIAED, patients with non-enzyme-inducing AEDs; IQR, interquartile range; NA, not available. *P* value was calculated from the comparison between control group and entire epilepsy group.

<table>
<thead>
<tr>
<th>Table 1 Characteristics of patients with epilepsy and controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epilepsy</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age, median (IQR), year</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Focal seizures, n (%)</td>
</tr>
<tr>
<td>Generalized seizures, n (%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
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<tr>
<td>Smoker, n (%)</td>
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<td>Alcohol, n (%)</td>
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<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
</tr>
<tr>
<td>Migraine, n (%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
</tr>
<tr>
<td>Head injury, n (%)</td>
</tr>
<tr>
<td>Febrile convulsion, n (%)</td>
</tr>
<tr>
<td>Head surgery, n (%)</td>
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<tr>
<td>Time from first seizure, median (IQR), month</td>
</tr>
<tr>
<td>AED duration, median (IQR), month</td>
</tr>
<tr>
<td>EIAED, median (IQR), month</td>
</tr>
</tbody>
</table>

ARWMC, age-related white matter changes scale; NE, patients with newly diagnosed epilepsy; AED, antiepileptic drug; EIAED, patients with enzyme-inducing AEDs; NEIAED, patients with non-enzyme-inducing AEDs; IQR, interquartile range; NA, not available. *P* value was calculated from the comparison between control group and entire epilepsy group.
of metabolic syndrome [28,29], possibly leading to accelerated atherosclerosis [25]. In our study, we found a trend of higher prevalence of WMHs in people with epilepsy receiving NEIAEDs, of which valproic acid was the most common agent. This supports the notion that valproic acid may also increase atherosclerotic burden.

We also found increased WMHs in newly diagnosed patients, implying that seizures or the epileptogenic process per se may also play a role. It may be postulated that white matter changes on MRI represents cerebrovascular endothelial dysfunction due to increased blood-brain barrier permeability after epileptic discharges [30]. The existence of white matter tract injuries has also been demonstrated by MRI studies in these patients [31,32]. In addition, several animal models have demonstrated increased oxidative stress in neural cells after seizures, especially in mitochondria, leading to subsequent cell damage [33–35]. Oxidative stress is recognized to play an important role in atherosclerosis development [36]. Therefore, recurrent seizures may also contribute to atherosclerosis in patients with epilepsy [37].

White matter hyperintensities is recognized as a reliable predictor of stroke events, cognitive impairment, and mortality. A systematic review including 22 longitudinal studies demonstrated that WMHs were associated with substantially increased risks of stroke (hazard ratio 3.3, 95% CI 2.6–4.4), dementia (hazard ratio 1.9), and premature death (hazard ratio 2.0, 1.6–2.7) [11]. The observed increase of WMH among patients with epilepsy might, therefore, explain their increased prevalence of stroke risk, dementia, and mortality. WMHs might be considered as a useful tool to predict risk of comorbidities or outcomes in people with epilepsy.

Previous studies showed that duration of AED treatment (PHT, CBZ, and VPA) was associated with increased CCA IMT, which is a marker of atherosclerosis [25]. Our study did not find any relationship between AED duration and WMHs, which may be due to the heterogeneous treatment regimens. This study reinforced the previous finding that age is a major predictor of WMHs [11,38]. The prevalence of WMH in the general population has been reported to be 11–21% in people aged 64, rising to 94% in 82-year-olds using 1.5 T or lower MRIs [11]. The median age of the patients included in our study was 36 years (IQR, 26–50). So far, no study has reported WMHs on 3.0 T MRI in the healthy population aged younger than 50. Abnormal ARWMC score was found in 43.5% of control group. This was higher than the prevalence (5.3%) of white matter lesions previously reported in young healthy population (age, 16–65 years; mean, 37 years) [39], possibly due to the increased sensitivity accorded by the high-field MRI performed in our study. Another possible explanation for the observation is that the controls were not truly “healthy controls” as they were selected from people seen in neurology clinics rather than randomly recruited from the “normal population”.

Our study has limitations. As this was a cross-sectional analysis of MRI, demonstration of association does not necessarily imply causation. While recurrent seizures and use of EIAEDs might have contributed to WMHs, an alternative interpretation of the data might be that WMHs are a causative factor of epilepsy. For practical purpose, controls were recruited from neurology clinics rather than the general population. However, any selection bias would likely lead to underestimation of the burden of WMHs in the epilepsy patients. Underreporting of smoking and alcohol drinking cannot be ruled out. Classifying AEDs is controversial in the context of vascular risks. OXC, for instance, has intermediate effects on enzyme induction although it does not affect lipids metabolism as CBZ does [40]. However, including patients receiving OXC in either EIAED group or NEIAED group is unlikely to affect the results given the small number of patients treated with this drug. In addition, our study lacks information about clinical outcomes, such as stroke events, seizure frequency, and seizure severity postdiagnosis, which should be investigated in future studies.

### Table 2

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>ARWMC score</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.02–1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.96</td>
<td>0.70–1.30</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.53</td>
<td>0.89–2.62</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.04</td>
<td>0.71–1.53</td>
<td>0.83</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.02</td>
<td>0.71–1.47</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.37</td>
<td>1.64–3.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.73</td>
<td>1.87–3.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Migraine</td>
<td>1.19</td>
<td>0.61–2.31</td>
<td>0.61</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.73</td>
<td>1.48–5.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Head injury</td>
<td>1.08</td>
<td>0.77–1.51</td>
<td>0.67</td>
</tr>
<tr>
<td>Febrile convulsion</td>
<td>0.93</td>
<td>0.56–1.54</td>
<td>0.78</td>
</tr>
<tr>
<td>Head surgery</td>
<td>0.92</td>
<td>0.55–1.54</td>
<td>0.76</td>
</tr>
<tr>
<td>Time from first seizure(month)</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>AED duration(month)</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.17</td>
</tr>
<tr>
<td>EIAED duration</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.048</td>
</tr>
<tr>
<td>NEIAED duration</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.39</td>
</tr>
</tbody>
</table>

ARWMC, age-related white matter changes; IRR, incidence ratio; CI, confidence interval; AED, antiepileptic drug; EIAED, enzyme-inducing antiepileptic drug; NEIAED, nonenzyme-inducing antiepileptic drug.
Conclusion

Compared to controls, WMHs were more prevalent in people with epilepsy, especially in those treated with EIAEDs. These findings shed new light on the potential mechanisms for the increased risk of stroke observed in people with epilepsy. Our findings suggest that people with epilepsy whose MRI showed WMHs may benefit from evaluation of stroke risk, particularly if they are receiving EIAEDs.

Conflicts of Interest

The authors declare no conflict of interest.

References


Acknowledgments

We would like to thank Dr. Francesco Gaillard for his advice on MRIs of control group. Dr. Kwan has received research grants from the National Health and Medical Research Council of Australia, Australian Research Council, Hong Kong Research Grants Council, and Health and Medical Research Fund. He/Her institution also received speaker fees and/or research grants from Eisai, GlaxoSmithKline, and UCB Pharma.

Supporting Information

The following supplementary material is available for this article:

Table S1. Baseline characteristics of study population.
Table S2. Distribution of AEDs in chronic epilepsy cohort (n = 150).
Table S3 ARWMC scores in regions.
Computed tomography perfusion as a diagnostic tool for seizures after ischemic stroke

Miriam Koome 1 · Leonid Churilov 2 · Ziyuan Chen 1,3 · Ziyi Chen 1,4 · Jillian Naylor 1,5 · Arthur Thevathanan 1 · Bernard Yan 1 · Patrick Kwan 1,5

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Abstract

Introduction Cerebral cortical ischemia is a risk factor for post-stroke seizures. However, the optimal imaging method is unclear. We investigated CT perfusion (CTP) in detecting cortical ischemia and its correlation with post-stroke seizures compared with non-contrast CT (NCCT).

Methods We included patients with acute ischemic stroke admitted to the Royal Melbourne Hospital between 2009 and 2014. Post-stroke seizure information was collected. Cortical involvement was determined on acute NCCT and CTP (Tmax, cerebral blood volume [CBV], and cerebral blood flow [CBF]). The association between cortical involvement detected by different imaging modalities and post-stroke seizures was examined.

Results Three-hundred fifty-two patients were included for analysis. Fifty-nine percent were male, and median age was 73 years (inter-quartile range 61–82). Follow-up was available for 96 %; median follow-up duration was 377 days (inter-quartile range 91–1018 days). Thirteen patients had post-stroke seizures (3.9 %). Cortical involvement was significantly associated with post-stroke seizures across all modalities. CBV had the highest hazard ratio (11.3, 95 % confidence interval (CI) 1.1–41.2), followed by NCCT (5.3, 95 % CI 1.5–18.0) and CBF (4.2, 95 % CI 1.1–15.2). Sensitivity was highest for Tmax (100 %), followed by CBV and CBF (both 76.9 %), and NCCT (63.6 %). Specificity was highest for CBV (77.8 %), then NCCT (75.6 %), CBF (54.0 %), and Tmax (29.1 %). Receiver-operating characteristic area under the curve was significantly different between imaging modalities (p < 0.001), CBV 0.77, NCCT 0.70, CBF 0.65, and Tmax 0.65.

Conclusion CTP may improve sensitivity and specificity of cortical involvement for post-stroke seizures compared to NCCT.

Keywords Ischemic stroke · CT perfusion · Non-contrast CT · Post-stroke epilepsy · Seizures

Introduction

Stroke is the most common risk factor identified in adults with new onset epilepsy in developed countries [1]. Up to 12 % of patients experience seizures after stroke [2–5]. Post-stroke seizures are associated with increased mortality, prolonged hospital stays, and loss of independence [6, 7]. Involvement of cerebral cortex, whether hemorrhagic or ischemic, is one of the most consistent risk factors for post-stroke seizures [2–5, 8, 9]. The association appears independent of infarct size [1].

The optimal method to detect cortical involvement has not been established. Studies have tended to combine findings from different modalities for analysis despite their differing sensitivities. Most studies have relied on non-contrast CT (NCCT) because of its widespread availability and its
essential role as the first line of imaging in patients presenting with acute stroke [5, 10]. Some studies have supplemented NCCT with MRI in selected patients using a variety of sequences, which have markedly different degrees of sensitivity in detecting acute ischemic stroke [3, 4, 11, 12]. Although MRI with diffusion-weighted imaging (DWI) is regarded as the gold standard to detect early ischemia, its use in mainstream acute stroke protocols is limited. In two separate studies of acute stroke imaging, fewer than 60% of eligible patients were able to undergo MRI protocol for reasons including incompatible devices, medical instability, and scanner unavailability [13, 14]. Therefore, an alternative with greater sensitivity than NCCT, but fewer practical limitations than MRI, is desirable.

CT perfusion (CTP) is gaining popularity in acute stroke imaging due to its ability to visualize early infarcted tissue as well as at-risk ischemic penumbra [15]. Combined NCCT/CT angiography (CTA)/CTP has been found to have 80% sensitivity in detecting acute ischemia compared to 58% with NCCT/CTA and 45% with NCCT alone [16]. Compared to DWI, CTP has similar sensitivity but has the advantages of being more widely available, requires considerably less scanning time, and avoids issues with incompatible devices [16, 17]. Its use has not yet been explored in relation to post-stroke seizures.

This study aimed to determine cortical involvement in ischemic stroke using NCCT and CTP and to subsequently estimate its association with post-stroke seizures depending on imaging modality. We hypothesized that the greater sensitivity of CTP would increase the detection of cortical involvement, thereby improving the utility of cortical involvement as a diagnostic marker for post-stroke seizures.

Methods

Subjects

Subjects were identified from a prospective database of patients admitted under the acute stroke unit at the Royal Melbourne Hospital. Patients who were diagnosed with ischemic stroke and underwent CTP at admission were eligible for inclusion. We included patients from April 2009 onward when CTP was introduced in stroke imaging in our hospital. Patients were included up to October 2014. The hospital provides services to adults over 18 years of age; no other age limit was imposed. Patients were contacted via phone survey for the occurrence of seizures before and after stroke using a questionnaire modified from Tan et al. [18], supplemented by hospital records. Patients with no follow-up information, history of seizures prior to stroke or previous stroke, were excluded (Fig. 1). Ethical approval was granted by the Melbourne Health Human Research Ethics Committee (project number QA2010089).

Data collection

Information extracted from the database included age, sex, vascular risk factors, presentation time, Oxfordshire stroke classification, and use of thrombolytic treatment. Follow-up information collected included time from stroke to first seizure, seizure recurrence, and use of anti-epileptic medications. In accordance with guidelines from the International League Against Epilepsy [19, 20], seizures within 7 days of stroke were classified as early seizures and those after 7 days as late seizures. Post-stroke epilepsy was defined as recurrent late seizures or a single seizure occurring more than 1 month after stroke.

Imaging protocols

CT scans were acquired with a Siemens Somatom multidetector scanner (Siemens, Erlangen, Germany). Acute NCCT scans (5-mm-thick slices) within 12 h of stroke onset were included. For CTP, 40 mL of iodinated contrast was injected intravenously at 8 mL/s in the cubital fossa where possible. CTP processing at the Royal Melbourne Hospital changed during early 2012. Prior to this (n = 132), two separate slabs at the ganglionic and supraganglionic levels were obtained as
2 × 12-mm-thick slices each. Images were taken every second for 40 s following an initial 4-s delay. Perfusion maps were acquired using Siemens software (Siemens Syngo, NeuroPCT, Siemens). More recent scans (n = 220) obtained full brain coverage with 10 × 10-mm-thick slices. Following an initial 4-s delay, images were taken every second for 300 s. Perfusion maps were acquired using RAPID software (RAPID, noncommercial research version, Stanford University). Inter-test variability was performed on those patients with perfusion maps obtained with both types of processing during the transition.

MRI with DWI was also performed for a subset of patients (n = 179), at clinical discretion, where ischemic lesions were not initially detected with NCCT or CTP, or to assess reperfusion or extension post-intervention. DWI images were acquired with a 1.5-T scanner (Sigma, GE Healthcare, Milwaukee, WI). DWI images (5-mm-thick slices) acquired within 7 days of stroke onset were included for analysis.

Image analysis

Acute NCCT, DWI and CTP scans were evaluated for the presence or absence of cerebral cortical involvement (Fig. 2). Perfusion maps included were $T_{\text{max}}$, cerebral blood volume (CBV), and cerebral blood flow (CBF). Areas of reduced CBV, CBF, and elevated $T_{\text{max}}$ indicate infarcted tissue, while areas of elevated $T_{\text{max}}$ with preserved CBV and CBF indicate ischemic penumbra. For NCCT, criteria for cortical involvement were loss of grey-white matter differentiation and sulcal effacement. Involvement on $T_{\text{max}}$ required a value greater than 6 s, a previously validated threshold [17], in a cortical region. Involvement on CBV and CBF was counted where there was unequivocal asymmetric reduction in a cortical region. For DWI images, cortical involvement was determined by increased signal intensity. In all cases, changes needed to be visible in at least two adjacent slices to determine cortical involvement. Analysis was performed by a research fellow with training in advanced neuroimaging. Images were analyzed out of time with seizure data collection to avoid interviewer bias. Ten percent of scans were randomly selected for analysis by an experienced neuroradiologist for inter-rater variability.

Statistical analysis

Continuous variables were compared using Wilcoxon Mann–Whitney U test, and categorical variables were compared using Fisher’s exact test. Inter-rater and inter-method agreement was estimated with Cohen’s kappa. Time-to-event analysis with Cox proportional hazard model was performed with the event of interest defined as time to the first post-stroke seizure. To investigate the utility of cortical involvement as a diagnostic marker for seizures after stroke, receiver-operating characteristic (ROC) curve analysis was performed for all four imaging modalities. Areas under the ROC curve (AUC) for different modalities were compared with the chi-squared test, using data from patients who had undergone all four types of scans. Analysis was performed with Stata statistical software (Stata 13.0, College Station, TX, Statacorp LP). A two-tailed $p$ value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 352 patients were eligible for inclusion. Their median age was 73 (inter-quartile range 61–82) and 59 % were...
male. The median onset to presentation time was 126 min (inter-quartile range 68–298 min), 45 % were treated with intravenous tissue plasminogen activator (IVtPA), and the most common stroke type was partial anterior circulation infarct (PACI).

Comparisons of characteristics of those who received CTP and those who did not over the same time period are shown in Table 1. There was no significant difference in age, sex, or pre-morbid function as measured by modified Rankin scale (mRS). As expected, those who underwent CTP presented earlier, and a higher proportion received IVtPA. They were also more likely to have atrial fibrillation, hypertension, and an anterior circulation stroke compared to those who did not have CTP imaging.

Seizure data follow-up

Follow-up information was available for 341 out of 352 patients. Median follow-up time after stroke was 377 days (inter-quartile range 91 to 1018 days). Four patients were excluded due to a history of pre-stroke seizures, leaving 337 for analysis. Of these 337 patients, 13 reported post-stroke seizures (3.9 %), 5 (1.5 %) had early seizures, and 9 (2.7 %) had post-stroke epilepsy (one patient had both). The median time from stroke to seizure occurrence was 76 days (IQR 5–167 days). Characteristics of those with post-stroke seizures and those without are shown in Table 2. Those with post-stroke seizures were more likely to be female and have a total anterior circulation infarct (TACI) than those without post-stroke seizures.

Image analysis

Inter-method agreement in identifying cortical involvement between Siemens and RAPID processing software was substantial (kappa 0.65). Inter-rater agreement for cortical involvement on CTP was almost perfect; kappa for $T_{\text{max}}$ was 1.0, CBV 0.89, and CBF 1.0, and on NCCT was substantial (kappa 0.79) [21].

Five patients’ $T_{\text{max}}$ maps were excluded due to inadequate quality, and 27 patients did not have a NCCT within 12 h. Eighty over three hundred ten (26 %) of the patients were found to have cortical involvement on NCCT, 82/337 (24 %) on CBV, 159/337 (47 %) on CBF, and 239/332 (72 %) on $T_{\text{max}}$. Because of the small number, all patients reporting seizures were combined for analysis. Survival analysis and ROC analysis results are shown in Table 3. Across all imaging modalities, those with cortical involvement were more likely to experience a post-stroke seizure. Cortical involvement on CBV had the highest hazard ratio for post-stroke seizures at 11.3 (95 % confidence interval (95 % CI) 3.1–41.2, $p<0.001$). The corresponding hazard ratio on

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of patients who received CTP imaging and those who did not during the study period (April 2009 to October 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP performed</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
</tr>
<tr>
<td>Sex (male)</td>
</tr>
<tr>
<td>Oxfordshire stroke subtype</td>
</tr>
<tr>
<td>TACI</td>
</tr>
<tr>
<td>PACI</td>
</tr>
<tr>
<td>POCI</td>
</tr>
<tr>
<td>LACI</td>
</tr>
<tr>
<td>Pre-morbid mRS (median, IQR)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>IVtPA received</td>
</tr>
<tr>
<td>Onset to presentation, minutes (median, IQR)</td>
</tr>
</tbody>
</table>

CTP CT perfusion, TACI total anterior circulation infarct, PACI partial anterior circulation infarct, POCI posterior circulation infarct, LACI lacunar infarct, mRS modified Rankin scale, IQR inter-quartile range, IVtPA intravenous tissue plasminogen activator

$^a$ Dichotomous variables were tested with Fisher’s exact test; continuous variables were tested with Mann–Whitney U test
CBF was 4.2 (95 % CI 1.1–15.2, p = 0.030) and NCCT was 5.3 (95 % CI 1.5–18.0, p = 0.008). All patients with post-stroke seizures had cortical involvement on T<sub>max</sub>; hence, no hazard ratio was calculated. Accordingly, T<sub>max</sub> was the modality where cortical involvement exhibited the highest sensitivity for seizures, at 100 %. On both CBV and CBF, cortical involvement had 76.9 % sensitivity, and on NCCT, it was 63.6 %. The modality with the highest specificity of cortical involvement as a diagnostic marker for post-stroke seizures was CBV at 77.8 %, followed closely by NCCT at 75.6 %, CBF at 54.0 %, and T<sub>max</sub> at 29.1 %. Because of the low number of post-stroke seizures in this cohort, all modalities had high negative predictive values (T<sub>max</sub> 100 %, CBV 98.8 %, CBF 98.3 %, and NCCT 98.3 %) but low positive predictive values (CBV 21.2 %, NCCT 8.8 %, CBF 6.3 %, and T<sub>max</sub> 5.0 %). ROC AUC in descending order was CBV 0.77 (95 % CI 0.65–0.89), NCCT 0.70 (95 % CI 0.55–0.85), CBF 0.65 (95 % CI 0.53–0.78), and T<sub>max</sub> 0.65 (95 % CI 0.62–0.67). There was a significant overall difference in AUC between modalities (p < 0.001), suggesting that the utility of cortical involvement as a diagnostic marker for post-stroke seizures depends on the imaging modality.

Table 2  Characteristics of patients with and without post-stroke seizures

<table>
<thead>
<tr>
<th></th>
<th>Post-stroke seizure</th>
<th>No seizure</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>324</td>
<td></td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>75 (56–79)</td>
<td>73 (61–81)</td>
<td>0.70</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>31 %</td>
<td>60 %</td>
<td>0.04</td>
</tr>
<tr>
<td>Oxfordshire stroke type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>53.9 %</td>
<td>23.8 %</td>
<td>0.02</td>
</tr>
<tr>
<td>PACI</td>
<td>38.5 %</td>
<td>55.8 %</td>
<td>0.26</td>
</tr>
<tr>
<td>POCI</td>
<td>7.7 %</td>
<td>10.4 %</td>
<td>0.61</td>
</tr>
<tr>
<td>LACI</td>
<td>0.0 %</td>
<td>9.2 %</td>
<td>0.62</td>
</tr>
<tr>
<td>Pre-morbid mRS (median, IQR)</td>
<td>0 (0, 0)</td>
<td>0 (0, 1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39 %</td>
<td>23 %</td>
<td>0.19</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>23 %</td>
<td>38 %</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85 %</td>
<td>59 %</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>45 %</td>
<td>47 %</td>
<td>0.58</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 %</td>
<td>21 %</td>
<td>0.46</td>
</tr>
<tr>
<td>ivtPA received</td>
<td>46 %</td>
<td>46 %</td>
<td>0.61</td>
</tr>
<tr>
<td>Onset to presentation, min (median, IQR)</td>
<td>125 (61, 425)</td>
<td>127 (68, 296)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

<sup>a</sup>Dichotomous variables were tested with Fisher’s exact test; continuous variables were tested with Mann-Whitney U test. The groups differ significantly in sex, the proportion with TACI, and pre-morbid mRS.

Table 3  Survival analysis and receiver-operating characteristic analysis for the risk of post-stroke seizures with cortical involvement, by imaging modality

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95 % confidence interval)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
<th>ROC AUC (95 % confidence interval)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt; (n = 332)</td>
<td>–</td>
<td>100 %</td>
<td>90 %</td>
<td>5.0</td>
<td>0.65</td>
<td>(0.62–0.67)</td>
</tr>
<tr>
<td>CBV (n = 337)</td>
<td>11.3 (3.1–41.2)</td>
<td>76.9 %</td>
<td>77.8 %</td>
<td>98.8%</td>
<td>21.2 %</td>
<td>0.77 (0.65–0.89)</td>
</tr>
<tr>
<td>CBF (n = 337)</td>
<td>4.2 (1.1–15.2)</td>
<td>76.9 %</td>
<td>54.0 %</td>
<td>98.3 %</td>
<td>6.3 %</td>
<td>0.65 (0.53–0.78)</td>
</tr>
<tr>
<td>NCCT&lt;sup&gt;c&lt;/sup&gt; (n = 310)</td>
<td>5.3 (1.5–18.0)</td>
<td>63.6 %</td>
<td>75.6 %</td>
<td>98.3 %</td>
<td>8.8 %</td>
<td>0.70 (0.55–0.85)</td>
</tr>
</tbody>
</table>

<sup>a</sup>ROC AUC was significantly different between modalities (p < 0.001, chi-squared test)

<sup>b</sup>No hazard ratio was calculated for T<sub>max</sub> as it showed cortical involvement in all patients with post-stroke seizures. Five patients’ T<sub>max</sub> maps were excluded due to inadequate quality

<sup>c</sup>Twenty-seven patients did not have NCCT
179 patients with DWI within 7 days of stroke onset, 118 (65.9 %) had cortical involvement and 61 (34.1 %) did not. Five in the former group and one in the latter group developed post-stroke seizures.

Discussion

As far as we are aware, this is the first study to report the use of CTP in the investigation of post-stroke seizures. A limitation of the previous research in this field is the lack of standardization of imaging methods, employing different methods between and even within studies to detect cortical involvement. This study aimed to address this by separating analysis depending on the type of neuroimaging. The analysis confirmed the importance of cerebral cortical involvement in epileptogenesis, as cortical involvement was associated with a significantly increased risk of post-stroke seizures regardless of the imaging modality used. The analysis also showed that the imaging modalities used in this study are not equal in their detection of cortical involvement and therefore may be of differing utility in the prediction of post-stroke seizures. Although they all displayed high degrees of sensitivity, CBV had the highest specificity (77.8 %), positive predictive value (21.2 %), hazard ratio (11.3), and ROC AUC (0.77), suggesting that it may be the most clinically useful of the modalities examined.

Owing to the small number of patients with post-stroke seizures, it was not feasible to perform separate subgroup analyses for early seizures, late seizures, and post-stroke epilepsy. The etiology of these different types of seizures is thought to differ; however, cortical involvement has been implicated in all types of post-stroke seizures [2–5, 8, 9]. Analyzing the subgroups of seizures separately would be of interest in future, larger studies. It would have been useful to examine follow-up NCCT, which has greater sensitivity than acute NCCT in detecting ischemic infarction [22]. However, in practice, follow-up NCCT is not always performed. In this cohort, only 217 patients (64 %) received a follow-up NCCT between 12 and 72 h post-stroke. This study is also limited by the relatively short duration of follow-up, with the median at just over 1 year. However, it has been shown that the majority of late onset seizures occur within the first year after stroke [23]. Further, the overall rate of post-stroke seizures in this study is consistent with the literature [2–4]. With these limitations in mind, the data nonetheless provide clear direction for further research focusing on the CBV parameter in selecting patients at increased risk of post-stroke seizures.

It is unknown whether CTP would be equally useful in the larger group of acute stroke patients who did not receive CTP as part of their routine investigations. Under current practice, patients who present early are more likely to undergo CTP imaging to guide thrombolysis and endovascular treatment decisions [15]. We have previously shown that IVtPA treatment does not influence the development of post-stroke seizures [18]. Those in the CTP group were more likely to have hypertension and atrial fibrillation, although these risk factors were not associated with the development of post-stroke seizures in this study nor in others [24, 25]. There was a higher proportion of anterior circulation strokes in those receiving perfusion imaging, which has been reported as a risk factor for post-stroke seizures compared to non-anterior circulation stroke [2].

CTP has been shown recently to improve acute stroke management [15]. Findings from this study suggest that it may also inform longer-term outcome. The apparent difference between imaging modalities suggests that carefully targeted neuroimaging should be considered in future studies. For example, risk factors for post-stroke seizures have been combined in an overall risk scale, one of which is cortical involvement [11]. Ensuring the use of the most appropriate imaging modality to identify cortical involvement could be one way to improve the scale.

The findings from this study may also help to guide stratification of stroke patients for follow-up. Undiagnosed and uncontrolled epilepsy can markedly impair patients’ quality of life and incurs substantial costs for health services [26, 27]. It would be useful to select patients at increased risk of post-stroke seizures for more prolonged specialist follow-up, ensuring timely diagnosis and treatment as this is better done under specialist care than in the community [26]. This study indicates that targeted neuroimaging can be used to help select these patients. It is possible that those with cortical involvement on CBV are suitable candidates for longer-term monitoring. Finally, this study provides support for CTP to become more widely used in acute stroke imaging, as it has the potential to better inform clinicians of patients’ seizure risk.

Conclusion

These findings highlight the difference in the ability of different imaging modalities as potential diagnostic tools for post-stroke seizures. They also provide support for the increasing use of CTP in clinical practice. It seems that CTP may provide a way to enhance our detection of patients at higher risk, with CBV showing particular promise.
Compliance with ethical standards  We declare that all human and
animal studies have been approved by the Melbourne Health Human
Research Ethics Committee and have therefore been performed in ac-
dance with the ethical standards laid down in the 1964 Declaration of
Helsinki and its later amendments. We declare that all patients gave in-
formed consent prior to inclusion in this study.

Conflict of interest  We declare that we have no conflict of interest.

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10.1161/STROKEAHA.111.000220

predictors of late-onset seizures and epilepsy in patients with


Tissue plasminogen activator does not alter development of acquired epilepsy

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SUMMARY

Purpose: Tissue plasminogen activator (t-PA), a proven therapy for acute ischemic stroke, is an endogenous serine protease associated with neuronal activity and synaptic plasticity in the brain. Its expression is enhanced after seizures, and is involved in seizure propagation throughout the brain. Therefore, the increased use of t-PA to treat stroke may have important implications for the development of poststroke epilepsy. Using experimental and clinical approaches, we investigated the role of t-PA in the development of epilepsy.

Methods: Mice deficient in t-PA (t-PA<sup>−/−</sup>) or mice genetically modified to overexpress neuronal t-PA (T4) underwent amygdala kindling, and seizure threshold and rates of kindling were compared to those in wild-type mice. For the clinical study, we recruited acute ischemic stroke patients who either received intravenous t-PA treatment on admission to hospital (n = 177; cases) or did not (n = 158; controls). We then assessed the incidence of early and late onset seizures and epilepsy in these patients.

Key Findings: T4 mice were more seizure-prone than wild-type mice, exhibiting lower seizure thresholds (p = 0.002), but there were no significant differences observed in the rate of kindling development when comparing either T4 mice, or t-PA<sup>−/−</sup> mice, to their wild-type controls. Furthermore, we found no significant differences between the proportion of poststroke patients experiencing early or late seizures, or developing epilepsy, between those who received t-PA and those who did not.

Significance: Overexpression of endogenous t-PA lowers seizure threshold but does not influence kindling epileptogenesis. Moreover, the therapeutic administration of t-PA in humans does not influence the development of acquired poststroke epilepsy.

KEY WORDS: Tissue plasminogen activator, Epilepsy, Ischemic stroke, Electrical kindling.

An important contributor to the long-term morbidity in stroke survivors is poststroke epilepsy (Bladin et al., 2000). Stroke has been shown to be associated with a 17-fold higher risk for epilepsy than in the general population (Ryvlin et al., 2006), with the estimated incidence of poststroke seizures ranging from 3% to 11% (So et al., 1996; Wang et al., 1998; Gingrich & Traynelis, 2000; Barnes & Thomas, 2008) and pathologic processes (Tsirka et al., 1995; Tsirka, 1997; Wang et al., 1998; Gingrich & Traynelis, 2000; Wu et al., 2000). An accumulating body of evidence has implicated t-PA as playing a role in the development of epilepsy (i.e., epileptogenesis): t-PA expression is increased after seizures (Qian et al., 1993), whereas t-PA<sup>−/−</sup> mice are resistant to chemoconvulsant-induced seizures (Tsirka et al., 1995). Further studies have demonstrated that t-PA mediates kainic acid–induced seizure propagation (Yepes et al., 2002).

Seizures can occur in an otherwise healthy brain as a result of any number of acute environmental challenges, but the development of the disease state of epilepsy itself requires pathologic reorganization of neuronal circuits to occur over time. The aforementioned studies document the influence of t-PA in modulating seizure activity, but do not address whether t-PA plays a role in disease development. This led us to investigate whether acute or chronic alterations in t-PA nonfibrinolytic roles in the central nervous system, both in physiologic (Baranes et al., 1998; Horwood et al., 2001; Pawlak et al., 2003; Pang et al., 2004; Barnes & Thomas, 2008) and pathologic processes (Tsirka et al., 1995; Tsirka, 1997; Wang et al., 1998; Gingrich & Traynelis, 2000; Wu et al., 2000).
play a role in the development of acquired epilepsy. Combining basic science and clinical investigations, we examined the following: (1) the effect of t-PA on amygdala kindling epileptogenesis in mice; and (2) whether t-PA therapy influences the incidence of poststroke epilepsy following acute ischemic stroke.

**Methods**

**Preclinical study**

**Animals**

We performed two electrical amygdala-kindling experiments using mice sourced from our own colonies. The first compared adult male t-PA−/− mice (total n = 19) to C57Bl/6 wild-type controls (n = 16), whereas the second compared transgenic heterozygous T4 mice (overexpressing t-PA selectively in neurons (Madani et al., 1999; n = 44) to their wild-type C57Bl/6 littermates (n = 22).

**Surgical implantation of electrodes**

Electrode implantation was performed as described previously with modifications (Salzberg et al., 2007). Briefly, mice were anesthetized by intraperitoneal injection of ketamine (100 mg/kg) and xylazine (20 mg/kg). Four holes were drilled into the exposed skull, facilitating the implantation of three extradural recording electrodes, and a bipolar electrode (Plastics One, Roanoke, VA, U.S.A.) into the left amygdala complex (AP: −1.5; ML: +3.5 relative to bregma; DV: −4.0 relative to the dura; Paxinos & Franklin, 2008).

**Seizure threshold test**

Mice were stimulated via the bipolar electrode using an Accupulser Pulse Generator/Stimulator connected to a battery-operated constant stimulus isolator (WPI, Sarasota, FL, U.S.A.). Stimulations consisted of a 1-s train of 1-msec biphasic square wave pulses at a frequency of 60 Hz. To determine the afterdischarge threshold, mice were initially stimulated with a current intensity of 60 μA. To determine the afterdischarge threshold, mice were initially stimulated with a current intensity of 60 Hz. To determine the afterdischarge threshold, mice were initially stimulated with a current intensity of 60 μA. If no seizure was evoked, the current was increased by 20-μA increments until an afterdischarge of at least 6-s duration appeared on the EEG trace (Compumedics, Melbourne, Australia).

**Amygdala kindling**

Mice underwent either conventional amygdala kindling, consisting of bi-daily electrical stimulations with at least 4 h separating the stimulations, or sham kindling. Behavioral changes during kindling were classified according to the Racine (1972) scale, and seizure durations measured by offline analysis. Mice were kindled until they experienced five class V seizures. To assess the influence of seizures on endogenous t-PA activity (below), 1 week following completion of kindling, all mice received a final stimulation, or sham stimulation, and the brains were processed for post-mortem analysis.

**Amidolytic assay for determination of t-PA activity**

Four hours after the final stimulation, brains were excised and the contralateral hippocampus, amygdala, and somatosensory cortex were subdissected for determination of t-PA activity using our previously described S2251 amidolytic assay (Sashindranath et al., 2011). Briefly, 0.1 mL PBS+1% Triton X-100 were added to the tissue, and the samples homogenized and centrifuged at 13,000 g for 4 min. S2251, CNBr-fibrinogen, and plasminogen were added to the supernatant. Using a fluorescence plate reader (BMG Fluostar Optima, BMG Labtech, Ortenberg, Germany), absorbance at λ=405 nm was measured and second-order polynomial equations were best-fitted to each “absorbance at λ = 405 nm versus time” curve (Niego et al., 2008) using GRAPHPAD PRISM (La Jolla, CA, U.S.A.). The second-order coefficient of each best-fit polynomial equation was taken as half the rate of plasminogen activation.

**Data analysis**

Seizure thresholds were compared between t-PA−/− and wild-type, or between t-PA, T4, and wild-type, using unpaired Student’s t-tests. Seizure durations and kindling rates were compared using analysis of variance (ANOVA). t-PA activities were analyzed using unpaired Student’s t-test. Data were analyzed using Statistica software (Statsoft, Tulsa, OK, U.S.A.), and statistical significance was defined as p < 0.05.

**Clinical study**

**Patients**

Three hundred thirty-five acute ischemic stroke patients were eligible for inclusion: 177 patients who received intravenous (IV) t-PA (cases) and 158 who did not (controls). The exclusion criteria for both groups were a history of seizures or epilepsy, poststroke seizure-free patients taking antiepileptic drugs, intraarterial thrombolysis or endovascular embolectomy treatment, and a diagnosis of intracerebral hemorrhage and transient ischemic attack on presentation. The IV t-PA cases were recruited from the electronic stroke database between January 2003 and June 2009, and were consecutive acute ischemic stroke patients who fulfilled criteria for thrombolysis. The non-IV t-PA controls were recruited from July 2008 to December 2008, and were consecutive patients admitted to the Royal Melbourne Hospital Stroke Care Unit ineligible to receive t-PA.

**Clinical data collection**

Patient information was obtained through telephone survey and medical record review. Information on age, gender, vascular risk factors, stroke type, and severity, morbidity, and mortality were collected for each group. Stroke type and severity were classified according to clinical presentation as partial anterior circulation infarct, total anterior circulation infarct, lacunar infarct, or posterior circulation
infarct, according to the Oxfordshire Stroke Syndrome Classification (Bamford et al., 1991). Patients underwent a standardized clinical neurologic evaluation, with morbidity graded according to the 90-day modified Rankin Scale scores (van Swieten et al., 1988).

Patients were followed for 2 years following stroke onset by telephone interview, or until death. Patients who developed seizures within 2 years poststroke had the date of the first seizure recorded, together with the type of seizures and any recurrence. Patients who experienced recurrent seizures (two or more seizures) were considered to have epilepsy. A cut-off point of 2 weeks after stroke onset distinguished between early- and late-onset seizures. Patients who died before 2 years following their stroke were identified, and their date of death was recorded. The questionnaire used to generate this information is included as Data S1.

Statistical analysis

Data analysis was performed using SPSS (IBM, Armonk, NY, U.S.A.) and SAS (Cary, NC, U.S.A.), with a two-tailed p-value < 0.05 considered statistically significant. Chi-square testing assessed whether intravenous t-PA is associated with increased incidence of seizures or epilepsy following acute ischemic stroke. Kaplan-Meier survival curves were constructed whereby patients who died seizure-free before 2 years poststroke, or were lost to follow up, were censored (Bland & Altman, 1998). The primary end point was defined as the occurrence of a poststroke seizure, and this was compared between the cases and controls using the log rank method. Multivariate analysis was performed using a Cox proportional hazards model. Variables in the analysis for cases and controls were determined based on results of univariate analysis. In the multivariate analysis for risk of any seizure, variables used were age, hemorrhagic transformation, and stroke severity. In the multivariate analysis for risk of recurrent seizures, the same variables were used but with the addition of late-onset seizures.

Standard protocol approvals

All animal work was approved by the University of Melbourne Animal Ethics committee, and all human experimentation was approved by the Melbourne Health Human Ethics committee. Informed consent was sought from all patients, and in cases where informed consent could not be sought, relatives or caretakers were interviewed.

Results

Preclinical study

Electrically evoked limbic seizures increase t-PA activity in discrete brain regions

* t-PA–mediated plasminogen activation was not detected in t-PA−/− mice after seizure, or sham seizure (Fig. 1). In wild-type mice, electrically evoked seizures significantly enhanced t-PA activity compared to sham-stimulated controls, with a 168% increase in t-PA activity in the amygdala (p = 0.011). Despite the higher baseline activity of t-PA in T4 mice, electrically evoked seizures further increased t-PA levels by 117%. Increases in t-PA activity were also observed in the hippocampus of both wild-type and T4 mice following a seizure (117% and 36%, p = 0.001). Smaller nonsignificant increases were also seen in the cortex of wild-type and T4 mice (74% and 47%) after seizure. These results demonstrate that t-PA activity is acutely enhanced after kindled seizures throughout the brain, validating this

Figure 1. Electrically evoked seizures increase t-PA activity in brain regions remote from the site of seizure initiation. Plasminogen activation was detected in the amygdala of T4, wild-type (WT), and t-PA−/− mice 30 min following an electrically stimulated tonic–clonic seizure (green-blue bars), or sham seizure (open bars). Sample sizes: T4 seizure = 9, sham = 7; WT seizure = 11, sham = 6; t-PA−/− seizure = 4, sham = 3. *p < 0.05 compared to sham-stimulated control. Data represent group mean + standard error of the mean (SEM).

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Figure 2. Overexpression of t-PA lowers the threshold for electrically induced seizures. Threshold for electrically evoked seizures is significantly reduced in T4 mice (red bar), but is not altered in t-PA−/− mice (blue bar), compared to respective wild-type (WT) controls. Sample sizes: T4 = 15, WT littermates = 13; t-PA−/− = 18, WT control = 12. **p < 0.01. Data represent group mean + SEM.

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model as one in which epileptogenesis could be influenced by increased expression of this enzyme.

**Overexpression of t-PA lowers seizure threshold**

T4 mice required significantly less current to induce a seizure compared to wild-type littermates (p < 0.01) (Fig. 2), suggesting an inherent brain hyperexcitability in T4 mice. In contrast, the afterdischarge threshold did not differ between t-PA−/− mice and wild-type (p > 0.05) (Fig. 2), indicating that the absence of this enzyme does not influence electrically induced seizure threshold.

**Tissue plasminogen activator does not influence amygdala kindling epileptogenesis**

Kindling progressed in all mice as expected, evidenced by increases in seizure severity and duration induced by additional stimulations. However, no significant differences were observed in kindling rates (p > 0.05) (Fig. 3A) or seizure durations (p > 0.05) (Fig. 3B) when comparing t-PA−/− and wild-type mice, or when comparing these outcomes in T4 versus wild-type mice (kindling rate: p > 0.05; seizure duration: p > 0.05) (Fig. 3C,D). This implies that neither t-PA deletion or overexpression, nor seizure-induced t-PA, influences kindling epileptogenesis.

**Clinical study**

**Patient characteristics**

Of the 335 patients, 38 (11.3%) were unable to be included in the analysis because follow-up data were unavailable. This comprised 18/177 IV t-PA cases and 20/158 non-IV t-PA controls. A comparison of baseline characteristics showed that the nature of stroke differed significantly between cases and controls, with patients receiving t-PA more likely to have a total anterior circulation infarction (TACI) (p < 0.001) and less likely to have lacunar infarctions (LACIs) (p = 0.047) or posterior circulation infarctions (POCIs) (p < 0.001) (Table 1). Those receiving t-PA more often had a severe stroke (p < 0.001), anterior circulation stroke (p < 0.001), and a higher mean diastolic blood pressure (p = 0.012). Stroke outcomes also differed between the groups, with t-PA-treated patients more likely to have hemorrhagic transformation (p = 0.006) and a poorer modified Rankin scale (mRS) (p = 0.004), compared to the non–t-PA control group.

**Tissue plasminogen activator administration for acute ischemic stroke does not alter the incidence of seizures**

The cumulative incidence of a seizure over 2 years post-stroke, whether early ($\chi^2 = 0.001; p = 0.973$) or late ($\chi^2 = 0.179; p = 0.672$), was not different between the t-PA treated and nontreated groups. Early onset seizures (i.e., within 2 weeks) occurred in 8 of 159 IV t-PA–treated patients (5.0%) and late-onset seizures occurred in 16 (10.1%). In comparison, 8 (5.8%) and 11 (8.0%) of 138 non–t-PA treated controls experienced an early- and late-onset seizure, respectively. The odds ratio of experiencing any seizure after IV t-PA compared to controls was 1.114 (95% confidence interval [95% CI] 0.581–2.134). The Kaplan-Meier survival curve also indicated no significant difference in any seizure development between t-PA–treated cases and untreated controls ($\chi^2 = 0.432; p = 0.511$; Fig. 4).

**Administration of t-PA for acute ischemic stroke does not alter the incidence of poststroke epilepsy**

The cumulative incidence of epilepsy in the 2 years post-stroke showed no statistical difference between the groups ($\chi^2 = 0.103; p = 0.748$). Epilepsy occurred in 13 (8.2%) of...

Abnormal neuronal and axonal remodeling is thought to be a fundamental component of the pathogenesis of acquired epilepsy following a brain insult, such as postischemic stroke. These neuroplastic events could be influenced by synaptic remodelers, such as serine proteases, centrally acting molecules that can regulate neuronal plasticity (Wang et al., 2008). t-PA is upregulated after seizures (Qian et al., 1993), is involved in seizure propagation through the brain (Yepes et al., 2002), and is involved in excitotoxicity and axonal remodeling (Tsirka et al., 1995), properties that could potentially mediate a vulnerability to acquired epilepsy following a brain insult. Despite the fact that T4 mice, which overexpress t-PA in neurons, exhibit lower thresholds for electrically evoked seizures, we found no evidence that an excess or deficiency of t-PA influenced the development of epilepsy (i.e., epileptogenesis). t-PA deletion or overexpression did not influence the rate of electrical amygdala kindling in mice, a well-validated model of limbic epileptogenesis; in addition, acute treatment with t-PA following ischemic stroke did not alter the occurrence of poststroke epilepsy.

The lower seizure threshold for electrically evoked seizures observed in T4 mice is perhaps unlikely to be due to elevated circulating t-PA levels at the time of stimulation, since, compared to t-PA−/−, wild-type mice also display a relative elevation in t-PA levels but without a difference in threshold. It is therefore possible that this effect is instead reliant on preexisting alterations in brain cytoarchitecture caused by chronic exposure to elevated t-PA. As a protease, several substrates for t-PA exist, which could potentially mediate such alterations. Plasminogen, the predominant substrate, promotes plasmin-dependent fibrinolysis, and this action underlies its clinical utility as a treatment for acute ischemic stroke (Cesarman-Maus & Hajjar, 2005). However, plasmin also mediates neurodegeneration under certain conditions (Skrzypiec et al., 2009), and activates the complement system (Goldberger & Colten, 1980), both of which could be related to changes in seizure threshold. In addition to plasminogen, other substrates for t-PA exist, some of which have been demonstrated to mediate effects of t-PA in the brain. For example, t-PA has been reported to interact with the NR1 subunit of NMDA receptors to potentiate NMDA receptor–mediated neurotransmission (Nicole

### Table 1. Baseline characteristics of stroke patients treated with IV t-PA (cases) or not treated (controls)

<table>
<thead>
<tr>
<th>Variable</th>
<th>t-PA cases (n = 159)</th>
<th>Non–t-PA controls (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient demographics</td>
<td></td>
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<tr>
<td>Age (years), mean ± SD</td>
<td>71.51 ± 14.7</td>
<td>69.99 ± 15.6</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>66 (41.51)</td>
<td>73 (52.90)</td>
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<td>Pre-mRS score</td>
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<tr>
<td>0–1, no. (%)</td>
<td>127 (79.87)</td>
<td>93 (69.40)</td>
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<tr>
<td>2–6, no. (%)</td>
<td>32 (20.13)</td>
<td>41 (30.60)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>118 (74.21)</td>
<td>95 (68.84)</td>
</tr>
<tr>
<td>Smoking history, no. (%)</td>
<td>52 (32.70)</td>
<td>51 (36.96)</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>39 (24.53)</td>
<td>42 (30.43)</td>
</tr>
<tr>
<td>Hypercholesterolemia, no. (%)</td>
<td>77 (48.43)</td>
<td>51 (36.96)</td>
</tr>
<tr>
<td>Ischemic heart disease, no. (%)</td>
<td>61 (38.36)</td>
<td>41 (29.71)</td>
</tr>
<tr>
<td>Atarial fibrillation, no. (%)</td>
<td>41 (25.95)</td>
<td>34 (24.82)</td>
</tr>
<tr>
<td>Previous stroke, no. (%)</td>
<td>21 (13.21)</td>
<td>30 (21.74)</td>
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<tr>
<td>Stroke presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxfordshire Community Stroke Project (OCSP)</td>
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<tr>
<td>PACI, no. (%)</td>
<td>82 (51.57)</td>
<td>78 (56.52)</td>
</tr>
<tr>
<td>TACI, no. (%)</td>
<td>66 (41.51)</td>
<td>14 (10.14)</td>
</tr>
<tr>
<td>LACI, no. (%)</td>
<td>5 (3.14)</td>
<td>12 (8.70)</td>
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<tr>
<td>POCI, no. (%)</td>
<td>6 (3.77)</td>
<td>34 (24.64)</td>
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<tr>
<td>Stroke severity</td>
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<tr>
<td>Moderate, no. (%)</td>
<td>93 (58.49)</td>
<td>124 (89.66)</td>
</tr>
<tr>
<td>Severe, no. (%)</td>
<td>66 (41.51)</td>
<td>14 (10.14)</td>
</tr>
<tr>
<td>Admission glucose, mean ± SD</td>
<td>7.78 ± 3.51</td>
<td>7.67 ± 3.09</td>
</tr>
<tr>
<td>Admission systolic, mean ± SD</td>
<td>150.52 ± 30.24</td>
<td>150.61 ± 29.20</td>
</tr>
<tr>
<td>Admission diastolic, mean ± SD</td>
<td>83.62 ± 14.36*</td>
<td>79.40 ± 14.25</td>
</tr>
</tbody>
</table>

**Variables:** PACI, partial anterior circulation infarction; TACI, total anterior circulation infarction; LACI, lacunar infarction; POCI, posterior circulation infarction; mRS, modified Rankin scale.

### Occurrence of poststroke seizures or epilepsy is associated with a poorer functional outcome but does not alter mortality

Patients with either a seizure or epilepsy were observed to have a poorer functional outcome (10.8% mRS 0–1; 89.2% mRS 2–6; \( \chi^2 = 10.355; p = 0.001 \)) compared to seizure-free patients (37.8% mRS 0–1; 62.2% mRS 2–6), despite no significant difference in pre-mRS scores (\( \chi^2 = 1.076; p = 0.300 \)). However, the presence of seizures was not associated with an increased risk of mortality: 4 (9.3%) and 12 (27.9%) of 43 seizure or epilepsy patients died within 30 days and 2 years, respectively, compared with 41 (16.1%; \( \chi^2 = 0.859; p = 0.354 \)) and 81 (31.9%; \( \chi^2 = 0.118; p = 0.732 \)) of 254 seizure-free patients (Table S1).

### Discussion

159 IV t-PA patients and 9 (6.5%) of 138 controls. Cox proportional hazards analysis showed that the only risk factor for epilepsy for both IV t-PA (hazards ratio [HR] 159 IV t-PA patients and 9 (6.5%) of 138 controls. Cox proportional hazards analysis showed that the only risk factor for epilepsy for both IV t-PA (hazards ratio [HR] 138.561; 95% CI 23.472–817.972; \( \chi^2 = 19.516; p < 0.001 \)) compared to non-IV t-PA controls (HR 6.179; 95% CI 1.086–35.158; \( \chi^2 = 4.214; p = 0.040 \)) was the occurrence of a late poststroke seizure (i.e., >2 weeks following the stroke).
et al., 2001), although this finding remains controversial (Samson et al., 2008; Medcalf, 2011). Alterations in NMDA receptor–mediated neurotransmission, such as might be expected in T4 mice, may lead to neuronal hyperexcitability and result in a lowered seizure threshold. Alternatively, excessive cleavage of pro-brain-derived neurotrophic factor into its mature form (Pang et al., 2004) that may be caused by t-PA overexpression would also be expected to lower seizure threshold, since this growth factor is heavily implicated in seizures (Ernfors et al., 1991) and epilepsy (Binder et al., 2001; He et al., 2004). These speculative mechanisms require further elucidation to determine how excessive t-PA results in reduced threshold for electrically evoked seizures.

It is also interesting to note that t-PA–deficient mice did not demonstrate a raised threshold for seizures, even though other seizure induction paradigms utilizing chemoconvulsants indicate seizure protection in t-PA−/− mice (Tsirka et al., 1995). This discrepancy either indicates the existence of some biologic mechanisms that compensate for the loss of t-PA to maintain normal physiology, or that the electrical method of inducing seizures relies on parameters different from chemoconvulsant models.

The observation that altering t-PA levels does not alter susceptibility to kindling epileptogenesis was somewhat surprising, given the role of t-PA in seizure spread (Yepes et al., 2002) and its role in seizure-induced pathologic mossy fiber sprouting (Wu et al., 2000). However, the results of this study strongly indicate that seizure-induced increases in t-PA expression (Qian et al., 1993) and activity (Sashindranath et al., 2011) do not play a role in the subsequent kindling epileptogenic process. Consistent with this, mice that do not express t-PA kindle at the same rates as wild-type mice.

As far as comparisons can be made between the different paradigms and treatment regimens, the results of the clinical study were consistent with those of the animal study. It is postulated that neuroplastic changes in the brain that occur during recovery from ischemic stroke, with sprouting and growth of new axons and synaptic connections into territories that they do not normally innervate, create aberrant synaptic networks that may play a role in lowering the seizure threshold (Jefferys, 2010). Therefore, given the recognized role of t-PA in neuronal plasticity and the accumulating number of studies demonstrating the association between t-PA and seizures in experimental animals, we asked whether the use of t-PA for acute ischemic stroke would increase the incidence of poststroke seizures and epilepsy. However, we demonstrated that acute treatment with IV-t-PA does not alter the incidence of poststroke seizures and epilepsy compared with nontreated patients. Our findings agree with the results of the only other clinical study that investigated the association between t-PA and seizures. This study recruited three groups of patients (38 IV t-PA patients, 269 anticoagulant patients, and 769 antithrombotic patients) (De Reuck & Van Maele, 2010), demonstrating no association between t-PA and seizures, although the small sample size for the treatment group and the less rigorous method of follow-up used (i.e., reliance on patient readmission following a possible seizure event) limits the strength of conclusions drawn from this study.

In conclusion, our study demonstrates that overexpression of t-PA lowers limbic seizure threshold in mice, but that t-PA itself—either exogenously applied poststroke, or increased or reduced endogenous expression by genetic manipulation—does not appear to influence the development of the disease state of epilepsy.

**Acknowledgment**

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**Disclosure**

The authors declare no conflicts of interest, financial or otherwise, associated with this work. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**


Section 5 Advances in therapeutics for stroke

This is the final section of publications I wish to present. And this comprises the most specific and relevant publications related to my specialty of stroke intervention neurologist. This is a subspecialty warmly endorsed quite recently on the 6\textsuperscript{th} April 2017 by Professor Matthew Kiernan, President of the Australian and New Zealand Association of Neurologists, that in a direct quote “In the last twelve months, there have been four very significant clot retrieval trials – including an Australian study (\textit{EXTEND-IA}) - showing outcomes are dramatically better when clots are removed in the first few hours after a stroke. Some patients can walk out of hospital without disability having presented with a life-threatening stroke.”

Due to the recent publication of the results of the positive findings comparing endovascular treatment with standard care, the currently accepted most favoured treatment in comprehensive stroke centres with access is acute reperfusion by endovascular clot retrieval. However, this form of therapy is appropriate in patients with large vessel occlusion which may only comprise up to 20% of the patient population. As a result, intravenous thrombolysis remains the mainstay in up to 80% of acute stroke patients. Intravenous tissue plasminogen activator (tPA) improves clinical outcomes in patients with acute ischaemic stroke and in the landmark study, NINDS, and in the subsequent ECASS III, the chance of better clinical outcomes increases with tPA compared with placebo if administered within 4.5 hours of ictal onset. The mechanism of action is the conversion of plasminogen, a naturally occurring thrombolytic precursor, to its active form, plasmin, which in turn initiates and accelerates the dissolution of thrombus.

List of my publications submitted in full


Every 15-min delay in recanalization by intra-arterial therapy in acute ischemic stroke increases risk of poor outcome

Anna H. He1, Leonid Churilov2, Peter J. Mitchell3, Richard J. Dowling3, and Bernard Yan1,3*

**Background** Intra-arterial therapy has improved recanalization rates compared with intravenous thrombolysis for acute ischemic stroke; however, superior clinical efficacy has not been convincingly demonstrated. Time to recanalization is postulated as a mechanism hindering the efficacy of intra-arterial therapy. **Aim** To investigate the effects of time to recanalization on clinical outcome postintra-arterial therapy for acute ischemic stroke. **Methods** Clinical data were collected prospectively for consecutive patients undergoing intra-arterial therapy for acute ischemic stroke at a single center between 2009 and 2013. Ninety-day functional outcome was assessed by the modified Rankin scale. Univariate analyses identified candidate clinical variables for inclusion in the multivariable model; multivariable logistic regression analyses identified variables independently associated with good outcome, defined as modified Rankin scale 0–2. **Results** One hundred and seven patients were included in the analysis. Median (interquartile range) age was 67 (54–77) years, 41 (38%) were female, and median (interquartile range) baseline National Institute of Health Stroke Severity score was 18 (13–22). Median time from symptom onset to recanalization was 330 min (interquartile range 277–397). Fifty-four (50%) patients achieved a favorable modified Rankin scale at 90 days. Age, successful recanalization, and time to recanalization were independently associated with good outcome at 90 days in multivariable logistic regression analysis. For every 15 min delay in recanalization, the odds of good outcome decreased by 10%. **Conclusions** Longer time to recanalization was associated with poorer functional outcome post intra-arterial therapy. We recommend that a systematic approach to minimize time delay to treatment is warranted in intra-arterial therapy for acute ischemic stroke. **Key words:** acute stroke therapy, intervention, reperfusion

**Introduction**

Various forms of intra-arterial therapy (IAT) have been developed for acute ischemic stroke since 1994 (1–10) and offer treatment alternatives for patients ineligible for intravenous tissue plasminogen activator (IV tPA) or for those who are poor responders post IV tPA. Several trials comparing IV tPA to IAT, both as stand-alone and adjunctive therapy, have failed to demonstrate clinical efficacy superiority of IAT over IV tPA (1–6). In these studies, the average time to treatment achieved with IAT was consistently longer than that of IV tPA. This discrepancy of time to treatment potentially negates any benefit imparted by IAT.

In the context of IV tPA, a significant correlation between time to treatment and treatment benefit has been demonstrated (11,12). On pathophysiological grounds, it is plausible that the same holds true for IAT, thereby providing one possible explanation for the lack of treatment efficacy observed in studies comparing IAT to IV tPA; however, there is currently no consensus on this issue (5,13–22).

**Aims/Hypothesis**

In this single-center retrospective observational study, we analyzed outcome data for patients undergoing IAT for acute anterior circulation stroke; we hypothesize that delayed time to treatment – specifically, a delay in time between stroke onset and angiographic recanalization by intra-arterial therapy for acute ischemic stroke – is associated with a poorer functional outcome.

**Methods**

**Patients and procedures** Data were prospectively collected on 107 consecutive patients receiving IAT for acute ischemic anterior circulation stroke at our center between October 2009 and February 2013. The collection and use of these data for research purposes were approved by the Hospital Ethics Committee in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Baseline information gathered included demographics, National Institutes of Health Stroke Scale (NIHSS) score on presentation, baseline blood tests, and brain imaging [in all cases, noncontrast computed tomography (CT) using Siemens Sensation 16 (Siemens, Erlangen, Germany); 120 kV, 320mAs, rotation time 1·0 s, slice thickness 4·5 mm, detector combination 12 × 0·75 mm]. In all cases after January 1, 2011, perfusion imaging was also performed as a standard part of the stroke protocol. In some cases, parts of the assessment were performed at an external facility prior to transfer to our center.

Those patients eligible for IV tPA were treated according to standard care and did not preclude consideration for IAT. IAT was considered for those patients presenting with stroke symptoms who had a large vessel anterior circulation stroke on CT angiography (including common carotid, internal carotid, middle...
cerebral artery M1 division and proximal M2), had imaging exclusion of hemorrhage or established infarct, were less than six-hours from symptom onset at the time of arrival to the angiography suite, and had no contraindication to angiography. Suitability for IAT was determined based on a combination of factors including premorbid modified Rankin scale (mRS), burden of medical comorbidities, severity and nonresolution of symptoms, and presence of a hyperdense middle cerebral artery sign on noncontrast imaging. For those undergoing perfusion imaging, the size of the infarct core and tissue at risk (as defined by a relative cerebral blood flow of <30% of the contralateral hemisphere and time-to-peak of >6 seconds, respectively) was also assessed prior to therapy; however, mismatch between infarct core and tissue at risk was not an absolute requirement. The final decision to proceed with IAT was a joint decision made at the discretion of the treating neurologist and neurointerventionist. All patients and/or their next of kin gave informed consent prior to the procedure.

Digital subtraction angiography was performed via a transfemoral approach (transbrachial in one case). The site and number of occlusions were noted. The choice of intervention was at the discretion of the neurointerventionist based on device familiarity and availability, lesion location and appearance, and presence of underlying stenosis. These included clot retrieval using the Solitaire AB Device (ev3 Neurovascular, Inc., Irvine, CA, USA), mechanical thrombectomy with the Merci Retrieval System (Concentric Medical, Inc., Hertenbosch, the Netherlands), percutaneous transluminal angioplasty with gateway balloon catheter and ultrafast (Boston Scientific Corporation, Natick, MA, USA), and IA thrombolysis (urokinase, dose ranges from 500 000 units to 1,000,000 units).

At the end of the interventional procedure, the grade of distal reperfusion, presence of any residual stenosis, and evidence of any procedure-related complications was recorded by the treating neurointerventionist. Distal reperfusion was graded according to the modified Thrombolysis in Cerebral Infarction (TICI) score (23). The time to recanalization (TTR) was taken as the time (in minutes) between symptom onset and the time of the last angiographic run postprocedure.

Each patient received a follow-up noncontrast CT of the brain within 24 h of his/her procedure. The presence of any intracranial hemorrhage was graded as a grade 1 or 2 hemorrhagic infarction or parenchymal hematoma according to the PROACT II protocol (24).

Patients were followed up at three-months poststroke, and their functional outcome was assessed in person by an independent neurologist using the mRS. Information regarding the patient’s TTR, though not deliberately concealed, was not readily available to the neurologist at the time of mRS assessment.

Statistical analysis
Statistical analysis was performed using StataCorp version 12 (Stata-Corp, College Station, TX, USA).

Univariate analysis was performed to determine whether a significant association exists between TTR and outcome. The outcome variable of interest was functional outcome at 90 days, dichotomized into good functional outcome, defined as mRS 0–2, and poor functional outcome, defined as mRS 3–6.

In order to identify and adjust for other variables that affect outcome, univariate analyses were performed on baseline clinical and procedure-related variables. These included age, gender, treatment with IV tPA, type of IAT (Solitaire stent retriever (Ev3, Plymouth, MN, USA), MERCI clot retriever (Concentric Medical, Inc, Mountain View, CA, USA), percutaneous transluminal angioplasty, percutaneous transluminal angioplasty with stent, intra-arterial thrombolysis), comorbidities (type 2 diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, ischemic heart disease, previous stroke/transient ischemic attack), use of general anesthetic vs. conscious sedation, procedure duration, TICI score, vessel perforation, intracerebral hemorrhage (ICH) postprocedure, and symptomatic ICH postprocedure.

Depending on the nature of the underlying distributions, the univariate analyses were conducted using either chi-squared/Fisher’s exact test or Wilcoxon–Mann–Whitney U-test.

Variables associated with functional outcome at a significance level of P < 0.1 on univariate analysis were used for adjustment purposes in multivariable logistic regression model. TTR was modeled in 15-min time bins in order to achieve a more clinically meaningful result. Standard tests of collinearity and model fit were performed.

Results
Data for 107 consecutive patients with anterior circulation strokes treated with IAT were used for analysis. Median age at presentation was 67 years [interquartile range (IQR) 54–77]; 41 (38%) were female; median NIHSS on presentation was 18 (IQR 13–22, range 2–36). Forty-nine (46%) patients received IV tPA prior to IAT.

Baseline characteristics of the study population are given in Table 1.

A range of IATs were employed. The most common was clot retrieval (84%) with either the Solitaire stent retriever (68%) or Merci device (16%). Percutaneous transluminal angioplasty was performed in 21% of cases; a further 9% had stent insertion. Intra-arterial thrombolysis was given in 44% of cases.

Seventy-three (68%) patients achieved successful angiographic reperfusion, as defined by a TICI score of 2b or 3. Vessel perforation occurred in one case. Postprocedural ICH occurred in 26 (24%) patients, of which five were symptomatic (5%). Median TTR was 330 min (IQR 277–397). Fifty-four (50%) patients achieved a favorable 90-day functional outcome. Thirty-day mortality was 12% (n = 13); 90-day mortality was 19% (n = 20).

Univariate analysis demonstrated that shorter TTR was significantly associated with better outcome [median (IQR) 305 (266–372) min for good outcome vs. 360 (295–429) min for poor outcome, P < 0.01, see Fig. 1]. The following baseline variables were also found to be associated with good functional outcome in univariate analysis, at a significance level of P < 0.1 (see Table 2): younger age [median (IQR) 64 (54–77) vs. 71 (57–78) years for poor vs. good outcome, respectively, P = 0.09]; lower baseline NIHSS [median (IQR) 20 (15–23) vs. 14.5 (10–19.25); P < 0.01]; use of percutaneous transluminal angioplasty and stenting.
Table 1 Baseline and treatment characteristics of 107 patients treated with intra-arterial therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>41 (38)</td>
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<tr>
<td>Age, median (IQR)</td>
<td>67 (54–77)</td>
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<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>18 (13–22)</td>
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<td>Treatment variables</td>
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<tr>
<td>IV tPA, n (%)</td>
<td>49 (46)</td>
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<td>Solitaire, n (%)</td>
<td>73 (68)</td>
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<td>PTA, n (%)</td>
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<td>PTAS, n (%)</td>
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<td>MERCI, n (%)</td>
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<td>IA thrombolysis, n (%)</td>
<td>47 (44)</td>
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<td>General anesthetic, n (%)</td>
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<td>Procedure duration (min), median (IQR)</td>
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<td>Successful recanalization (TICI 2b/3), n (%)</td>
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<td>Vessel perforation, n (%)</td>
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<td>Type 2 diabetes mellitus, n (%)</td>
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<td>Hypertension, n (%)</td>
<td>31 (29)</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
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<td>Atrial fibrillation, n (%)</td>
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<tr>
<td>Ischemic heart disease, n (%)</td>
<td>14 (13)</td>
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<tr>
<td>Previous stroke/TIA, n (%)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Procedure duration (min), median (IQR)</td>
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</tr>
<tr>
<td>Successful recanalization (TICI 2b/3), n (%)</td>
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</tr>
<tr>
<td>TICI score, n (%)</td>
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<td>14 (13)</td>
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<td>2b</td>
<td>23 (21)</td>
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<td>50 (47)</td>
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<tr>
<td>Vessel perforation, n (%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Comorbidities</td>
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<td>Type 2 diabetes mellitus, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<td>Atrial fibrillation, n (%)</td>
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<td>50 (47)</td>
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<tr>
<td>Vessel perforation, n (%)</td>
<td>1 (1)</td>
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</table>

IV tPA, intravenous tissue plasminogen activator; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PTA, percutaneous transluminal angioplasty; PTAS, percutaneous transluminal angioplasty and stenting; TICI, Thrombolysis In Cerebral Infarction score; TIA, transient ischemic attack.

There is conflicting evidence regarding the importance of TTR in determining whether IAT is a worthwhile intervention for acute ischemic stroke. Recently, a subanalysis of the Interventional Management of Stroke III trial (25) examined the outcomes of 182 patients undergoing endovascular treatment for acute proximal anterior circulation strokes and found that after adjustment for age, baseline NIHSS, gender, and baseline blood glucose level, longer time to angiographic reperfusion was associated with a poorer functional outcome at three-months. Every 30-min delay decreased odds of good outcome by 12%. This closely mirrors the findings of our study. Together, these studies emphasize the importance of minimizing delays to therapy in the interventional management of stroke.

In contrast, in a study of 859 patients with anterior circulation stroke treated with IAT, Jung and colleagues (15) demonstrated that by using imaging criteria to select patients for treatment beyond six-hours or at an unknown time since onset, similar outcomes could be achieved compared with those treated within six-hours. Likewise, Turk and colleagues (26,27) selected 247 patients with acute stroke to undergo IAT based on imaging criteria and demonstrated that patients treated less than eight-hours poststroke onset fared no better than those treated beyond eight-hours. Together, these studies demonstrated the feasibility of using imaging in patient selection for IAT beyond six-hours post-symptom onset. While our study does not preclude the use of imaging selection for IAT beyond six-hours, it demonstrates that for patients presenting within six-hours, for every 15 min elapsed,
the odds of a good outcome diminishes by 10%, thus providing a strong argument in favour of faster recanalization times.

Galimanis and colleagues (16) used data from 623 stroke patients undergoing IAT to identify factors associated with good outcome. It demonstrated an association between TTR and outcome in univariate analysis and in multivariable models only when presence of collateral circulation was excluded from the model, highlighting the importance of collateral blood supply in extending the treatment window for IAT.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Poor outcome (n = 53)</th>
<th>Good outcome (n = 54)</th>
<th>P value</th>
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<tbody>
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<td>18 (33)</td>
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<td>64 (54–77)</td>
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<tr>
<td>Comorbidities</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (19)</td>
<td>6 (11)</td>
<td>0.261</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>25 (47)</td>
<td>23 (43)</td>
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<td>Hypercholesterolemia, n (%)</td>
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<td>Ischemic heart disease, n (%)</td>
<td>4 (8)</td>
<td>10 (19)</td>
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<tr>
<td>Previous stroke/TIA, n (%)</td>
<td>10 (19)</td>
<td>6 (11)</td>
<td>0.261</td>
</tr>
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<td>Baseline NIHSS, median (IQR)</td>
<td>20 (15–23)</td>
<td>14 (10–19)</td>
<td>&lt;0.0001</td>
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<td>Treatment variables</td>
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<td>IV tPA, n (%)</td>
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<td>26 (48)</td>
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<td>Solitaire n (%)</td>
<td>34 (64)</td>
<td>39 (72)</td>
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<td>PTA n (%)</td>
<td>14 (26)</td>
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<td>PTAS n (%)</td>
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<td>MERCI n (%)</td>
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<td>IA thrombolysis n (%)</td>
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<td>General anesthetic n (%)</td>
<td>47 (89)</td>
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<td>Procedure duration, min, median (IQR)</td>
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<td>TICI score, n (%)</td>
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<tr>
<td>3</td>
<td>16 (30)</td>
<td>34 (63)</td>
<td></td>
</tr>
<tr>
<td>Time to recanalization, min, median (IQR)</td>
<td>360 (295–429)</td>
<td>305 (266–372)</td>
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<tr>
<td>Vessel perforation, n (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
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<tr>
<td>Intracerebral hemorrhage, n (%)</td>
<td>16 (30)</td>
<td>10 (19)</td>
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<tr>
<td>Symptomatic intracerebral hemorrhage, n (%)</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>0.163</td>
</tr>
</tbody>
</table>

IV tPA, intravenous tissue plasminogen activator; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; PTA, percutaneous transluminal angioplasty; PTAS, percutaneous transluminal angioplasty and stenting; TICI, Thrombolysis In Cerebral Infarction score; TIA, transient ischemic attack.

Given that collateralization is not currently modifiable, earlier recanalization may nonetheless result in more favorable outcomes in any given state of collateralization.

Younger age and successful radiographic reperfusion were also independently associated with good 90-day functional outcome. These covariates have gained wide acceptance as being predictors of outcome following IAT. A lower NIHSS on admission showed a trend toward being correlated to good outcome, but did not reach statistical significance.
Our overall proportion of good functional outcomes was 50%. Our rate of successful reperfusion was 68%, which is similar to rates reported elsewhere (1–6,16,22). Our rate of successful reperfusion was 76% when using the Solitaire device, which was the most commonly employed IAT within our study cohort.

Our study has a number of limitations. This is a retrospective analysis of a prospectively collected, observational database without a control arm, which carries with it a number of potential sources of bias. First, the assessment of angiographic reperfusion is performed by the treating neurointerventionist who is aware of the TTR, which introduces a potential source of confounding between these two variables. Second, the lack of randomization of patients into a control arm means that outcomes of IAT cannot be compared against standard treatment. It cannot be excluded that the better outcomes seen with earlier TTR is purely a function of earlier presentation time and earlier initiation of standard stroke care, including IV tPA. Of note, IV tPA was not associated with good outcome in our cohort, making this less likely. Furthermore, our study does not exclude the possibility of IAT beyond six-hours offering benefit compared with a control population, but rather demonstrates a decay in IAT outcomes over time. Lastly, there may exist other potential confounders aside from modeled variables. It is unlikely, however, that such unaccounted for variables exhibit collinearity with treatment times.

In conclusion, our study highlights the importance of TTR in the interventional management of acute ischemic stroke. In our dataset, every 15 min of delay decreased the odds of a good outcome by 10%. In contrast to many nonmodifiable predictors of outcome in stroke, such delays to treatment can be greatly improved upon with appropriate systemic changes. Our data provide a strong argument for greater efforts to be put into more efficient and timely service delivery, in every step of the ‘chain of survival’ from community stroke awareness and recognition, timely dispatch of emergency services, prenotification of hospitals, and at a hospital level, more efficient patient flow from door to the angiography suite, to allow faster recanalization times to be achieved.

Author contributions

A. H. H.: Literature research, statistical analysis, manuscript preparation.
L. C.: Statistical analysis, manuscript review.
P. J. M.: Study design, data acquisition, manuscript review.
R. J. D.: Study design, data acquisition, manuscript review.
B. Y.: Study design, data acquisition, manuscript preparation, manuscript review.

References
17 Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. Stroke 2010; 41:1996–2000.


**Supporting information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Fig. S1 Adjusted effects of individual covariates on probability of good outcome after intra-arterial therapy for acute ischemic stroke, as estimated by multivariable logistic regression model. Variables were plotted as a function of time to recanalization. Continuous variables were plotted by quartiles. Panel A: Age; B: baseline NIHSS: National Institutes of Health Stroke Scale; C: successful reperfusion (as defined by Thrombolysis In Cerebral Infarction score of 2b or 4); D: use of conscious sedation or general anesthesia during procedure; E: history of IHD: ischemic heart disease; F: use of PTAS: percutaneous transluminal angioplasty and stenting; G: procedure duration.
Safeguarding the safety of stroke patients: credentialing of neurointerventionists for mechanical thrombectomy

Emergent mechanical thrombectomy for acute ischemic stroke with large artery occlusion significantly improves clinical outcomes, as proven in the five recently published randomized controlled clinical trials, A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke (MR CLEAN) (1), Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke (ESCAPE) (2), Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection (EXTEND-IA) (3), Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke (SWIFT-PRIME) (4), and Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke (REVASCAT) (5). It is anticipated that referrals for mechanical thrombectomy will increase, obliging health systems to allocate resources to meet the rising demand. A potential decisive factor in the allocation of resources is the limited number of neurointerventionists. A knee-jerk reflex for health system planners is to relax the training requirements of neurointerventionists in order to increase the available numbers. However, it must be recognized that intracranial endovascular therapy is a highly specialized field and mechanical thrombectomy is a procedure with infrequent, albeit potential, lethal harm to the patient. In MR CLEAN, procedural-related complications include 5-6% risk of distal arterial embolization leading to new ischemic infarcts (1). Furthermore, REVASCAT reported 4-9% risk of intracranial arterial perforation by endovascular devices (5), leading to fatality. It is the aim of this article to outline the specific hazardous scenarios during mechanical thrombectomy and the requisite training of a neurointerventionist as a safeguard for the stroke patient.

Arterial access and hostile configuration of the aortic arch

Endovascular mechanical thrombectomy requires, as a first step, the safe placement of a large caliber guide catheter in the cervical segment of the parent artery, for example, the proximal internal carotid artery or the vertebral artery. The first hurdle is the configuration of the aortic arch from which the great cervical vessels originate. In elderly patients, the angle at which cervical arteries emerge is frequently acute and tortuous, necessitating the careful handling of complex-shaped diagnostic catheters within the aortic arch. The danger relates to the aortic arch atheroma, which serves as a potential source of arterial emboli if in the event of inadvertent dislodgement of atherosclerotic material by the mis-handling of catheters. Tortuous parent artery (cervical segments) poses additional challenges to the neurointerventionist. In an attempt to traverse a tortuous segment, increasing force is often required to ‘track’ the guide catheter to the target placement region. Potential complications include, in increasing degrees of severity, arterial vasospasm to arterial dissection with pseudoaneurysm formation.

Placement of microcatheters into second-order and third-order intracranial arteries

The safe placement of guide catheters in the cervical vessels is followed by the navigation of microcatheter, under radiological roadmap guidance, into the intracranial vasculature. In the situation of middle cerebral artery M1 (first order) segment occlusion, it is necessary to place the tip of the microcatheter into one of the M2 segments (second order). This is the minimum requirement to allow for the deployment of a stentriever. Herein lies the danger as the bifurcation of the M1 to M2 segments is highly variable and may not be obvious without careful, considered understanding of the anatomic variations. The novice practitioner is at moderate risk of eventuating perforation of intracranial arteries leading to potentially fatal subarachnoid haemorrhage. This dreaded complication is the dominant driver of fatality in mechanical thrombectomy.

Tandem arterial stenotic lesions

Approximately 20% of acute stroke cases harbor a tandem stenotic lesion separate from the culprit occlusive lesion (2). A typical scenario would be middle cerebral artery occlusion with a tandem proximal internal carotid artery critical stenosis or total occlusion. This scenario requires additional experience in carotid artery balloon angioplasty and carotid stenting. The steps here include traversal of the proximal carotid stenosis with a distal protection device, to avoid further embolic events, and the deployment of balloon angioplasty catheter and carotid stent. These skills, although similar to the handling of microcatheter, nevertheless require separate training for the familiarization of very different endovascular devices.

Credentialing of neurointerventionists

The principles of the credentialing of neurointerventionists for mechanical thrombectomy are intentioned to ensure satisfactory experience in endovascular mechanical thrombectomy and related techniques in order to manage challenging scenarios and arterial complications. It is generally recognized that endovascular-related treatment is the highest risk and most complex of the discipline termed interventional neuroradiology. Credentialing is not strictly uniform among different countries but in general terms, the agreed prerequisite is completion of a two- to three-year neurointervention fellowship after the attainment of one of the specialties of radiology, neurology, or neurosurgery.
The two- to three-year neurointervention fellowship has been published by the American Society of Neuroradiology and mandates at least two-years of full-time training within the precincts of a credentialed training center (6). The curriculum of cognitive training includes at minimum neurological diagnosis of cerebrovascular diseases and the preoperative and postoperative management of cerebrovascular patients. Operative training must include ‘hands-on’ experience in a broad range of cerebrovascular endovascular diagnostic techniques and participation in mechanical thrombectomy, carotid stenting, and intracranial stenting. It could be argued that experience in aneurysm coiling, placement of flow diversion devices, and embolization of arteriovenous malformation is not strictly necessary. However, the exposure to these treatment modalities would certainly enhance the repertoire of the neurointervention trainee and the experience in dealing with complications.

Mechanical thrombectomy represents a major breakthrough in the emergent treatment of acute ischemic stroke. However, the enthusiasm to widely adopt and disseminate this technological advance must be moderated by the knowledge of potential procedural-related complications and the recognition that neurointervention is a highly complex field requiring dedicated, focused training. A balanced and considered approach should include careful credentialing of the next generation of neurointerventionists in order to safeguard the safety of our patients.

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References
Strategies to enable equitable delivery of acute endovascular treatment to stroke patients

See paper by M. Alonso de Leciñana et al. on page 297.

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The recent publication of the five positive randomized controlled studies, MR CLEAN [1], ESCAPE [2], EXTEND-IA [3], REVASCAT [4] and SWIFT-PRIME [5], validating the superiority of mechanical thrombectomy over intravenous tissue plasminogen activator for acute stroke with large artery occlusion, has been regarded as a major breakthrough in the last 20 years of stroke medicine. Strengthened by the announcement of a consensus statement from the European Stroke Organization and European Society of Neuroradiology, mechanical thrombectomy is the current new standard of care for acute stroke patients. However, the provision of mechanical thrombectomy imposes intensive resource requirements, posing challenges to resource-poor health systems. These requirements include rapid access to advanced neuroimaging modalities capable of identification of arterial occlusion and access to a whole suite of endovascular neurointervention capacities, including neurovascular angiography laboratories, neurointerventionists and support staff. The corollary of such resource requirements threatens the equitable delivery of beneficial treatment, favouring city dwellers living in close proximity to tertiary health centres and disadvantaging those in rural areas. The consequence is the so-called evidence-treatment gap. The timely publication of the study by Alonso de Leciñana et al. [6] offers a model which regional governments can replicate in an effort to broaden the provision of mechanical thrombectomy to rural patients. Whilst the finer specifics may not be applicable to countries outside Spain, the underlying principles are laudable and are discussed in the following.

The stroke network espoused by Alonso de Leciñana et al. is based on the premise that a small core group of hospitals (termed hub hospitals) are given enough resources to treat referrals from a larger network of referral hospitals (spoke hospitals). The advantage of such a system (also termed hub-and-spoke) avoids the dilution of resources, especially the limited number of highly specialized neurointerventionists, and at the same time concentrates the volume of cases to the hub centres, allowing for maintenance of neurointerventional skills. The training of neurointerventionists requires explanation. The procedure of mechanical thrombectomy is not simply ‘find the blocked pipe and unblock it’. The handling of endovascular devices (microcatheters, microguidewires, stentrievers etc.) requires an intimate knowledge of intracranial neurovascular anatomy and meticulous care to avoid potentially fatal complications, namely arterial perforation by devices. There are established training fellowships, usually 2 years in addition to the attainment of a specialty such as radiology, neurology or neurosurgery, but only in centres whereby trainees can obtain quality training by credentialed supervisors. In addition, after the completion of neurointervention fellowship training, the maintenance of a minimum number of procedures per year is critical in the avoidance of ‘deskilling’ of the neurointerventionist. Therefore, the concentration of mechanical thrombectomy cases in a limited number of hub hospitals is essential to ensure the safety of patients.

It was to the credit of Alonso de Leciñana that the hub-and-spoke system was capable of providing mechanical thrombectomy to stroke patients residing in a 6.3 million population in Madrid. The authors described a weekly rota ensuring 24 h and 7 day cover. It was also of interest that the maximal distance for patient transport from a spoke hospital to core hospital was 12 km, resulting in an acceptable time delay to an angiography laboratory. Another notable achievement in the system was the availability of neuroimaging at the spoke hospital to be assessed by the hub hospital. The key aims of the study were to investigate the differences in onset to arterial puncture (a common metric for assessment of the in-hospital time barriers) and safety between patients primarily admitted to hub hospitals and those admitted to spoke hospitals with subsequent transfer to hub. Of a total of 303 stroke patients in the study period, 201 were treated by mechanical thrombectomy. Unsurprisingly, there was a significant difference in onset-to-arterial-puncture time between hub and spoke centres (230 min vs. 323 min, \( P < 0.001 \)). This was also partly explained by
the inter-hospital delays of 60 min (interquartile range 44; 86). However, it was encouraging to note the lack of significant differences in outcomes between transferred and non-transferred patients: functional independence (as defined by a modified Rankin Scale 0–2) 58% vs. 56%. Moreover, the rate of symptomatic haemorrhage was 3% in the two groups which was in line with the five published randomized controlled studies [1–5].

In summary, the demand for the provision of mechanical thrombectomy for acute ischaemic stroke with large artery occlusion will increase given the overwhelming positive results of the recent randomized controlled trials. However, mechanical thrombectomy is a highly specialized field and care must be given to preserve and maintain the valuable skills of the few in order to benefit the many. It follows that the designation of a few highly specialized centres to service a broader network of referring spoke centres is the preferred model. Alonso de Leciñana et al. [6] have demonstrated that such a hub-and-spoke model is pragmatic and safe and deserves to be emulated by regional health systems.

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References
Early Recanalization Postintravenous Thrombolysis in Ischemic Stroke with Large Vessel Occlusion: A Digital Subtraction Angiography Study

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Keywords
Digital subtraction angiography; Ischemic stroke; Large vessel occlusion; Recanalization; Thrombolysis.

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SUMMARY

Aims: We aimed to evaluate early recanalization postintravenous (i.v.) tissue plasminogen activator (t-PA) by digital subtraction angiography (DSA) in acute ischemic stroke (AIS) with large vessel occlusion (LVO). Methods: We performed baseline CT angiography to identify LVO in AIS. Recanalization pre- and post-intra-arterial therapy (IAT) was categorized to none, partial, and global recanalization (GR). Modified Rankin Scale score ≤2 at 3 months was considered a favorable outcome. Results: Among 1610 patients with AIS, 286 received IV t-PA. Of these, 55 patients with LVO were included. The median time from IV t-PA to DSA was 120 min (interquartile range, 79–152). Recanalization post-IV t-PA was observed in seven patients (12.7%). By occlusion sites, the recanalization rates were as follows: extracranial internal carotid artery 2 of 14 (14.3%); intracranial internal carotid artery 3 of 24 (12.5%); M1 of middle cerebral artery 3 of 39 (7.7%); M2 of middle cerebral artery 1 of 40 (2.5%); vertebral artery 0 of 4; and basilar artery 0 of 7. GR post-IAT was associated with favorable outcomes (odds ratio: 8.6; 95% confidence interval, 1.5–48.0; P = 0.014). Conclusion: Early recanalization assessed by DSA post-IV t-PA is rarely observed in acute ischemic stroke patients with LVO.

Introduction

Intravenous (i.v.) tissue plasminogen activator (t-PA) improves clinical outcome of patients with acute ischemic stroke (AIS) [1]. However, large vessel occlusion (LVO) responds poorly to t-PA, leading to reduced recanalization rates and unfavorable clinical outcomes [2–4]. Recently, updated evidence from several trials (MR CLEAN, ESCAPE, EXTEND-IA, etc.) showed that combined IV t-PA and intra-arterial (IA) intervention offered both superior recanalization and clinical outcomes in cases of LVO [5–9]. Early recanalization post-IVT in each arterial segment as well as whole arterial tree was rarely assessed by digital subtraction angiography (DSA) in real world. Multiple grading scales, such as Thrombolysis in Myocardial Infarction (TIMI) scale and Thrombolysis in Cerebral Infarction (TICI) scale, have been used to evaluate the recanalization status, only showing modest inter-rater agreement though [10,11]. In our study, we aimed to perform a simplified grading scale to assess recanalization success based on baseline CT angiography (CTA) followed by DSA in the cohort of AIS patients with LVO. We also explored the relationship between recanalization success and clinical outcomes.

Materials and Methods

Subjects

This was a retrospective study designed to analyze a prospectively collected data set of consecutive patients admitted for AIS from June 2010 to December 2013. Patients in current clinical trials were not included in our study. Human Ethics Committee in Royal Melbourne Hospital has approved the use of human subjects for our study. All patients’ information was anonymized and de-identified prior to analysis. Therefore, patient consent was not obtained. Our hospital was centrally located in the Greater Melbourne metropolitan covering a population of 4.2 million. Since 2007, a Code Stroke system has been implemented in our stroke service with a rapid notification to the stroke team by Emergency Department. In addition, combined IV-IA therapy was not broadly employed until 2010. All patients were examined, and National Institute of Health Stroke Scale (NIHSS) scores were obtained by trained neurologists or trained personnel before IV t-PA administration. Baseline information was collected, including demographics and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, as well as history of ischemic heart disease and
stroke). The decision in administering IV t-PA was modeled according to the inclusion criteria of European Cooperative Acute Stroke Study III [12], including patients older than 80 years if otherwise healthy and without contraindications.

For anterior circulation ischemic stroke, we followed protocol whereby patients were selected if the ischemic area was less than 1 of 3 of the middle cerebral artery territory [13,14]. In addition, other criteria were as follows: (1) acute anterior ischemic stroke within 4.5 h of stroke ictal onset or acute posterior circulation stroke within 24 h of onset; (2) NIHSS > 4 at presentation; (3) LVO on CTA of intracranial internal carotid artery (i-ICA, i.e., C2-C7), M1 of middle cerebral artery (M1-MCA), M2 of MCA (M2-MCA), vertebral artery (VA), and basilar artery (BA), with or without the occlusion of extracranial ICA (e-ICA, i.e., C1); (4) pre-stroke modified Rankin Scale (mRS) score of <2.

Vessel Assessment

All eligible patients underwent CTA of neck and brain following noncontrast CT (4.5 mm slices) before or immediately after t-PA bolus, if there were no contradictions, such as a past history of renal dysfunction and previous allergic reaction to contrast agents.

CT angiography was obtained via 16-slice multidetector scanner (Siemens, Erlangen, Germany) using 70 mL contrast at 5 mL/s, 100 kV, and 200 mA with slice thickness of 0.75 mm. Image acquisitions were auto-triggered by the appearance of contrast media in the ascending aorta. Occlusions were categorized into six segments: e-ICA, i-ICA, M1-MCA, M2-MCA, VA, and BA. A segment was defined as occluded if it contributed to the present AIS and did not opacify on CTA.

According to the initial angiogram, occlusive segments on baseline CTA were dichotomized as: (1) persistent occlusion—no continuous contrast material going through these segments; and (2) recanalization—continuous contrast material through the previously occluded segments. Of note, recanalization of M2-MCA was specified by opacification of all M2-MCA branches. This grading scale was consistent with the definition of occlusion on CTA. The angiograms were assessed by two independent observers (P.M. and B.Y.) separately and who were blinded to clinical outcomes. Patients were categorized to three groups: (1) no recanalization (NR)—all previously occluded segments remain occluded; (2) partial recanalization (PR)—not all previously occluded segments were patent; and (3) global recanalization (GR)—all previously occluded segments were patent. In the circumstances of occluded proximal ICA coinciding with opacified MCA on baseline CTA, contralateral ICA angiography would be attempted to confirm whether the ipsilateral MCA was patent.

Intra-arterial thrombolysis or thrombectomy was used either alone or in combination, and a permanent stent was used in severe stenotic e-ICA only if necessary to access to distal occlusion or to prevent acute reocclusion. Urokinase up to 500,000 units was used during IA thrombolysis. In our stroke center, stent retrievers (Solitaire FR, Covidien/eV3, Plymouth, MN, USA) were used in approximately 80% of AIS cases treated with combined IV-IA. The endpoint of intervention was mTICI ≥ 2b. The procedure would be abandoned beyond 8 h of stroke onset except for patients with BA occlusion. The final DSA acquisitions were assessed by mTICI.

Outcomes

The primary outcome was recanalization of any segment post-t-PA. Secondary outcomes were favorable outcomes, death at 30 days and 3 months due to any cause, and symptomatic intracerebral/intracranial hemorrhage (SICH) in the three patient groups defined by the pattern of recanalization as aforementioned. The definition of favorable outcomes was that mRS scores at 3 months were 0–2 or equal to premorbidity. SICH was defined as local or remote parenchymal hemorrhage type 2 within 36 h of treatment, combined with a neurological deterioration of ≥4 points compared with baseline NIHSS or the lowest NIHSS value between baseline and 24 h [15].

Statistics

The numerical variables were presented as medians and interquartile ranges (IQR) and tested by Mann–Whitney U-test where applicable. Categorical variables were presented as percentages and were evaluated using Fisher exact test where applicable. The inter-rater agreement on the recanalized status of each segment post-IV t-PA was assessed using κ value. The relationships between potential factors and outcomes were estimated as odds ratios (ORs) with corresponding 95% confidence interval (CI) using logistic regression modeling. We set significance level at alpha of 0.05, and all tests were 2-tailed. Statistical analysis was performed with the Stata/SE 12.0 statistical package (StataCorp LP, College Station, TX, USA).

Results

We collected 286 (17.8%) consecutive patients who received IV t-PA of 1610 patients with AIS admitted to our hospital between 2010 and 2013. Of 286 patients, 223 (80%) had CTA at baseline which identified LVO in 150 (67.3%) cases, in which 76 (50.6%) underwent combined IV-IA therapy (Figure 1). A total of 55 (72.4%) patients were included in the analyses, while 21 (27.6%) were recruited in EXTEND-IA trial. Demographics and vascular risk factors are shown in Table S1. Compared with the patients who were excluded from our study, included ones had younger median age (69 vs. 77; IQR, 58–77 and 67–85, respectively; P < 0.0001), higher median NIHSS score at baseline (16 vs. 11; IQR, 11–20 and 6–18, respectively; P = 0.003), and shorter median time from onset to treatment (OTT) (126 min vs. 132 min; IQR, 105–172 and 101–188, respectively; P = 0.82). Eight (14.6%) of 55 had AIS in posterior circulation.

Overall, 128 occlusive segments in 55 patients were identified by CTA at baseline. Between two observers, the agreement on recanalization status visualized by angiogram was excellent (κ = 0.94, P < 0.0001) and final assessment results were achieved by consensus. The median time from t-PA bolus to baseline angiogram was 120 (IQR: 79–152) min. Recanalization rates of occlusive segments were listed in Table 1. Of those segments, recanalization after IV therapy was seen in two occlusive e-ICA (2 of 14, 14.3%), followed by i-ICA (3 of 24, 12.5%), M1-MCA (3 of 39, 7.7%), M2-MCA (1 of 40, 2.5%), VA (0 of 4, 0), and BA (0 of 7, 0) (P = 0.47).
Early recanalization post-IV t-PA was only observed in 7 patients (12.7%) comprised of 2 (3.6%) with global recanalization and 5 with partial recanalization (9.1%). Baseline characteristics between patients with recanalization and ones with no recanalization were statistically similar (Table S2).

Recanalization after IV-IA treatment was observed in 46 patients (83.4%), of whom 38 (69.1%) achieved global recanalization. The median time from initial angiogram to end of procedure was 74 (IQR: 49–93) min. Compared with patients with no recanalization, ones with global recanalization were more likely to achieve favorable outcomes at 3 months (OR, 8.6; 95% CI, 1.5–48.0; \( P = 0.014 \)), which remained significant adjusted for age and baseline NIHSS score (adjusted OR, 6.5; 95% CI, 1.1–39.5; \( P = 0.041 \)); partial recanalization was not associated with favorable outcomes (OR, 1.2; 95% CI, 0.1–11.0; \( P = 0.89 \)). Favorable outcomes were observed in a higher proportion of patients with global recanalization and excellent reperfusion (OR, 13.5; 95% CI, 2.5–72.6; \( P = 0.002 \)), compared with patients with both incomplete recanalization and poor reperfusion (Table 2).

**Discussion**

Our study showed that early recanalization post-IV t-PA in either any arterial segment or whole arterial tree was rarely observed in AIS patients with LVO. Global recanalization postcombined IV-IA therapy was associated with good outcomes.

Early recanalization rate after IV t-PA has been reported previously utilizing different imaging modalities and grading scales. In a CTA-proven occlusion cohort of 127 patients, recanalization (more than TIBI 3 or TIMI 2) was, respectively, observed in 32.6% of 46 patients assessed by TCD and 11.7% of 103 performed by DSA (i-ICA: 4.4%; M1-MCA: 32.3%; M2-MCA: 30.8% and BA: 4%) [2]. Few studies used DSA to assess early recanalization after...
Early Recanalization post-IV t-PA in LVO

Y.-T. Mao et al.

Table 2. Relationships between clinical outcomes and recanalization status post-combined IV-IA therapy in multivariable logistic regression

<table>
<thead>
<tr>
<th>Recanalization status</th>
<th>mRS ≤ 2 at 3 months</th>
<th>mRS &gt; 2 at 3 months</th>
<th>SICH</th>
<th>Death at 30 days</th>
<th>Death at 3 months</th>
<th>No. (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>No. (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>No. (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>No. (%)</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>No. (%)</td>
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<td>P</td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>NR or PR co-occurring with mTICI &lt; 2b (n = 12)</td>
<td>1 (18.3)</td>
<td>0.14</td>
<td>1 (6.7)</td>
<td>0.14</td>
<td>1 (16.7)</td>
<td>0.14</td>
<td>1 (2.7)</td>
<td>0.14</td>
<td>1 (6.7)</td>
<td>0.14</td>
<td>1 (16.7)</td>
<td>0.14</td>
<td>1 (2.7)</td>
<td>0.14</td>
<td>1 (6.7)</td>
<td>0.14</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>PR co-occurring with mTICI ≥ 2b (n = 37)</td>
<td>1 (41.7)</td>
<td>0.045</td>
<td>1 (27.0)</td>
<td>0.013</td>
<td>1 (13.5)</td>
<td>0.045</td>
<td>5 (13.5)</td>
<td>0.2</td>
<td>0.004-0.7</td>
<td>0.7</td>
<td>6 (50.0)</td>
<td>1 (0.02-0.97)</td>
<td>0.45</td>
<td>5 (13.5)</td>
<td>0.2</td>
<td>0.004-0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>NR or PR co-occurring with mTICI ≥ 2b (n = 12)</td>
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<td>0.14</td>
<td>1 (16.7)</td>
<td>0.14</td>
<td>1 (2.7)</td>
<td>0.14</td>
<td>1 (6.7)</td>
<td>0.14</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

Reference group in regression model. IV, intravenous; IA, intra-arterial; NR, no recanalization; PR, partial recanalization; mTICI, modified Thrombolysis in Cerebral Infarction scale; SICH, symptomatic intracerebral/intracranial hemorrhage; OR, odds ratio; CI, confidence interval; NA, not available due to insufficient numbers; mRS, modified Rankin Scale.

IV t-PA. A DSA study of 31 patients with LVO on initial CTA found early recanalization (TICI 2 or 3) in 7 (22.6%) patients, among whom recanalization rate of ICA or proximal MCA, distal MCA and BA was 12.5%, 27.3% and 50%, respectively [16].

Our study showed that the rate of recanalization post-IV t-PA was 14% in e-ICA, followed by 12.5% in i-ICA, 7.7% in M1-MCA, and 2.5% in M2-MCA. Surprisingly, it appeared that recanalization was more frequent in the occlusion of larger caliber vessels, although the trend was not significant. The larger caliber vessels, actually, were more proximal arteries. It was possible that thrombus in proximal artery (e.g., ICA) could move forward to distal branches (e.g., MCA) after IV t-PA. We also showed a low recanalization rate of distal MCA. This finding was contrary to findings in previous studies. Distal MCA was often evaluated to be occluded in the scenario of proximal MCA occlusion due to absent antegrade flow. Recently, a 4D-CTA study demonstrated that occlusion extended from M1-MCA to M2-MCA in 29% of patients with isolated MCA occlusion [17]. In our study, M2-MCA was considered to be patent only if two or three branches are all open. By this definition, recanalization of M2-MCA was less than expected.

Despite imbalances in baseline characteristics including age, stroke severity, and OTT, early recanalization rate in our study was lower than that reported in the literature, ranging from 22.6% to 51.3% [2,16,18-22]. The differing recanalization rates were likely caused by variable measurements owing to the utilization of different imaging tools and grading scales. TCD was a non-invasive tool for recanalization evaluation in real-time post-IV thrombolysis. However, it is operator-dependent and insensitive to visualization of distal vessels and infeasible in patients with sub-optimal acoustic windows [23,24]. Therefore, recanalization status may not be reflected precisely by TCD. Furthermore, accuracy of recanalization rate was also hindered by inequality between pre- and post-thrombolytic scales. In certain DSA studies, TIMI/TICI system was used after IV t-PA to evaluate the status of baseline CTA-proven occlusion that was assumed to be equal to grade 0 or 1 in TIMI/TICI scale [2,16], which was inappropriate due to recanalization differing from reperfusion [25].

Based on the high degree of agreement (100%) on arterial occlusion between CTA and DSA [26], we adopted a simple criterion (“persistent occlusion/recanalization”) of arterial patency to assess status of each arterial segment on pre- and post-thrombolytic angiography. This method was simple to perform and showed excellent inter-rater reliability ($\kappa = 0.94$) compared with either arterial occlusive lesion ($\kappa = 0.39$) or TIMI ($\kappa = 0.40$) or TICI ($\kappa = 0.45$) [10,11].

To improve global cerebral circulation rather than merely one segment, we assessed, in addition to recanalization status of focal segments, also that of the whole arterial tree. Our study did not show an association of patency of all occlusive segments (i.e., global recanalization) post-IV t-PA with clinical good outcomes. This may be due to the small number of cases with recanalization leading to Type 2 error. However, global recanalization after IV-IA treatment, as expected, was associated with good outcomes. Conversely, if not all segments were recanalized (i.e., incomplete recanalization), favorable outcome was unlikely. Incomplete recanalization could be associated with clot burden, which was approximately measured as the number of arterial occlusions [27]. Previous studies showed that incomplete recanalization
might lead to reocclusion associated with clinical deterioration, which could be a possible explanation for our findings [28,29].

Digital subtraction angiography was the only tool for assessing recanalization post-IV t-PA in our study. Furthermore, same scale was applied to pre- and post-thrombolytic angiograms. Our study maintained consistency in measurements of recanalization status which may improve the accuracy of recanalization rate. In addition, we developed a simple and feasible grading scale for the evaluation of global recanalization status after treatment, which was associated with clinical outcomes. However, our study had several limitations. It was a retrospective analysis of prospective data and not all patients treated with IV t-PA underwent angiogram, leading to a potential for bias in the selection of subjects. Patients in our study were younger and had more severe stroke than the excluded patients with AIS. Our sample size was small. As a result, the number of patients with recanalization post-IV t-PA may not be adequate to demonstrate the association with clinical outcomes. In addition, adjustment for age and baseline stroke severity in analyzing the association of recanalization status with favorable outcomes at 3 months may be unstable statistically due to insufficient sample size. Given the invasive nature of DSA, baseline arterial status was measured by CTA in our study. However, CTA does not provide real-time flow hemodynamic information. Therefore, using CTA and DSA at different time points may cause a potential error in the definition of occlusion.

Conclusions
The rate of early recanalization postintravenous t-PA demonstrated by DSA was low in acute ischemic stroke patients with large vessel occlusion identified by baseline CTA in our center. This information may be useful for the consideration of patients for intra-arterial therapy.

Acknowledgments
We gratefully acknowledge the entire stroke team and all neuro-radiologists in Royal Melbourne Hospital.

Conflict of Interest
The authors declare no conflict of interest.

References
Evolution of Endovascular Therapy in Acute Stroke: Implications of Device Development

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Intravenous thrombolysis is an effective treatment for acute ischaemic stroke. However, vascular recanalization rates remain poor especially in the setting of large artery occlusion. On the other hand, endovascular intra-arterial therapy addresses this issue with superior recanalization rates compared with intravenous thrombolysis. Although previous randomized controlled studies of intra-arterial therapy failed to demonstrate superiority, the failings may be attributed to a combination of inferior intra-arterial devices and suboptimal selection criteria. The recent results of several randomized controlled trials have demonstrated significantly improved outcomes, underpinning the advantage of newer intra-arterial devices and superior recanalization rates, leading to renewed interest in establishing intra-arterial therapy as the gold standard for acute ischaemic stroke. The aim of this review is to outline the history and development of different intra-arterial devices and future directions in research.

Keywords Mechanical Thrombectomy; Acute Ischemic Stroke; Clot Retrieval; Endovascular; Stentriever

Introduction

Timely administration (< 4.5 hours) of intravenous recombinant tissue plasminogen activator (IV rt-PA or tPA) improves outcomes in acute ischemic stroke. However, IV tPA is associated with early recanalization in only 21% of cases, with worse rates in distal internal carotid and basilar artery occlusions, and frequent re-occlusions after IV tPA in 12%. Furthermore, the narrow time window and strict exclusion criteria limits the opportunity for IV thrombolysis, with a significant proportion of patients found to breach criteria in a recent randomized control trial.

Despite the perceived intuitive benefit of endovascular therapy of improved revascularisation and improved outcomes, three major initial randomized control trials- IMS III,6 MR RESCUE7 and SYNTHESIS8 could not demonstrate this. However, the negative findings from these studies must be interpreted in the context of several limitations. These include the use of first generation thrombectomy devices and intra-arterial thrombolytic agents to achieve recanalization, suboptimal patient selection due to the lack of sophisticated imaging techniques employed, and lengthy delays to initiation of treatment (mean time to groin puncture 208 minutes in IMS III and 381 minutes in MR RESCUE).6,7

The development of newer mechanical thrombectomy devices have resulted in superior recanalization in stroke therapy.9–11 In particular, stent retrievers such as Solitaire, TREVO and REVIVE have demonstrated markedly improved recanalization rates compared to their earlier generation counterparts.5,11

The incorporation of these devices, improving imaging based patient selection and more expedient treatment times has resulted in positive findings from seven trials, MR CLEAN,12 EXTEND-IA,13 ESCAPE,14 SWIFT PRIME,15 REVASCAT,16...
Intra-arterial (IA) thrombolysis

Advantages of IA thrombolytic therapy over IV therapy include direct infusion of a highly concentrated thrombolytic drug into the occluding thrombus, permitting lower total amounts of systemic concentration of thrombolytic agent to achieve recanalization. Precise depiction of the arterial anatomy through angiography confers several advantages including the characterization of the obstructive lesion, assessing the extent of collateral circulation, confirmation of degree and timing of recanalization, and providing an option of employing additional mechanical thrombectomy methods to best assist with vessel recanalization. Conversely, the disadvantages of IA approaches include the need for a specialized neurointerventional team and endovascular facilities, additional time delays required for angiography, and the risks of catheter manipulation.

Different agents have been used for the thrombolytic treatment of acute ischaemic stroke. These include tissue plasminogen activator (tPA), urokinase (UK) and pro-urokinase (pro-UK).

Efficacy and safety

IA Pro-UK

The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial evaluated the efficacy of IA Pro-Urokinase when administered within 6 hours of stroke onset. Forty-six patients with angiographically confirmed Thrombolysis in Acute Myocardial Infarction (TIMI) grade 0 or 1 occlusion of the M1 or M2 segment of the MCA were randomised into the treatment group (pro-UK and heparin) or placebo group (heparin only) in a 2:1 ratio. Treatment group was associated with superior recanalization compared to the placebo group (67% vs. 18% TIMI 2-3). However the 6 improvement in neurological outcomes, classified as a modified Rankin Scale (mRS) of 0-1, from IAProUK compared to placebo was not significant (30.8% vs. 21.4%, P = 0.72).

PROACT II addressed the shortcomings of its predecessor by using a control group (no IA infusion), and enrolling greater patient numbers. The definition of a good neurological outcome was also revised to a mRS of 2 or less. Successful recanalization was more commonly seen in the treatment group than in the control group (66% vs. 18%, P = 0.001). Despite similar results regarding clinical outcome to its predecessor (90-day mRS 0-1: 26% vs. 17%, P = 0.16), primary efficacy analysis with the revised outcomes showed improved morbidity in patients treated with IA pro-UK (mRS 0-2: 40 vs. 25%, P = 0.04).

IA-UK

The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) was prematurely aborted due to the approval of IV-rtPA in Japan. 114 ischemic stroke patients presenting within 6 hours of stroke onset, with angiographic occlusions of the M1 or M2 portion of the MCA, were randomised in a 1:1 manner. Recanalization (≥ 50%) was achieved in 30 (52.7%) patients. There was no statistical difference in the primary outcome between the UK and control group (mRS 0-2: 49.1% vs. 38.6%, P = 0.345). However, secondary analyses showed improved functional outcome (mRS 1 or less) in the treatment group compared to the control group (42.1% vs. 22.8%, P = 0.017). When compared to the PROACT trials, randomized patients in this study had lower baseline NIHSS scores, possibly contributing to the improved outcomes in the control group.

Combined IV and IA tPA

Several studies have been conducted to investigate the efficacy of IV and IA tPA. The Emergency Management of Stroke (EMS) trial, a double-blinded, randomized, placebo-controlled multicentre trial, aimed to investigate the feasibility and safety of a combined IV and IA approach to 7 thrombolysis. Thirty-five patients presenting within 3 hours of symptom onset were randomised into either the IV/IA group (n = 17) or placebo/IA group (n = 18). The primary outcome was defined as 7 point or greater improvement in the National Institutes of Health Stroke Scale (NIHSS) or a score of 0 or 1 at 7 days. Successful recanalization was demonstrated to be superior in the IV/IA treatment group (55% vs. 10%, P = 0.05). Despite superior recanalization rates, there was no difference in neurological outcome-24% in both groups. A lack of improvement in clinical outcome may be attributed to limited patient numbers, a high rate of adverse events in the IV/IA tPA group unrelated to treatment, and poor randomisation of stroke severity.

Using historical controls from the National Institute of Neurological Disorders and Stroke (NINDS) trial of IV tPA, IMS-II aimed to evaluate the effectiveness and safety of combined IV/IA therapy. Whenever possible, anEKOS micro-infusion catheter (EKOS Corporation Bothell, Washington, USA) was used in vessel-appropriate lesions to alter the structure of the thrombus and facilitate access of the thrombolytic agent to potentially accelerate thrombolysis. The 81 subjects enrolled into the IMS II study were also compared with the rt-PA and placebo-treated...
Recanalization (≥50% or TIMI 2-3) was achieved in 47-80% of patients receiving IA thrombolysis. Good neurological outcome at 90 days (mRS 0-2) was found in 40-57%. Intra-arterial thrombolysis was not shown to be significantly associated with greater symptomatic haemorrhagic transformation, with rates of 9-15.4% across all agents.

The multitude of different intra-arterial thrombolytic agents available have been shown to offer promising clinical outcome in selected patients with acute ischaemic stroke without a significant increase in haemorrhagic complications. However, there is no level 1 evidence whether intra-arterial thrombolysis alone confers outcome benefit over IV tPA therapy.

**Mechanical thrombectomy**

Mechanical thrombectomy devices are divided into 2 major groups based on their mechanism of action: those that use an approach distal (retrievers) or proximal to thrombi (aspiration devices).

**Retrievers**

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI, Concentric Medical, California, USA) was the first stroke mechanical thrombectomy device approved by the FDA in 2004 (Figure 1A). The MERCI is a flexible corkscrew-shaped device constructed of nitinol memory-wire, designed to remove blood clots from the brain in patients with ischaemic stroke.

A number of other specifically directed thrombectomy devices...
with various designs were subsequently developed. The CATCH device (Balt Extrusion, Montmorency, France) also employs a self-expanding Nitinol basket to retrieval thrombi using a distal approach (Figure 1B).

The Solitaire FR (Ev3, California, USA) was approved by the FDA in 2012 (Figure 1C). Solitaire FR comprises a stentriever, a retrievable stent-like device that is designed to act as retriever. It promotes restoration of blood flow by providing radial force to open and restore occluded vessels, administer adjunctive medical therapy and retrieve clots via an open-ended basket.

Other recent stentriever devices include the TREVO device (Concentric Medical, California, USA; Figure 1D) and the REVIVE system (Codman & Shurtleff Inc, Massachusetts, USA; Figure 1E). Both the TREVO and REVIVE stentriever employ a closed distal end of the stent to prevent clot embolization. However, the TREVO device’s stent wires are radio-opaque, allowing better visibility during angiography, compared to the REVIVE system.

Aspiration devices
Several aspiration techniques have also been developed for acute ischaemic stroke treatment, including the Penumbra System (Penumbra Inc, California, USA). The Penumbra system is composed of 3 main components: a reperfusion catheter, separator, and thrombus removal ring (Figure 2). This device removes the thrombus through 2 mechanisms: aspiration and extraction. Aspiration is achieved when the separator is gently pulled back and forth into the reperfusion catheter resulting in fragmentation with subsequent aspiration of the fragments when the reperfusion catheter is connected to a suction device. If residual thrombus remains after revascularization with aspiration, the thrombus removal ring is then used to directly engage and remove the thrombus.

In a similar vein, the QuickCat (DSM Inc, Philadelphia, USA) and PRONTO (Vascular Solutions Inc, Minnesota, USA) extraction devices are both monorail catheters which aspirate clot through negative pressure created by a connected 3 way stopcock. However, there is insufficient data for their use in acute stroke.

Efficacy and safety
Please refer to Table 1 for summary of devices.

MERCI
The Multi MERCI trial, an international, multicenter prospective study, enrolled 177 patients to evaluate the combined safety and efficacy of IV tPA with the MERCI device when used within 8 hours of stroke onset. Recanalization was assessed as TIMI score 2-3, and a good neurological outcome was defined as a 90 day mRS score of 0-2. 131 patients received mechanical thrombectomy with successful recanalization (TIMI 2-3) achieved in 57.3% of patients and 68.5% of patients after adjunctive therapy (IA-tPA). Thirty-six percent of patients in this study had favourable neurological outcomes.

The rate of symptomatic haemorrhage observed in the Multi-MERCI trial was similar to that found with other modes of intraarterial interventions (10%).

CATCH
The efficacy of the CATCH device was evaluated in a retrospective study of 40 patients presenting with anterior or posterior circulation strokes. Recanalization (TIMI 2-3) was achieved in 65% of the population, with half of these patients achieving full (TIMI 3) recanalization. A good neurological outcome (90 day mRS 0-2) was achieved in 14 patients (39%). These outcomes were deemed to be comparable to those achieved in the Multi MERCI trial.
However, the rates of symptomatic haemorrhage were much higher using the CATCH device (18%). Being a retrospective trial, there were several limitations to the study design. There was significant heterogeneity in adjunctive treatment. 36 (90%) patients received additional r-tPA. Other interventions included thromboaspiration, angioplasty, and stent placement in addition to CATCH thrombectomy.

**Table 1. Endovascular device advantages and disadvantages and trial results**

<table>
<thead>
<tr>
<th>Endovascular device</th>
<th>Study</th>
<th>Recanalization success (%)</th>
<th>Clinical outcome</th>
<th>Symptomatic haemorrhage</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Microcatheter infusion of Plurokinase</td>
<td>PROACT21</td>
<td>TIMI 2-3, 67%</td>
<td>90 day mRS 0-1, 30.8%</td>
<td>15.4%</td>
<td>Easy Navigation</td>
<td>Prolonged Infusion</td>
</tr>
<tr>
<td></td>
<td>PROACT II42</td>
<td>TIMI 2-3, 66%</td>
<td>90 day mRS 0-1, 26%</td>
<td>10%</td>
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<tr>
<td>Microcatheter infusion of Urokinase</td>
<td>MELT23</td>
<td>Complete, 5.3%</td>
<td>90 day mRS 0-2, 49.1%</td>
<td>9%</td>
<td>Easy Navigation</td>
<td>Prolonged Infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial ≥ 50%, 47.4%</td>
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<tr>
<td>Microcatheter infusion of tissue plasminogen activator</td>
<td>EMS43</td>
<td>TIMI 2-3, 55%</td>
<td>NIHSS 0-1 or ≥ 7 point improvement, 24% at 7 days</td>
<td>11.8%</td>
<td>Easy Navigation</td>
<td>Prolonged Infusion</td>
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<tr>
<td></td>
<td>IMS II5</td>
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<td>90 day mRS 0-1, 33%</td>
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<tr>
<td></td>
<td>RECANALISE26</td>
<td>TIMI 2-3, 87%</td>
<td>90 day mRS 0-2, 46%</td>
<td>9%</td>
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<tr>
<td>MERCI retriever</td>
<td>Multi MERCI38</td>
<td>TIMI 2-3, 57.3% with MERCI alone</td>
<td>90 day mRS 0-2, 36%</td>
<td>10%</td>
<td>Improved recanalization compared to IV and IA thrombolysis</td>
<td>May require multiple passes of device to achieve recanalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIMI 2-3, 68.5% with adjunctive IA therapy</td>
<td></td>
<td></td>
<td>Can be used when thrombolysis contraindicated</td>
<td>Steep operator learning curve</td>
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<tr>
<td>CATCH device</td>
<td>Mourand et al39</td>
<td>TIMI 2-3, 65%</td>
<td>90 day mRS 0-2, 39%</td>
<td>18%</td>
<td>Improved recanalization compared to IV and IA thrombolysis</td>
<td>May require multiple passes of device to achieve recanalization</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Can be used when thrombolysis contraindicated</td>
<td>Steep operator learning curve</td>
</tr>
<tr>
<td>SOLITAIRE stentriever</td>
<td>SWIFT9</td>
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<td>2%</td>
<td>Thrombectomy approach allowing faster and greater recanalization rates</td>
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<tr>
<td>TREVO stentriever</td>
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<td>Thrombectomy approach allowing faster and greater recanalization rates</td>
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<tr>
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<td></td>
<td>TICI 2b-3, 86.7% with adjunctive IA therapy</td>
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<tr>
<td></td>
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<td>90 day mRS 0-2, 40%</td>
<td>7%</td>
<td>Thrombectomy approach allowing faster and greater recanalization rates</td>
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<tr>
<td>REVIVE stentriever</td>
<td>Rohde et al31</td>
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<td>NIHSS 0-1 or &gt; 8 point improvement, 80% at 30 days</td>
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<td>PENUMBRA aspiration device</td>
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<td>11%</td>
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</tr>
<tr>
<td></td>
<td>POST48</td>
<td>TIMI 2-3, 87%</td>
<td>90 day mRS 0-2, 41%</td>
<td>6%</td>
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<tr>
<td></td>
<td>SPEED46</td>
<td>TIMI 2-3, 91%</td>
<td>90 day mRS 0-2, 34%</td>
<td>14%</td>
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</table>

**Solitaire**

The Solitaire With Intention For Thrombectomy (SWIFT) randomized clinical trial assigned 113 stroke patients who presented within 8 hours of symptom onset to 18 hospitals to either the Solitaire FR group (n = 58) or the Merci Retriever device group (n = 55).

The SWIFT study observed a significantly higher recanalization rate (TIMI score 2-3) obtained with the Solitaire device.
compared to the MERCI (61% vs. 24%, \( P < 0.0001 \)) and a more favourable 3-month neurological outcome (58% vs. 33%, \( P = 0.0001 \)) without increasing rates of symptomatic haemorrhagic transformation (2% vs. 11%)\(^9\)

**TREVO**

The efficacy and safety of the TREVO device was first evaluated through a prospective, single-center study of 60 patients anterior or posterior circulation strokes.\(^{32}\) Successful revascularisation (Thrombolysis in Cerebral Infarction 2b-3) was obtained in 44 (73.3%) of cases when only the TREVO device was used and in 52 (86.7%) when other devices or additional intra-arterial tPA were also required. Good clinical outcome (mRS 0-2) was achieved in 27 (45%) of patients and the mortality rate was 28.3%.\(^{11}\)

The TREVO 2 trial- a randomized control trial conducted across centers in the USA and Spain assessed the efficacy of the TREVO device compared to MERCI.\(^{10}\) Patients who had large vessel anterior circulation strokes were randomized to receive thrombectomy using either the TREVO or MERCI device (88 vs. 90 patients respectively). Significant improvements were demonstrated with the TREVO device for revascularisation (TICI 2a-3: 86% vs. 60%, \( P < 0.01 \)) and clinical outcome (90 day mRS 0-2: 40% vs. 22%, \( P = 0.01 \)).

Seven (11.7%) patients in the TREVO study experienced symptomatic intracranial haemorrhage.\(^{32}\) More extensive enquiry into the safety profile of the TREVO device was conducted in the TREVO 2 trial.\(^{10}\) No significant difference was found for the outcome of composite adverse events (15% vs. 23%, \( P = 0.23 \)) and symptomatic ICH (7% vs. 9%, \( P = 0.78 \)) between the TREVO and MERCI devices respectively. However, it was noted that vessel perforations were 10 times more common using the MERCI device (1% vs. 10%, \( P = 0.02 \)).

**REVIVE**

The REVIVE device was evaluated in a single center study, which enrolled 10 patients with acute large vessel occlusions into a study.\(^{11}\) Recanalization success as assessed using the Thrombolysis in Cerebral Infarction (TICI) score was achieved in 100% of patients without device-related complications.\(^{11,35}\) Clinical outcome was then assessed at 30 days post intervention using the National Institute of Health Stroke Scale (NIHSS) with 60% of patients achieving a clinical improvement of > 8 points or NIHSS of 0-1. Symptomatic intracranial haemorrhage occurred in 20% of patients.\(^{11}\)

**Penumbra**

The Penumbra Pivotal Stroke Trial, the Penumbra POST study, and recently the SPEED study have evaluated the safety and effectiveness of the Penumbra system.\(^{36-38}\) The Penumbra Pivotal Stroke Trial (n = 125) and POST study (n = 157) evaluated patients with stroke symptom onset within 8 hours and NIHSS ≥ 8, whilst the SPEED study (n = 87) examined cases with angiographic evidence of large vessel occlusion.\(^{36-38}\) Eighty one percent of patients from the Penumbra Pivotal Stroke trial, 87% from the Penumbra POST study, and 91% from the SPEED study achieved successful recanalization (TIMI 2-3) with 25%, 41% and 34% achieving good clinical outcome (mRS 0-2 at 90 days) respectively.\(^{36-38}\) Eleven percent from the Pivotal Trial, 6% in the POST study and 14% in the SPEED study experienced symptomatic intracranial haemorrhage.\(^{36-38}\)

**Summary**

Recanalization (TIMI 2-3 or TICI 2b-3) was achieved in 24-100% of patients and good clinical outcome (mRS 0-2, NIHSS score 0-1 or NIHSS improvement of > 8 points) noted in 22-60%,\(^{9-11,27,28,32,36-38}\) The rates of symptomatic haemorrhagic transformation were found to be between 6-20% across all devices.

**A new dawn for stroke therapy**

The MR CLEAN (Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands) study was a landmark trial and the first RCT to demonstrate the superiority of intra-arterial treatment.\(^{12}\) Five hundred patients across 17 centers in the Netherlands who presented with clinical and radiological evidence of a proximal anterior circulation stroke within 6 hours of onset were randomized to receive intra-arterial therapy with standard care versus standard care alone.\(^{12}\) The intervention group received chemical and/or mechanical endovascular therapy. Intra-arterial thrombolysis was achieved using alteplase and urokinase, whilst mechanical treatment involved thrombectomy, aspiration or stenting according to neurointerventionist preference.

The primary outcome was based on 90 day mRS score, which showed a significant improvement in outcomes for patients receiving intra-arterial therapy (adjusted odds ratio 1.67, 95% Confidence Interval 1.21-2.30). This benefit was conferred to all prespecified dichotomisations of the mRS except death 12. The incidence of functional independence, defined as mRS 0-2, was also greater in this population by 13.5% (32.6% vs. 19.1%) \(^{12}\). Secondary outcomes including clinical (NIHSS score after 5-7 days), radiological (TICI 2b or 3), and safety (adverse events) all favoured the intervention group.

Compared to the previous three negative randomized control trials examining the efficacy of IA therapy, MR CLEAN had sev-
eral advantages. It benefitted from the increased availability of CTA to confirm the presence of proximal anterior circulation occlusion, allowing its use in the inclusion criteria. 82% of all patients in the intervention group also were subject to intervention using stent retrievers, which have been demonstrated to be superior to first generation devices. Limitations include a broad inclusion criteria, including patients with characteristics that would confer poor baseline prognosis. This included those who had contraindications or non responders to IV tPA. Nonetheless, the trial was the first to offer compelling evidence for intra-arterial therapy to be used as a first line standard of care when patients with anterior circulation strokes present within 6 hours. Numerous subsequent trials were terminated prematurely for this reason. Please refer to Table 2 for summary of randomized control trials.

The EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial) randomized control trial confirmed the positive findings from MR CLEAN, and underlined the importance of prudent imaging based selection to maximise the efficacy of endovascular stroke therapy.13 Patients with ICA or MCA occlusions within 4.5 hours of onset, CT evidence of perfusion mismatch and core infarct volume of less than 70 mL were randomized to receive mechanical thrombectomy with the Solitaire device after IV tPA vs tPA alone. Endovascular therapy had to be commenced within 6 hours of stroke onset.

The trial had to be stopped after randomisation of 70 patients in a 1:1 manner. Endovascular therapy demonstrated significantly superior rates of early neurological improvement at 3 days (80% vs. 37%), and functional independence at 90 days (mRS 0-2 71% vs. 40%).13 The safety profile of patients in the endovascular treatment was also validated, with no significant differences in the rates of death or symptomatic ICH.

The imaging guided approach to identifying patients who would benefit from reperfusion therapy allowed more expedient randomisation and thus time to intervention. The high rates of revascularisation (TIMI 2-3 86%) compared to previous trials could be attributed to the sole use of the Solitaire FR stent retriever, previously shown to have superior outcomes compared to first generation devices used in initial trials.3,13 Limitations include the small population number. This may have therapeutic implications given the strict inclusion criteria- more than 7,798 patients were screened- and possibly overestimate treatment effect.

Concurrently released and published with EXTEND-IA, the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) trial also highlighted the efficacy of endovascular therapy in patients using CT guided patient selection within 12 hours of stroke onset.14 Three hundred Sixteen patients with CT Angiography evidence of proximal artery occlusion with good collateralisation and small infarct core using an ASPECTS (Alberta Stroke Program Early Computed Tomography Score) of 6 to 10, were randomized to receive medical management versus rapid endovascular treatment predominantly using stent retrievers, within 60 minutes.14,39 Both arms received IV tPA if patients presented within 4.5 hours.

One hundred Sixty-five patients were randomized to the intervention arm and were noted to have a superior primary outcome of functional independence (90 day mRS score of 0-2

<table>
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<tr>
<th>Randomized control trials</th>
<th>Recanalization success (%)</th>
<th>Devices</th>
<th>Clinical outcome</th>
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<tr>
<td>IMS III6</td>
<td>TICI 2-3, 81% for ICA occlusions, 86% for M1, 88% M2</td>
<td>Mixed (Microcatheter infusion of IA tPA 49.1%, MERCI 28.4%, Penumbra 16.2%, Solitaire 1.5%)</td>
<td>90 day mRS 0-2, 40.6% (vs. 38.7% with IV tPA, age adjusted absolute difference 1.5%, 95% CI 0.1-9.1%)</td>
<td>6.2%</td>
</tr>
<tr>
<td>SYNTHESIS8</td>
<td>Mixed</td>
<td></td>
<td>90 day mRS 0-1, 30.4% (vs. 34.8% with IV tPA, adjusted OR 0.71, P = 0.16)</td>
<td>10%</td>
</tr>
<tr>
<td>MR RESCUE7</td>
<td>TICI 2a-3, 67%</td>
<td>Mixed (MERCI alone 60.7%, Penumbra alone 23%, both devices 16.4%)</td>
<td>90 day mRS mean, 3.9 (vs. 3.9 with standard care, P = 0.99)</td>
<td>4.7%</td>
</tr>
<tr>
<td>MR CLEAN12</td>
<td>TICI 2b-3, 58.7%</td>
<td>Mixed (Microcatheter infusion of IA tPA, MERCI, Penumbra, Solitaire)</td>
<td>90 day mRS 0-2, 40.6% (vs. 19.1% with standard care, adjusted OR 2.18, 95% CI 1.39-3.38)</td>
<td>7.7%</td>
</tr>
<tr>
<td>EXTEND-IA13</td>
<td>TIMI 2-3, 88%</td>
<td>Solitaire</td>
<td>90 day mRS 0-2, 71% (vs. 40% with IV tPA, adjusted OR 4.2, 95% CI 1.4-12)</td>
<td>0%</td>
</tr>
<tr>
<td>ESCAPE14</td>
<td>TICI 2b-3, 72.4%</td>
<td>Mixed (Solitaire in 77%)</td>
<td>90 day mRS 0-2, 53% (vs. 29.3% with standard care, adjusted OR 1.7, 95% CI 1.3-2.2)</td>
<td>3.6%</td>
</tr>
<tr>
<td>SWIFTPRIME15</td>
<td>TICI 2b-3, 88%</td>
<td>Solitaire</td>
<td>90 day mRS 0-2, 60% (vs. 35% with IV tPA, OR 1.7, 95% CI 1.23-2.33)</td>
<td>3%</td>
</tr>
<tr>
<td>REVASCAT16</td>
<td>TICI 2b-3, 65.7%</td>
<td>Solitaire</td>
<td>90 day mRS 0-2, 43.7% (vs. 28.2% with standard care, adjusted OR 1.2, 95% CI 1.1-4)</td>
<td>1.9%</td>
</tr>
</tbody>
</table>
53.0% vs. 29.3% in the control group), with an associated reduction in mortality (10.4% vs. 19.0%) and no significant difference in adverse events.14

Given analysis of previous trials illustrating the importance of time to reperfusion, there was a strong emphasis on delivering rapid endovascular therapy, with a median time of 84 minutes from noncontrast CT to first reperfusion. The superior rates of recanalization compared to MR CLEAN (TICI 2b to 3 72.4%) could be attributed to this.12,14 These patients were predominantly treated at centers with significant experience in endovascular management and sophisticated imaging, allowing expedient treatment from stroke onset. This may impact the generalizability of results.

Presented at the 2015 International Stroke Conference with EXTEND-IA and ESCAPE, the SWIFT PRIME (“Solitaire” FR as Primary Treatment for Acute Ischemic Stroke”) study’s results also demonstrated the efficacy of endovascular therapy using the Solitaire device.15 196 patients with evidence of a small-moderate core infarct, defined as an ASPECTS score of > 6, were randomized to either receive combined IV tPA and endovascular therapy with the Solitaire device within 6 hours of anterior circulation stroke onset vs IV tPA alone. Primary outcomes included 3 month neurological outcome and recanalization rates.40

Patients who received endovascular therapy with IV tPA were again found to have unequivocally higher rates of 90 day functional independence (mRS 0-2: 60% vs. 35%, P < 0.001) compared to the control group, without any significant difference in mortality or adverse outcomes. Notably, 88% of patients had successful reperfusion (TICI 2b-3) immediately post intervention, which could be attributed to a high proportion of occlusions in the M1 segment (67%), and the sole use of the Solitaire device. This may impact generalizability of results, particularly with regards to M2 and ICA occlusions.

The REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 hours) trial was also published simultaneously with SWIFT PRIME, highlighting the efficacy using the Solitaire device for proximal anterior circulation stroke within 8 hours of onset.16 206 patients across 4 hospitals in were randomized in a 1:1 ratio between the treatment and control groups. Patients with a large infarct core, defined as ASPECT scores of < 7 and < 6 on non-contrast CT and MRI DWI respectively, were excluded from the study. Recanalization (TICI 2b-3) was achieved in 65.7% of patients. Treatment with thrombectomy was again found to be superior for restoring functional independence compared to standard medical therapy (90 day mRS 0-2: 43.7% vs. 28.2% in the control group), with a similar safety profile.

The inferior rates of functional independence compared to EXTEND IA, ESCAPE, and SWIFT PRIME may be in part due to the use of ASPECTS scoring criteria, which is less accurate than diffusion imaging for the estimation of infarct core volume, and longer times from stroke onset to reperfusion. Two further studies—THERAPY and THRACE—were concurrently presented with REVASCAT at the 2015 European Stroke Organisation conference.17,18 THRACE randomised 414 patients across 26 centres in France, who presented within 5 hours of symptom onset with either anterior or posterior large artery occlusions, to receive mechanical thrombectomy after. IV tPA vs IV tPA alone. Preliminary results suggested a significant benefit in 90 day functional independence (mRS 0-2) in patients undergoing endovascular therapy.17 THERAPY (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System’s Safety and Effectiveness in the Treatment of Acute Stroke) enrolled only 102 patients before recruitment was halted prematurely because of the positive results of its predecessors.18 Patients with large artery anterior circulation strokes due to a clot length > 8mm, who presented within 4.5 hours, were assigned to either IV tPA alone or IV tPA with adjunctive therapy using the Penumbra aspiration device. Preliminary results revealed that more patients were functionally independent (mRS 0-2) at 90 days, though this difference was not statistically significant likely due to inadequate patient numbers. THERAPY differed from other trials due to the sole use of the Penumbra aspiration device, and the inclusion of only patients with a large clot burden. We await the formal publication of results from these trials.

Current generation of randomized controlled studies

After illustrating the safety and recanalization efficacy of thrombectomy in the subgroup of patients with late presentation (> 8 hours) strokes and CT or MR evidence of proximal anterior vessel occlusions with viable penumbra, the investigators of the DAWN (DWI/PWI and CTP assessment in the triage of wake-up and late presenting strokes undergoing neurointervention) trial are furthering this hypothesis with a multicenter study aiming to demonstrate improved clinical outcomes at 90 days using the ‘Trevo Retriever with medical management compared to medical management alone.41,42 An estimated 500 patients will be randomized, with primary outcomes based on 90 day mRS scores and mortality.

The PISTE (Pragmatic Ischaemic Stroke Thrombectomy Evaluation) trial aims to randomise 800 patients across multiple centers in the UK, who present within 4.5 hours of symptom onset with a clinically significant neurological deficit (NIHSS ≥ 6) and imaging (CT/MRA/DSA) evidence of a large vessel...
Future endovascular device development

Given the success of the Solitaire device in mechanical embolectomy, it currently remains the most popular device used for the treatment of acute ischemic stroke. However, there are several new devices currently being developed with the aim of offering improved recanalization and safety profiles, with a particular emphasis on minimising distal clot embolization.

Conclusion

Endovascular intra-arterial therapy improves recanalization rates compared to intravenous thrombolysis. Initial approaches and randomized controlled trials could not demonstrate a corresponding association with improved neurological outcome. However, the development of superior intra-arterial devices, rapid treatment times and increasing availability of sophisticated imaging techniques has resulted in the establishment of intra-arterial therapy as a front line therapy for acute ischaemic stroke.

References


Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection


ABSTRACT

BACKGROUND

Trials of endovascular therapy for ischemic stroke have produced variable results. We conducted this study to test whether more advanced imaging selection, recently developed devices, and earlier intervention improve outcomes.

METHODS

We randomly assigned patients with ischemic stroke who were receiving 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy with the Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone. All the patients had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue and ischemic core of less than 70 ml on computed tomographic (CT) perfusion imaging. The coprimary outcomes were reperfusion at 24 hours and early neurologic improvement (≥8-point reduction on the National Institutes of Health Stroke Scale or a score of 0 or 1 at day 3). Secondary outcomes included the functional score on the modified Rankin scale at 90 days.

RESULTS

The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). The percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular-therapy group than in the alteplase-only group (median, 100% vs. 37%; P<0.001). Endovascular therapy, initiated at a median of 210 minutes after the onset of stroke, increased early neurologic improvement at 3 days (80% vs. 37%, P=0.002) and improved the functional outcome at 90 days, with more patients achieving functional independence (score of 0 to 2 on the modified Rankin scale, 71% vs. 40%; P=0.01). There were no significant differences in rates of death or symptomatic intracerebral hemorrhage.

CONCLUSIONS

In patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging, early thrombectomy with the Solitaire FR stent retriever, as compared with alteplase alone, improved reperfusion, early neurologic recovery, and functional outcome. (Funded by the Australian National Health and Medical Research Council and others; EXTEND-IA ClinicalTrials.gov number, NCT01492725, and Australian New Zealand Clinical Trials Registry number, ACTRN1261100969965.)
The results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, which showed reduced disability among patients with ischemic stroke who were treated with endovascular thrombectomy in addition to standard care, represent an advance in stroke care. The MR CLEAN study followed several trials that had neutral findings with respect to the use of endovascular thrombectomy. In the largest of these trials, the Interventional Management of Stroke 3 (IMS-3) study, investigators compared the administration of 0.9 mg of alteplase per kilogram of body weight to a bridging strategy of the use of alteplase (at a dose of 0.6 mg per kilogram for most of the trial) followed by endovascular therapy. The IMS-3 trial was halted for futility after 656 patients had been enrolled.

Potential contributors to the neutral results of previous studies include relatively low rates of angiographic reperfusion, delays in achieving reperfusion, and the lack of patient selection with the use of advanced imaging to ensure the presence of vessel occlusion and salvageable brain tissue. None of the previous studies raised any safety concerns, with rates of symptomatic hemorrhage of approximately 6% in both the alteplase group and the endovascular-therapy group. More recent advances in device technology have significantly improved the speed and efficacy of recanalization.

Computed tomographic (CT) perfusion imaging can indicate the extent of irreversibly injured brain in the ischemic core and potentially salvageable but hypoperfused ischemic penumbra. Furthermore, CT perfusion imaging has evolved, and fully automated, standardized volumetric processing can now be rapidly performed in the context of a multicenter clinical trial.

In the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial, we sought to test the hypothesis that patients with anterior circulation ischemic stroke who are selected with a dual target of vessel occlusion and evidence of salvageable tissue on perfusion imaging within 4.5 hours after the onset of stroke will have improved reperfusion and early neurologic improvement when treated with early endovascular thrombectomy with the use of the Solitaire FR (Flow Restoration) stent retriever after intravenous administration of alteplase, as compared with the use of alteplase alone. The release of the MR CLEAN trial results prompted the data and safety monitoring board for our study to review the data, and the trial was stopped early because efficacy was clearly shown.

METHODS

TRIAL DESIGN AND OVERSIGHT

The EXTEND-IA trial was an investigator-initiated, multicenter, prospective, randomized, open-label, blinded-end-point study involving patients with ischemic stroke who were receiving intravenous alteplase within 4.5 hours after stroke onset. Details of the methods used in the trial have been published previously. The study protocol is available with the full text of this article at NEJM.org.

The design, analysis, and data collection for the trial were performed by members of the executive committee and investigators at the study sites (see the Supplementary Appendix, available at NEJM.org). The first author wrote the first draft of the manuscript. All the investigators vouch for the accuracy and completeness of the presented data and fidelity of the report to the study protocol. Covidien supplied the Solitaire FR device and an unrestricted grant to support trial infrastructure, but the company was not involved in the study design or conduct or in the preparation of the manuscript, except to review the protocol to ensure that the specified use of devices in the study followed the approved instructions for use.

STUDY PATIENTS

We planned to enroll 100 patients at 14 centers in Australia and New Zealand. Patients were eligible if they could receive intravenous alteplase within 4.5 hours after the onset of anterior circulation ischemic stroke and had occlusion of the internal carotid artery or of the first or second segment of the middle cerebral artery, as seen on CT angiography. In addition, CT perfusion imaging, which was processed with the use of fully automated software (RAPID, noncommercial research version, Stanford University), was used to identify potentially salvageable brain tissue. Brain tissue at risk for infarction (“ischemic penumbra”) was distinguished from minimally hypoperfused tissue if the time to maximum (Tmax) delay was more than 6 seconds. Irreversibly injured brain (“ischemic core”) was diagnosed if the relative
cerebral blood flow was less than 30% of that in normal tissue.\textsuperscript{10}

Endovascular therapy had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset. There were no restrictions on age or clinical severity, as assessed according to the score on the National Institutes of Health Stroke Scale (NIHSS), which ranges from 0 (normal) to 42 (death). However, patients were required to have functional independence before the stroke episode, which was defined as a score of less than 2 on the modified Rankin Scale, which ranges from 0 (normal) to 6 (death).

The study was approved by the institutional ethics committee at each study site. Written informed consent was obtained from patients or a legal representative before enrollment. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

**STUDY TREATMENTS**

All patients received alteplase at a dose of 0.9 mg per kilogram as standard care. Patients were randomly assigned in a 1:1 ratio to receive either alteplase plus endovascular therapy (endovascular-therapy group) or no further therapy (alteplase-only group) by means of a centralized website and stratified according to the site of arterial occlusion: the internal carotid artery or the first or second segment of the middle cerebral artery.

The use of conscious sedation or general anesthesia for endovascular treatment was at the discretion of the neurointerventionist. The site of vessel occlusion was confirmed with the use of digital subtraction angiography. If there was no lesion amenable to thrombectomy, the procedure was terminated. The Solitaire FR retrievable stent (Covidien) was deployed at the site of intracranial-vessel occlusion and then removed under negative-pressure aspiration. Control angiography was performed at the conclusion of the procedure and centrally graded for angiographic revascularization, with the use of the modified Treatment in Cerebral Ischemia classification, on a scale ranging from 0 (no flow) to 3 (normal flow),\textsuperscript{16} and any embolization of thrombus into previously uninvolved vascular territories.

**STUDY OUTCOMES**

The coprimary outcomes were reperfusion (which was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and imaging at 24 hours, which can be negative if hypoperfusion worsens) and early neurologic improvement (which was defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 at 3 days). Secondary outcomes were the score on the modified Rankin scale at 90 days, death due to any cause, and symptomatic intracranial hemorrhage, including any subarachnoid hemorrhage associated with clinical symptoms and symptomatic intracerebral hemorrhage, which was defined as parenchymal hematoma type 2 within 36 hours after treatment combined with an increase on the NIHSS of at least 4 points from baseline.\textsuperscript{17} Further details are provided in the Methods section in the Supplementary Appendix.

**STATISTICAL ANALYSIS**

After the release of the results of the MR CLEAN study, recruitment into the trial was suspended on October 31, 2014, and the data and safety monitoring board reviewed data for the 70 enrolled patients. A prespecified Haybittle–Peto stopping boundary was applied to the coprimary outcome in the intention-to-treat population with the use of Holm’s step-down procedure,\textsuperscript{18} so that one coprimary outcome was tested at a z value of more than 3.29 and the other at a z value of more than 3. The data and safety monitoring board stopped the trial for efficacy after this analysis.

For the intention-to-treat analysis of the coprimary outcome, we compared the median percentage reperfusion between the endovascular-therapy group and the alteplase-only group after adjustment for baseline arterial occlusion strata using the van Elteren test, a stratified version of the Wilcoxon rank-sum test. We used logistic regression to compare the between-group difference in the proportion of patients with early neurologic recovery, as indicated by a reduction of 8 or more points on the NIHSS or a score of 0 or 1 at 3 days, after adjustment for age and baseline NIHSS score.

Although results are reported with and without adjustment for baseline covariates, the analysis with adjustment was prespecified as the primary analysis. The results are also reported for the target group who underwent endovascular thrombectomy according to the protocol, as compared with the alteplase-only group, to adjust for effects such as recanalization before cerebral angiography was performed and any off-protocol interventions.
As prespecified in the protocol, the initial analysis of the secondary outcome for the score on the modified Rankin scale was designed to be an assumption-free ordinal analysis\textsuperscript{19,20} that uses the Wilcoxon–Mann–Whitney generalized odds ratio across the full range of the modified Rankin scale (from 0 to 6). Then, we used a logistic-regression model to compare the proportions of patients with scores of 0 or 1 (defined as an excellent outcome) and those with scores of 0 to 2 (defined as a functionally independent outcome) in the two study groups after adjustment for age and baseline NIHSS score.

### RESULTS

**CHARACTERISTICS OF THE PATIENTS**

From August 2012 through October 2014, a total of 70 patients underwent randomization (35 to the endovascular-therapy group and 35 to the alteplase-only group) at 10 study centers (9 in Australia and 1 in New Zealand) (Fig. S1 in the Supplementary Appendix). Baseline characteristics of the patients are provided in Table 1, and procedural characteristics in Table 2.

Approximately 25% of clinically eligible patients with vessel occlusion were excluded on the basis of perfusion-imaging criteria (Fig. S2 in the Supplementary Appendix). The majority of the thrombus had been lysed before angiography in 4 of 35 patients (11%) in the endovascular-therapy group. Four other patients in the endovascular-therapy group did not undergo thrombectomy because they had either major clinical deterioration or major clinical improvement, stenting of the extracranial internal carotid artery to obtain access achieved a flow with a rating of 2b on the modified Treatment in Cerebral Ischemia classification without requiring thrombectomy, or the procedure was terminated before deployment of the Solitaire FR stent retriever owing to vessel perforation caused by microcatheter manipulation.

**Efficacy**

Patients in the endovascular-therapy group had significant improvements in both coprimary endpoints, as compared with the alteplase-only group (Table 3). Endovascular therapy resulted in increased reperfusion at 24 hours (P<0.001) (Fig. 1A) and a probability of reperfusion of more than 90% without symptomatic intracerebral hemorrhage, as compared with the alteplase-only group (89% vs. 34%, P<0.001). The improvement in reperfusion remained highly significant in a sensitivity analysis in which 100% reperfusion was imputed for the three patients in the alteplase-

---

Table 1. Characteristics of the Patients at Baseline.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alteplase-Only Group (N = 35)</th>
<th>Endovascular-Therapy Group (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>70.2±11.8</td>
<td>68.6±12.3</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>17 (49)</td>
<td>17 (49)</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)†</td>
<td>13 (9–19)</td>
<td>17 (13–20)</td>
</tr>
<tr>
<td>Clinical history — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (31)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (66)</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (23)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (43)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Serum glucose — mmol/liter</td>
<td>7.6±3.6</td>
<td>7.1±2.5</td>
</tr>
<tr>
<td>Cause of stroke — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic occlusion</td>
<td>14 (40)</td>
<td>23 (66)</td>
</tr>
<tr>
<td>Large-artery occlusion</td>
<td>13 (37)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Undetermined or other</td>
<td>8 (23)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Median time from stroke onset to hospital arrival (IQR) — min</td>
<td>80 (56–115)</td>
<td>78 (54–112)</td>
</tr>
<tr>
<td>Median time from stroke onset to initiation of alteplase (IQR) — min</td>
<td>145 (105–180)</td>
<td>127 (93–162)</td>
</tr>
<tr>
<td>Site of vessel occlusion — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>11 (31)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First segment</td>
<td>18 (51)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Second segment</td>
<td>6 (17)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Ischemic core volume at initial imaging — ml‡</td>
<td>19.6±17.4</td>
<td>18.9±18.5</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>18 (4–29)</td>
<td>12 (4–32)</td>
</tr>
<tr>
<td>Perfusion-lesion volume at initial imaging — ml§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>116±48</td>
<td>105±39</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>115 (72–158)</td>
<td>106 (76–137)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Plus–minus values are means ±SD. There were no significant differences between the two groups. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. IQR denotes interquartile range.

\textsuperscript{†} Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal) to 42 (death), with lower scores indicating less severe stroke.

\textsuperscript{‡} Irreversibly injured brain (ischemic core) was defined as cerebral blood flow of less than 30% of that in normal tissue.

\textsuperscript{§} To identify brain tissue at risk for infarction, a perfusion lesion was defined as one with a time to maximum (Tmax) delay of more than 6 seconds on computed tomographic perfusion imaging.
only group who had missing data owing to poor clinical status.

Endovascular therapy led to greater early neurologic recovery at 3 days ($P=0.002$) (Fig. 1B) and improved functional outcome in an ordinal analysis of the score on the modified Rankin scale at 90 days (generalized odds ratio, 2.0; 95% confidence interval [CI], 1.2 to 3.8; $P=0.006$) (Fig. 2). We determined that 2.8 patients would need to be treated with endovascular therapy to achieve improvement of at least 1 point on the functional score, as compared with the use of alteplase alone. Patients in the endovascular-therapy group were also more likely to be independent (functional score, 0 to 2) at day 90 (71% vs. 40%, $P=0.01$); we determined that 3.2 patients would need to be treated to achieve an independent outcome, as compared with alteplase alone.

The median number of days spent at home (as compared with in the hospital or other inpatient facility) in the first 90 days after stroke was 64 days greater in the endovascular-therapy group than in the alteplase-only group ($P=0.001$).

Consistent results were seen across the range of tertiary clinical and imaging end points (Table 3, and Table S3 in the Supplementary Appendix) and the target-group analysis (Table S5 in the Supplementary Appendix). Patients with reperfusion of 90% or more in the affected vascular territory, as compared with those with reperfusion of less than 90%, had improved functional outcome on the ordinal modified Rankin scale at 90 days (generalized odds ratio, 4.5; 95% CI, 2.2 to 9.0; $P<0.001$) and had increased independence (score, 0 to 2; 72% vs. 30%; $P<0.001$) and an excellent outcome (score of 0 or 1, 58% vs. 11%; $P<0.001$).

### SAFETY

Symptomatic intracerebral hemorrhage occurred in two patients in the alteplase-only group (both with fatal results) and in none of the patients in the endovascular-therapy group. However, a large parenchymal hematoma developed in two patients in the endovascular-therapy group without causing major clinical deterioration; in one patient, the bleeding was caused by perforation by a wire during angiography and before deployment of the Solitaire FR stent retriever. Both patients survived, with scores of 3 and 4 on the modified Rankin scale at day 90. Embolization into a different vascular territory occurred in 2 of 35 patients (6%) in the endovascular-therapy group but did not cause clinical symptoms. There was no significant difference in mortality between the two groups, although two of the three patients in the endovascular-therapy group who died had a deterioration in their condition during the initial alteplase infusion before angiography because of a second cerebral embolism. The other adverse procedural event was a groin hematoma requiring transfusion in the endovascular-therapy group. Details regarding adverse events are provided in Table S4 in the Supplementary Appendix.

### DISCUSSION

In patients with acute ischemic stroke with major vessel occlusion and salvageable tissue on CT perfusion imaging, early mechanical thrombectomy with the Solitaire FR stent retriever after the intravenous administration of alteplase was associated with faster and more complete reperfusion than the use of alteplase alone. The increase in reperfusion led to a reduction in infarct growth.

<table>
<thead>
<tr>
<th>Table 2. Characteristics of Endovascular Procedures.†</th>
</tr>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Median time from stroke onset to groin puncture (IQR) — min</td>
</tr>
<tr>
<td>Median time from hospital arrival to groin puncture (IQR) — min</td>
</tr>
<tr>
<td>Median time from initial imaging to groin puncture (IQR) — min</td>
</tr>
<tr>
<td>Median time from initiation of alteplase to groin puncture (IQR) — min</td>
</tr>
<tr>
<td>Median time from groin puncture to rTICI 2b or 3 or completion of procedure (IQR) — min</td>
</tr>
<tr>
<td>Median time from stroke onset to rTICI 2b or 3 or completion of procedure (IQR) — min</td>
</tr>
<tr>
<td>Proportion of patients receiving general anesthesia — no./total no. (%)†</td>
</tr>
<tr>
<td>Final score on rTICI — no./total no. (%)†</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2b</td>
</tr>
<tr>
<td>2a</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

*The abbreviation rTICI denotes modified Treatment in Cerebral Ischemia classification, with scores ranging from 0 (no flow) to 3 (normal flow). None of the patients who had angiographic reperfusion at the end of the procedure had reocclusion on imaging at 24 hours. Further details are provided in Table S2 in the Supplementary Appendix.

†The final score was measured in the 29 patients who had an initial occlusion on angiography.
and substantial clinical benefit in early neurologic recovery and functional outcome at 3 months. This reduction in infarct growth is consistent with salvage of ischemic penumbra as the mechanism of underlying clinical benefit.23 The magnitude of the clinical benefit of en-

<table>
<thead>
<tr>
<th>Table 3. Study Outcomes.†</th>
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<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Primary outcomes</td>
</tr>
<tr>
<td>Median reperfusion at 24 hr (IQR) — (%)‡</td>
</tr>
<tr>
<td>Early neurologic improvement — no. (%)§</td>
</tr>
<tr>
<td>Secondary outcomes</td>
</tr>
<tr>
<td>Median score (IQR) on ordinal analysis</td>
</tr>
<tr>
<td>Independent outcome — no. (%)</td>
</tr>
<tr>
<td>Excellent outcome — no. (%)</td>
</tr>
<tr>
<td>Safety — no. (%)</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
</tr>
<tr>
<td>Parenchymal hematoma</td>
</tr>
<tr>
<td>Tertiary outcomes††‡‡</td>
</tr>
<tr>
<td>Recanalization at 24 hr — no. (%)‡‡</td>
</tr>
<tr>
<td>Median infarct growth at 24 hr (IQR) — ml§§</td>
</tr>
<tr>
<td>Median home time (IQR) — days¶¶</td>
</tr>
</tbody>
</table>

* NA denotes not applicable. † Values are odds ratios unless otherwise indicated. Odds ratios or median differences are for the endovascular-therapy group as compared with the alteplase-only group. ‡ Reperfusion was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and 24-hour imaging. This value can be negative if hypoperfusion becomes more severe over time. This analysis was adjusted for the site of vessel occlusion at baseline. The effect size in this category is the Wilcoxon–Mann–Whitney generalized odds ratio. § Early neurologic improvement was defined as a reduction of 8 points or more on the National Institutes of Health Stroke Scale (NIHSS) or a score of 0 or 1 at 3 days. This analysis was adjusted for the NIHSS score and age at baseline. ¶ The initial analysis of the modified Rankin scale was an ordinal analysis that used the full range of the scale from 0 (normal function) to 6 (death) and is expressed as a Wilcoxon–Mann–Whitney generalized odds ratio. The analysis was adjusted for the baseline NIHSS score (≤15 vs. >15) and age (≤70 years vs. >70 years) with the use of a permutation method to accommodate small stratum size. This method does not produce confidence intervals. In addition, scores on the modified Rankin scale were analyzed for an outcome with functional independence (score of 0 to 2) or an excellent outcome (score of 0 or 1), adjusted for the full range of ages and baseline score on the NIHSS. ‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score. || The effect size in this category is a risk difference, as measured in percentage points for symptomatic intracerebral hemorrhage and parenchymal hematoma. ††‡‡ A more detailed list of tertary outcomes is provided in Table S3 in the Supplementary Appendix. §§ Recanalization was defined as a Thrombolysis in Myocardial Infarction score of 2 or 3 (partial or complete restoration of flow at the site of arterial occlusion).21 This analysis was adjusted for the site of vessel occlusion at baseline. ¶¶ Home time (the number of days spent at home during the first 90 days after the diagnosis of stroke) was adjusted for the NIHSS score and age at baseline. || The effect size in this category is the median difference in infarct growth (as measured in milliliters and transformed by an exponent of 0.2 owing to a non-normal distribution) and the median difference in days for home time, as calculated by median regression.
dovascular thrombectomy in our study was larger than that in previous trials, despite similar clinical severities and demographic characteristics. The results of this trial were unequivocal, despite the small sample size. Key differences between our study and the previous trials include the use of CT perfusion imaging to select patients with the greatest potential to benefit from endovascular therapy, shorter time to the onset of treatment, and improved rates of angiographic revascularization.

A unique feature of our study was the use of standardized, universal CT perfusion-imaging selection to exclude patients with large ischemic cores and without evidence of clinically significant salvageable ischemic brain. Such patients have a low probability of a good outcome and have a higher risk of symptomatic hemorrhage and malignant edema. In the time window of less than 4.5 hours, patients with large ischemic cores comprise 10 to 15% of an unselected population, a rate that was generally consistent with the estimate of 25% of patients (95% CI, 11 to 45) who were excluded from our study on the basis of perfusion-imaging criteria. Such patients may not only undergo futile reperfusion but also have a reduced treatment effect if reperfusion leads to hemorrhage or malignant edema. This factor may be particularly relevant if the intervention has a higher reperfusion rate than that in controls, which was shown in our study to be applicable to endovascular therapy. CT perfusion imaging was also performed in about 65% of patients in the MR CLEAN trial (Majoie C: personal communication). Such imaging was not required according to the protocol for the MR CLEAN trial but may have influenced patient selection. Hence, positive results in the MR CLEAN trial may not be entirely attributable to imaging selection on the basis of vessel occlusion alone.

The interval between the initiation of alteplase and randomization was 30 minutes in our study, as compared with 100 minutes in the MR CLEAN trial, because of our approach of identifying patients with the greatest potential to benefit from reperfusion and then maximizing early reperfusion with the use of combined alteplase and endovascular therapy, rather than waiting to assess clinical response to alteplase. As a result, the time from stroke onset to the initiation of the endovascular procedure was a median of 50 minutes shorter than the similar interval in the MR CLEAN trial, which may also have contributed to the substantially higher proportion of patients with independent functional outcomes observed in our study. Only 11% of the patients in our study had no retrievable thrombus on initial angiography, which is consistent with results that have been reported previously and mitigates any concern regarding unnecessary angiography. As endovascular therapy becomes standard care, there is further potential to

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**Figure 1. Reperfusion and Functional Scores.**
Panel A shows box plots for the rate of reperfusion at 24 hours (the coprimary end point) among patients receiving intravenous alteplase plus endovascular therapy (endovascular-therapy group) and those receiving alteplase only (100% vs. 37%, P<0.001). The horizontal line within the box plot for the alteplase-only group represents the median, the top and bottom of each box indicate the interquartile range, I bars indicate 1.5 times the interquartile range, and the circles indicate outliers. For the endovascular-therapy group, the median was 100%, with six outliers. Panel B shows box plots for the changes in the distribution of scores on the National Institutes of Health Stroke Scale (NIHSS) from baseline to 24 hours, 3 days, and 90 days. NIHSS is a standardized neurologic examination and ranges from 0 (normal) to 42 (death), with lower scores indicating less severe stroke. There was an early and sustained reduction in NIHSS scores in the endovascular-therapy group, as compared with the alteplase-only group.
scores on the modified rankin scale at 90 days in the intention-to-treat population.

Shown are the percentages of patients in the endovascular-therapy group and the alteplase-only group with scores from 0 to 6 on the modified Rankin scale as follows: 0, no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (requiring constant nursing care and attention); and 6, death. In the endovascular group, no patients had a score of 5.

Figure 2. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

streamline the “door-to-puncture” process and perhaps achieve even greater clinical benefits.

The rate of successful revascularization immediately after the procedure (86% of patients had a restoration of flow to >50% of the stroke-affected territory) was higher in our study than in previous randomized trials but is consistent with registry studies in which the Solitaire FR stent retriever was used. This finding probably relates to the use of earlier-generation devices and techniques in the IMS-3 and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trials. The reperfusion rate in our study was also higher than the 58% reported in MR CLEAN, in which stent retrievers were used in 81.5% of patients. There is some evidence that the success of recanalization is increased in patients with good collateral flow, which correlates strongly with the presence of a “mismatch” pattern on perfusion imaging between a small, irreversibly injured ischemic core and a larger perfusion lesion indicating the presence of salvageable ischemic penumbra. The imaging selection of patients may therefore have chosen patients with a better chance of recanalization.

Our study, which was conducted at multiple centers with varying levels of imaging expertise, shows the practicality and generalizability of fully automated image processing. The time that is required to acquire, process, and interpret images is largely a function of computer-network speed and processing power, and should be less than 15 minutes.

Analysis of the CT perfusion images occurred in parallel with administration of alteplase so that there was no treatment delay.

Strengths of our study include the selection of patients who were most likely to benefit from reperfusion, earlier intervention, and a standardized stent-retriever intervention with more complete revascularization. Also, the routine assessment of reperfusion at 24 hours has the advantage of being quantitative, blinded, and objective because of the automated software that was used. The 24-hour interval provides assurance that reocclusion after initial successful recanalization is uncommon in such patients. Previous studies have been restricted to assessing angiographic reperfusion rates in only the endovascular group or, in some cases, recanalization at 24 hours in a subgroup of patients.

Limitations of the study include the inability to perform subgroup analyses, given the small number of patients. Such analyses will require individual patient meta-analysis of multiple trials. We cannot rule out the possibility that some of the patients who were excluded from the trial on the basis of a large ischemic core or absence of significant salvageable ischemic brain tissue might have benefited from endovascular therapy. Purely volume-based criteria do not account for the location of the core, which is also relevant to the clinical outcome. The early termination of the trial does create potential for overestimation of the effect size. However, the investigators believed that the new information from the MR CLEAN trial ethically mandated review by the independent data and safety monitoring board. The details of the statistical stopping rule were highly conservative and were agreed on between investigators and the data and safety monitoring board in advance of accessing the data.

In conclusion, we found that patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging had improved reperfusion, early neurologic recovery, and functional outcome if endovascular thrombectomy with the Solitaire FR stent retriever was performed without delay after the initiation of intravenous alteplase. Further studies...
will be needed to clarify remaining uncertainties regarding the benefit in patients with more distal occlusions, later time windows, and the influence of the type of device that is used and variability in the endovascular technique.

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**APPENDIX**

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**REFERENCES**


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The Interventional Management of Stroke (IMS) III trial was the largest randomized open-label trial of endovascular therapy (EVT) following intravenous thrombolysis for acute ischemic stroke. The trial was stopped early because of futility, which in combination with data from other trials has resulted in a reassessment of the use of EVT as an adjunct treatment for intravenous thrombolysis treated patients, despite superior reperfusion with EVT.1–3 To better understand

**Background and Purpose**—General anesthesia (GA) for endovascular therapy (EVT) of acute ischemic stroke may be associated with worse outcomes.

**Methods**—The Interventional Management of Stroke III trial randomized patients within 3 hours of acute ischemic stroke onset to intravenous tissue-type plasminogen activator+EVT. GA use within 7 hours of stroke onset was recorded per protocol. Good outcome was defined as 90-day modified Rankin Scale ≤2. A multivariable analysis adjusting for dichotomized National Institutes of Health Stroke Scale (NIHSS; 8–19 versus ≥20), age, and time from onset to groin puncture was performed.

**Results**—Four hundred thirty-four patients were randomized to EVT, 269 (62%) were treated under local anesthesia and 147 (33.9%) under GA; 18 (4%) were undetermined. The 2 groups were comparable except for median baseline NIHSS (16 local anesthesia versus 18 GA; \( P<0.0001 \)). The GA group was less likely to achieve a good outcome (adjusted relative risk, 0.68; confidence interval, 0.52–0.90; \( P=0.0056 \)) and had increased in-hospital mortality (adjusted relative risk, 2.84; confidence interval, 1.65–4.91; \( P=0.0002 \)). Those with medically indicated GA had worse outcomes (adjusted relative risk, 0.49; confidence interval, 0.30–0.81; \( P=0.005 \)) and increased mortality (relative risk, 3.93; confidence interval, 2.18–7.10; \( P<0.0001 \)) with a trend for higher mortality with routine GA. There was no significant difference in the adjusted risks of subarachnoid hemorrhage (\( P=0.32 \)) or symptomatic intracerebral hemorrhage (\( P=0.37 \)).

**Conclusions**—GA was associated with worse neurological outcomes and increased mortality in the EVT arm; this was primarily true among patients with medical indications for GA. Relative risk estimates, though not statistically significant, suggest reduced risk for subarachnoid hemorrhage and symptomatic intracerebral hemorrhage under local anesthesia. Although the reasons for these associations are not clear, these data support the use of local anesthesia when possible during EVT.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359424.

**Key Words:** anesthesia ■ embolectomy ■ endovascular procedures ■ injections, intra-arterial ■ stroke ■ thrombolysis
the discrepancy between superior reperfusion and similar clinical outcomes, it is important to investigate factors associated with EVT that may positively or negatively affect clinical outcome. Although newer device technologies have garnered the majority of attention, another potentially important factor contributing to outcomes is periprocedural patient management, such as blood pressure (BP), glucose, and temperature management, all of which are linked with stroke outcomes. The choice of procedural anesthesia may also be important.

Several retrospective registries have shown worse outcomes in patients treated with EVT under general anesthesia (GA) when compared with local anesthesia (LA) or conscious sedation (will be collectively referred to as LA in this article). The largest of these was a multicenter retrospective study of 980 patients that found that GA was associated with poor outcome at 90 days and increased mortality. In a retrospective analysis of 75 patients from the IMS II study, patients treated with lesser degrees of anesthesia fared better with improved neurological outcomes and lower mortality. These data were retrospective and have been controversial as there are proponents of GA who cite increased safety during the procedure as the primary indication, although the retrospective data have shown that the risk of subarachnoid hemorrhage (SAH) or symptomatic intracerebral hemorrhage (sICH) has been equivalent or lower with LA.

The IMS III trial afforded an opportunity to study the possible impact of anesthesia on EVT outcomes in a planned analysis. The following primary hypotheses were tested in this study: (1) GA is associated with poorer outcomes, (2) there is a difference in the risk of SAH and sICH in patients undergoing GA compared with LA, and (3) GA is associated with longer time to EVT initiation.

Methods

The IMS III trial was a multicenter, randomized, open-label trial of EVT following intravenous thrombolysis in patients with moderate to severe acute ischemic stroke treated within 3 hours of stroke onset sponsored by the National Institute of Neurological Disorders and Stroke. The protocol, patient selection criteria, treatment approaches, and final results have been previously published. Randomization and analysis were stratified by severity, defined according to National Institutes of Health Stroke Scale (NIHSS) ≤19 or ≥20. The primary clinical outcome was a modified Rankin Scale (mRS) score of ≤2 at 90 days, performed by blinded investigators. Recanalization success was defined as a Thrombolyis in Cerebral Infarction (TICI) score ≥2. The primary safety end points were death, SAH, and sICH (defined as any intracranial hemorrhage within 24±6 hours of randomization temporally related to a decline in neurological status as well as new or worsening neurological symptoms in the judgment of the clinical investigator and which may have warranted medical intervention). Local institutional review board approval was obtained at all centers.

Periprocedural anesthesia was defined as GA if the subject underwent endotracheal intubation within 7 hours of stroke onset. This time period was chosen to capture all patients who were intubated before or during procedure because the protocol mandated initiation of the angiographic procedure within 5 hours and completion within 7 hours after stroke onset. All other EVT subjects were defined as having undergone LA, regardless of whether or not they received conscious sedation. Subjects were intubated based on the judgment of the treating team and not per protocol. The primary reason for intubation was categorized by each investigator as: (1) routine practice (ie, routine practice to intubate and use GA before EVT) or (2) medically indicated (ie, concern for ability to protect airway/aspiration risk, cardiopulmonary deterioration, signs of herniation/increased intracranial pressure, inadequate pain control or agitation, or other). The study protocol did not mandate one approach over the other. The endovascular approach was previously described.

Statistical Analysis

Subjects with intubation status unknown (n=18) were excluded from the analysis. For consistency with the primary publication, an unfavorable outcome was imputed for subjects with mRS missing or obtained outside of window. The generalized linear model was used to test the association between GA and outcome, with the log link used to produce relative risk estimates. Confidence intervals (CI) provided are 95% intervals. Because the limited sample size and small number of safety events, particularly with respect to sICH, limited the number of potential covariate adjustments, these were prespecified based on clinical relevance rather than selected according to statistical significance. For models of good outcome and in-hospital mortality, adjusted models included severity stratum, age, and time from onset to groin puncture (T_gro; models of safety outcomes were adjusted only for mechanical embolectomy. Procedural times are described via means±SD; the effect of GA on these times is assessed via t test.

Results

A total of 434 patients were randomized to the EVT arm of IMS III. GA was used in 147 (33.9%) patients. The GA and LA cohorts were comparable in baseline demographics, medical comorbidities, time to tissue-type plasminogen activator (tPA), T_gro, time from intravenous tPA initiation to EVT initiation, time from onset to recanalization, 40-minute post tPA bolus systolic BP, and occlusion side (Table 1). The LA cohort tended to have lower NIHSS scores (median 16 versus 18; P=0.0001) and slightly lower incidence of internal carotid artery occlusion (P=0.06). Intubation was associated with stroke severity as measured by NIHSS quartiles (≤14, 15–19, 20–24, ≥25; P value <0.0001) as well as by baseline Alberta Stroke Program Early CT Score (ASPECTS; P value=0.0395). Reperfusion success (TICI, 2–3) was achieved in 76.4% of the GA cohort versus 72.8% of the LA cohort, P=0.48 (Table 2). Good outcome was achieved in 129/269 (48.0%) LA patients and in 45/147 (30.6%) GA patients (Table 2). The GA group was significantly less likely to achieve a good outcome (relative risk [RR], 0.64; CI, 0.49–0.84; P=0.0013; Figure). There was a significant association between intubation and in-hospital death with 23.1% (34/147) mortality in the GA cohort and 7.4% (20/269) in the LA cohort (RR, 3.11; CI, 1.86–5.20; P=0.0001). When adjusted for severity stratum (NIHSS≤19 or NIHSS≥20), age, and T_gro there remained a significant negative association between GA and good outcomes (RR, 0.68; CI, 0.52–0.90; P=0.0056) and in-hospital mortality (RR, 2.84; CI, 1.65–4.91; P=0.0002; Table 3).

Compared with LA, medically indicated GA was associated with lower probability of a good outcome (adjusted RR, 0.49; CI, 0.30–0.81; P=0.005) and increased mortality (adjusted RR, 3.93; CI, 2.18–7.10; P=0.0001; Table 3). Differences between routine GA and LA subjects did not reach statistical significance for either good outcome (adjusted RR, 0.80; CI, 0.60–1.06; P=0.12) or mortality (adjusted RR, 1.82; CI, 0.87–3.77; P=0.11). There was higher in-hospital mortality among the medically indicated GA cohort than the routine cohort (adjusted RR, 2.16; CI, 1.09–4.29; P=0.0274).
but the difference in good outcomes did not reach significance (adjusted RR, 0.62; CI, 0.36–1.07; \(P=0.0840\)). The results were not substantively affected by adjusting for a more detailed severity designation (NIHSS \(\leq 14\), 15–19, 20–24, \(\geq 25\)).

There was a significant association between GA and SAH (RR, 1.79; CI, 1.04–3.08; \(P=0.035\)). This relationship was confounded by endovascular approach. After adjustment for mechanical embolectomy, the association was not significant (adjusted RR, 1.34; CI, 0.76–2.38; \(P=0.32\)), Table 3. The

### Table 1. Patient and Procedural Details

<table>
<thead>
<tr>
<th>Endovascular Therapy (n=434)*</th>
<th>Intravenous tPA Only (n=222)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endotracheal Intubation Status</strong></td>
<td><strong>All Intubated</strong></td>
</tr>
<tr>
<td>(n=147)</td>
<td>(n=76)</td>
</tr>
<tr>
<td>Demographics, n (%)</td>
<td></td>
</tr>
<tr>
<td>Age (range)</td>
<td>69 (23–83)</td>
</tr>
<tr>
<td>Female</td>
<td>72 (49)</td>
</tr>
<tr>
<td>White</td>
<td>126 (85.7)</td>
</tr>
<tr>
<td>Clinical history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>108 (73.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (25.2)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>60 (40.8)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>19 (12.9)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>65 (44.2)</td>
</tr>
<tr>
<td>Prior antiplatelet use</td>
<td>65 (44.2)</td>
</tr>
<tr>
<td>Clinical status, mean (range)</td>
<td></td>
</tr>
<tr>
<td>NIHSS (median)</td>
<td>18 (7–40)</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>7.5 (0–10)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>6.8 (3.9–23.3)</td>
</tr>
<tr>
<td>Onset to intravenous tPA, min</td>
<td>117 (29–189)</td>
</tr>
<tr>
<td>Onset to groin puncture, min</td>
<td>210 (110–315)</td>
</tr>
<tr>
<td>40-min systolic blood pressure</td>
<td>142.5 (87–208)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>82 (55.8)</td>
</tr>
<tr>
<td>Occlusion location, n (%)§</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>34 (26.6)</td>
</tr>
<tr>
<td>Middle cerebral artery trunk</td>
<td>53 (41.4)</td>
</tr>
<tr>
<td>Middle cerebral artery branch</td>
<td>36 (28.1)</td>
</tr>
<tr>
<td>Vertebro-basilar</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Endovascular approach, n (%)#</td>
<td></td>
</tr>
<tr>
<td>Standard microcatheter</td>
<td>42 (32.6)</td>
</tr>
<tr>
<td>EKOS</td>
<td>13 (10.1)</td>
</tr>
<tr>
<td>Merci</td>
<td>39 (30.2)</td>
</tr>
<tr>
<td>Penumbra</td>
<td>27 (20.9)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (6.2)</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

*Eighteen subjects with unknown intubation status were excluded from analysis.
†Nine subjects with unknown intubation status were excluded from analysis.
‡Two patients received endovascular therapy.
§One hundred eighty subjects excluded from percentage denominator; 97 with no endovascular therapy, 5 with occlusion not identified on angiogram.
||\(P=0.06\).
¶An additional 2 (0.7%) patients had anterior cerebral artery occlusion.
#Ninety seven subjects with no endovascular therapy excluded from percentage denominator.

| Occlusion location, n (%)§ | | | | | |
| Internal carotid artery | 34 (26.6) | 19 (28.8) | 15 (24.2) | 33 (17.7) | \(\ldots\) | \(\ldots\) |
| Middle cerebral artery trunk | 53 (41.4) | 27 (40.9) | 26 (41.9) | 77 (41.4) | \(\ldots\) | \(\ldots\) |
| Middle cerebral artery branch | 36 (28.1) | 18 (27.3) | 18 (29.0) | 68 (36.6) | \(\ldots\) | \(\ldots\) |
| Vertebro-basilar | 5 (3.9) | 2 (3.0) | 3 (4.8) | 6 (3.2) | \(\ldots\) | \(\ldots\) |
| Endovascular approach, n (%)# | | | | | |
| Standard microcatheter | 42 (32.6) | 16 (23.9) | 26 (41.9) | 94 (49.5) | \(\ldots\) | \(\ldots\) |
| EKOS | 13 (10.1) | 9 (13.4) | 4 (6.5) | 9 (4.7) | \(\ldots\) | \(\ldots\) |
| Merci | 39 (30.2) | 18 (26.9) | 21 (33.9) | 47 (24.7) | \(\ldots\) | \(\ldots\) |
| Penumbra | 27 (20.9) | 20 (29.9) | 7 (11.3) | 27 (14.2) | \(\ldots\) | \(\ldots\) |
| Other | 8 (6.2) | 4 (6.0) | 4 (6.5) | 13 (6.8) | \(\ldots\) | \(\ldots\) |
association with risk of SAH (RR, 1.45; \( P = 0.21 \)) or sICH (RR, 1.47; \( P = 0.35 \)) was not statistically significant. These findings were maintained after adjustment.

In both the unadjusted and adjusted analyses, there was insufficient evidence to conclude that there was a significant difference in good outcomes between the LA (48%) and routine GA (40.8%) cohorts compared with intravenous tPA alone (42.9%). However, in-hospital mortality was significantly reduced in the LA cohort compared with intravenous therapy (adjusted RR, 0.56; CI, 0.33–0.97; \( P = 0.0002 \)). The medically indicated GA cohort had lower probability of good outcomes compared with intravenous therapy (adjusted RR, 0.57; CI, 0.35–0.93; \( P = 0.0154 \)) and significantly increased mortality (adjusted RR, 2.0; CI, 1.23–3.26; \( P = 0.0002 \)).

### Discussion

The use of GA in the EVT arm in the IMS III Trial was associated with worse neurological outcomes and increased mortality. There was a 17% absolute difference in the proportion of patients with good outcomes in favor of LA (48%) and routine GA (40.8%) cohorts compared with intravenous tPA alone (42.9%). However, in-hospital mortality was significantly reduced in the LA cohort compared with intravenous therapy (adjusted RR, 0.56; CI, 0.33–0.97; \( P = 0.0002 \)). The medically indicated GA cohort had lower probability of good outcomes compared with intravenous therapy (adjusted RR, 0.57; CI, 0.35–0.93; \( P = 0.0154 \)) and significantly increased mortality (adjusted RR, 2.0; CI, 1.23–3.26; \( P = 0.0002 \)).

The exact reasons why GA seems to be associated with worse outcomes is likely multifactorial. One possibility is hemodynamic perturbations, especially hypotension associated with the induction of GA.\(^5\)\(^6\)\(^9\) In a retrospective single center study of 96 EVT patients, Davis et al\(^11\) found a negative association between GA use and good outcomes (15% probability of good outcomes versus 60% in the LA patients). They also found an association of good outcomes with systolic BP >140 mm Hg, the presence of which was negatively correlated with GA use, leading them to postulate that the deleterious effects of GA were because of the changes in systolic BP. This association is supported by another retrospective study of 216 EVT patients, 60% of whom were treated with GA and the remainder with conscious sedation using dexmedetomidine. This study found greater variations in BP in the GA group and that higher procedural BP was associated with better outcomes.\(^12\) In this current study, the closest preprocedural BP reading collected, the systolic BP 40 minutes after the initiation of intravenous tPA, was numerically higher in the LA cohort although the difference was not statistically significant. A higher preanesthesia BP could be associated with improved outcomes and could explain some of the findings in this study but that is purely conjectural because no other periprocedural readings were collected.\(^11\)\(^12\)

**Figure.** Distribution of modified Rankin Scale scores of disability at 3 months.

**Table 2. Outcomes**

<table>
<thead>
<tr>
<th>Endotracheal Intubation Status</th>
<th>All Intubated</th>
<th>Routine Intubation</th>
<th>Medically Indicated Intubation</th>
<th>Not Intubated</th>
<th>Present Intubation</th>
<th>Not Present Intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>(n=147)</td>
<td>(n=76)</td>
<td>(n=71)</td>
<td>(n=269)</td>
<td>(n=17)</td>
<td>(n=196)</td>
</tr>
<tr>
<td>THI 2–3†</td>
<td>94 (76.4)</td>
<td>51 (79.7)</td>
<td>43 (72.9)</td>
<td>131 (72.8)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Modified Rankin Scale ≤2</td>
<td>45 (30.6)</td>
<td>31 (40.8)</td>
<td>14 (19.7)</td>
<td>129 (48)</td>
<td>0 (0)</td>
<td>84 (42.9)</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>34 (23.1)</td>
<td>10 (13.2)</td>
<td>24 (33.8)</td>
<td>20 (7.4)</td>
<td>7 (41.2)</td>
<td>27 (13.8)</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
<td>12 (8.2)</td>
<td>5 (6.6)</td>
<td>7 (9.9)</td>
<td>13 (4.8)</td>
<td>2 (11.8)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage§</td>
<td>23 (16.0)</td>
<td>11 (14.7)</td>
<td>12 (17.4)</td>
<td>23 (8.9)</td>
<td>1 (7.1)</td>
<td>10 (5.4)</td>
</tr>
</tbody>
</table>

TICI indicates Thrombolysis In Cerebral Infarction recanalization grade; and tPA, tissue-type plasminogen activator.

†Eighteen subjects with unknown intubation status were excluded from analysis.

‡Nine subjects with unknown intubation status were excluded from analysis.

§Twenty-nine subjects with unknown subarachnoid hemorrhage status excluded from percentage denominator; 14 endovascular subjects and 15 IV tPA only subjects.

GA- general anesthesia, LA- local anesthesia

The largest of these was a multicenter retrospective study of 980 IAT patients, 44% of whom were treated under GA.\(^3\) In that study, GA was associated with increased odds of poor outcome (mRS ≥3; odds ratio [OR], 2.33; 95% CI, 1.63–3.44; \( P < 0.0001 \)) and mortality (OR, 1.68; 95% CI, 1.23–2.30; \( P < 0.0001 \)).

The exact reasons why GA seems to be associated with worse outcomes is likely multifactorial. One possibility is hemodynamic perturbations, especially hypotension associated with the induction of GA.\(^5\)\(^6\)\(^9\) In a retrospective single center study of 96 EVT patients, Davis et al\(^11\) found a negative association between GA use and good outcomes (15% probability of good outcomes versus 60% in the LA patients). They also found an association of good outcomes with systolic BP >140 mm Hg, the presence of which was negatively correlated with GA use, leading them to postulate that the deleterious effects of GA were because of the changes in systolic BP. This association is supported by another retrospective study of 216 EVT patients, 60% of whom were treated with GA and the remainder with conscious sedation using dexmedetomidine. This study found greater variations in BP in the GA group and that higher procedural BP was associated with better outcomes.\(^12\) In this current study, the closest preprocedural BP reading collected, the systolic BP 40 minutes after the initiation of intravenous tPA, was numerically higher in the LA cohort although the difference was not statistically significant. A higher preanesthesia BP could be associated with improved outcomes and could explain some of the findings in this study but that is purely conjectural because no other periprocedural readings were collected.\(^11\)\(^12\)
The mechanism by which reduction in BP could worsen outcomes is unknown but is likely via a reduction in cerebral blood flow to the ischemic penumbra potentiating the extent of injury.13 Additionally increases in cerebral venous pressure, which have been noted to occur with GA and endotracheal intubation, could potentiate the effect of lower BP.14 Future trials should study the effect of BP on outcomes and its possible interaction with type of anesthesia.5,6,9 There are theoretical concerns of neurotoxicity of certain anesthetic agents but only a prospective study comparing different agents can confirm or disprove this effect.15

A major weakness of the retrospective studies published to date is that the reasons for initiating anesthesia were not known and the association between GA and poor outcomes could have been because of underlying medical comorbidities or stroke severity that necessitated GA. We attempted to control for as many factors as possible but the small number of events limited the number of variables that we could assess. Although the median NIHSS was slightly lower in the LA group, a finding seen in some of the earlier series, the difference in outcomes in favor of LA persisted after adjustment for the dichotomized severity stratum (NIHSS ≤19 versus ≥20).5,9 Davis et al11 also found that GA patients had more severe strokes than LA patients, but in their institution GA was reserved for patients who cannot cooperate and those with acute critical events, such as airway obstruction. In IMS III, we attempted to control for this variable by differentiating the GA cohort into those intubated as part of routine practice and those intubated because of a medical indication. The worst outcomes were in those who had a medical indication. This would suggest that sicker patients (ie, cardiopulmonary failure) do worse, perhaps because of their underlying medical conditions or an interaction with GA. However, the differences in medical comorbidities were not significant between the GA and LA cohorts. In addition, the GA patients tended to have higher NIHSS scores, but the differences were unlikely significant enough to account for the major differences in outcomes and a 3-fold higher mortality in the GA cohort compared with LA. A major limitation of this study is the fact that medically indicated was broadly defined in the protocol and included patients with cardiopulmonary deterioration, neurological deterioration with concern for the patient’s ability to predict the airway and those with inadequate pain control or agitation. In retrospect, separating these indications for intubation may have helped to better clarify which group(s) of patients had worse outcomes related to the underlying medical condition rather than some possible effect from GA. It is known that some centers perform GA as medically indicated in patients with aphasia or who are unable to follow commands.21 In IMS III, this approach is suggested by the higher proportion of left hemispheric strokes in the GA group as a whole (Table 1). This practice at some centers may explain in part the relatively higher NIHSS in that group because the NIHSS is biased toward higher scores in dominant hemisphere patients.16 The differences could also be accounted for in the lower proportion of patients with angiographic occlusion in the LA group but the on-treatment analysis was not different.

In addition to hemodynamic perturbations, GA may affect outcomes by masking neurological deterioration or headache during the EVT procedure, which could lead to an adjustment of the endovascular approach and avoidance of a major complication, such as vessel perforation.5,17,18 A contrary point of view is that GA may be safer by preventing patient movement which could lead to wire perforation of one of the cerebral vessels. Our theory that there would be a difference in the primary safety measures of sICH and SAH has not been corroborated by the findings. This is in keeping with the findings from other studies that the risk of sICH was the same or lower in the LA group.5,6,9,11 Therefore, there is to date no evidence that GA is safer than LA.19-21 In addition, GA has been associated with significantly higher treatment costs. In a preplanned analysis of costs in the IMS III trial, the average cost of EVT with GA was $46,444 compared with a cost of $30,350 for EVT with LA.22

With the rapid rise of retrievable stents as the new standard of interventional care, the applicability of our results to patients treated with such devices is unclear because a minority (n=7) of patients in IMS III was treated with retrievable stents. However, a recent retrospective series of patients treated only with Solitaire FR (Covidien Inc, Irvine, CA) and analyzed for the effect of anesthesia found a significant negative effect of GA compared with LA.23 In that study, the OR for good outcome was 1.3 (1.01–1.6), P=0.04 in favor of LA when adjusted for anterior circulation strokes and electively intubated patients only. The OR for mortality with GA was 3.3 (1.6–7.1, P=0.001). This study was a follow-up to the earlier study examining the effect of GA by Abou-Chebl et al21 and both data sets were garnered from essentially the same centers and operators with the major difference being the use of retrievable stents in the latter study. This suggests

Table 3. Adjusted Outcomes Analysis

<table>
<thead>
<tr>
<th>Endovascular Therapy (n=434)*</th>
<th>All Intubated</th>
<th>Routine Intubation</th>
<th>Medically Indicated Intubation</th>
<th>Not Intubated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified Rankin Scale ≤2</strong></td>
<td>RR, 0.68; CI, 0.52–0.90; P=0.0056</td>
<td>RR, 0.80; CI 0.60–1.06; P=0.12</td>
<td>RR, 0.49; CI, 0.30–0.81; P=0.005</td>
<td>1</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>RR, 2.84; CI, 1.65–4.91; P=0.0002</td>
<td>RR, 1.82; CI, 0.87–3.77; P=0.11</td>
<td>RR, 3.93; CI, 2.18–7.10; P&lt;0.0001</td>
<td>1</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
<td>RR, 1.45; CI, 0.64–3.27; P=0.37</td>
<td>...</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>RR, 1.34; CI, 0.76–2.38; P=0.32</td>
<td>...</td>
<td>...</td>
<td>1</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and RR, relative risk.

*Eighteen subjects with unknown intubation status were excluded from analysis.
that the effect of GA may be independent of the type of devices used. Further substantiating this assumption is that an analysis of the recent Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, which was comparable with IMS III but included use of retrievable stents in 97% of endovascular patients, also showed that there was an association with better outcomes (mRS≤2) in patients treated with LA (OR, 2.79 (1.70–4.59; Berkhemer OA, Impact of General Anesthesia On Treatment Effect in the MR CLEAN Trial, Oral Presentation, ISC, February 13, 2015, Nashville, TN)."24 Importantly, the 3 recent trials of endovascular thrombectomy where GA was rarely used (9% in Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times [ESCAPE]) provide empirical evidence that the procedure can be safely performed under LA a large majority of the time.25

Surprisingly, GA was not associated with significantly longer treatment times.26 One possible explanation is that when all aspects of EVT preparation are relatively slow, the impact of GA is not perceptible. As these processes become more efficient, the time needed for induction of GA may become increasingly important. However, we did not adjust for case complexity, time of day, etc, factors which could prolong the measured time to groin puncture. These data suggest that in IMS III the observed negative association with GA was unlikely to have been purely because of a delay in treatment.

A final important finding of this study is that compared with intravenous thrombolysis only patients, those receiving EVT without GA had lower in-hospital mortality. Also the medically indicated GA cohort, although small, had significantly worse outcomes and higher mortality compared with the intravenous thrombolysis patients. In combination with other subgroup analyses such as the cohort of patients who had computerized tomographic angiography proven occlusion, these findings may help in the design and patient selection for future trials of EVT: for example, future trials may exclude patients likely to need GA for EVT, increasing their power to detect a benefit.

This study has several limitations. First, not all data were available in all patients. Second, although there was a distinction in reasons for intubation, the definition of medically indicated was not prespecified and could have been open to interpretation as discussed above. Furthermore, we did not collect information on the exact timing of the intubation for GA. If a substantial number of patients were intubated postoperatively for a complication within 7 hours of stroke onset, the results would have been heavily biased against the use of GA. Although anecdotal and post hoc, discussions with the investigators at the highest enrolling centers suggest that the overwhelming majority of patients were intubated preprocedure. The study may have been underpowered to detect a statistically significant difference between routine GA and LA. Finally, BP data during the induction of anesthesia and the EVT procedure were not collected.

In conclusion, in IMS III, GA use in the EVT arm was associated with worse neurological outcomes and increased mortality. The worst outcomes were in the patients with medically indicated GA, although there was a trend for worse outcomes in those patients treated with GA as part of routine care compared with LA. GA was not safer than LA in terms of hemorrhage risk. Finally, GA was not associated with a significant delay in treatment. This is the first prospective study to evaluate a technical aspect of EVT and its effect on outcomes and strongly supports the standardization of EVT procedural details in future trials. These data do not address the potential mechanisms of the GA effect but confirm that there is an effect that should be studied in a prospective, randomized trial. Based on these data, the only data from a prospective study, LA is a viable, safe, and cost-effective option for periprocedural patient management in patients without a clear medical indication for intubation.

Acknowledgments

We would like to thank the IMS III enrolling centers and investigators (see online-only Data Supplement for a listing).

Sources of Funding

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Disclosures

Dr Yeatts: Consultant/Advisory Board: Genentech. Dr Cockcroft: Other: Coviad, Actuated Medical. Dr Goyal: Consultant/Advisory Board: Covidien. Dr Jovin: Grant, nonfinancial, and other support: Fundación Ictus Malaltia Vascular; Nonfinancial support: Covidien/Medtronic; Personal fees: Silk Road Medical and Air Liquide; Nonfinancial support: Covidien/Medtronic and Stryker Neurovascular outside the submitted work. Dr Khatri: Research support: Genentech, Penumbra; DSBM member: Biogen. Dr Sugg: Speakers’ Bureau: Genentech. Dr Wartenberg: Speakers’ Bureau: Bard Medical. Dr Tomsick: Research grant: Covidien. Broderick: Research grant: Genentech; Research support: Concentric, Cordis, Elken; Travel to Australian stroke conference: Boehringer Ingelheim. Dr Hill: Research grant: Covidien; Consultant/Advisory Board: Merck. The other authors report no conflicts.

References


Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke


Abstract

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Background

Endovascular therapy is increasingly used after the administration of intravenous tissue plasminogen activator (t-PA) for patients with moderate-to-severe acute ischemic stroke, but whether a combined approach is more effective than intravenous t-PA alone is uncertain.

Methods

We randomly assigned eligible patients who had received intravenous t-PA within 3 hours after symptom onset to receive additional endovascular therapy or intravenous t-PA alone, in a 2:1 ratio. The primary outcome measure was a modified Rankin scale score of 2 or less (indicating functional independence) at 90 days (scores range from 0 to 6, with higher scores indicating greater disability).

Results

The study was stopped early because of futility after 656 participants had undergone randomization (434 patients to endovascular therapy and 222 to intravenous t-PA alone). The proportion of participants with a modified Rankin score of 2 or less at 90 days did not differ significantly according to treatment (40.8% with endovascular therapy and 38.7% with intravenous t-PA; absolute adjusted difference, 1.5 percentage points; 95% confidence interval [CI], −6.1 to 9.1, with adjustment for the National Institutes of Health Stroke Scale [NIHSS] score [8–19, indicating moderately severe stroke, or ≥20, indicating severe stroke]), nor were there significant differences for the predefined subgroups of patients with an NIHSS score of 20 or higher (6.8 percentage points; 95% CI, −4.4 to 18.1) and those with a score of 19 or lower (−1.0 percentage point; 95% CI, −10.8 to 8.8). Findings in the endovascular-therapy and intravenous t-PA groups were similar for mortality at 90 days (19.1% and 21.6%, respectively; P=0.52) and the proportion of patients with symptomatic intracerebral hemorrhage within 30 hours after initiation of t-PA (6.2% and 5.9%, respectively; P=0.83).

Conclusions

The trial showed similar safety outcomes and no significant difference in functional independence with endovascular therapy after intravenous t-PA, as compared with intravenous t-PA alone. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00359424.)
Intravenous tissue plasminogen activator (t-PA; alteplase [Activase, Genentech, or Actilyse, Boehringer Ingelheim]) is the only proven reperfusion therapy for acute ischemic stroke, and its clinical effectiveness is critically time-dependent.\(^1,2\) A key advantage of intravenous t-PA is that it can be started rapidly after clinical assessment and computed tomography (CT) of the brain without the use of contrast material. However, few patients with ischemic stroke (<10%) meet current eligibility criteria for the use of intravenous t-PA, including arrival within a relatively short therapeutic time window (<4.5 hours) after symptom onset.\(^1,3\) Limitations of intravenous t-PA include dependence on available serum plasminogen, the resistance of an old or large thrombus to fibrinolysis, and the risks of systemic and cerebral hemorrhage.\(^1,2,4,5\)

Endovascular therapy recanalizes occlusions in large arteries more frequently and rapidly than intravenous t-PA in patients with acute ischemic stroke and is increasingly used to treat patients with occlusions of the large intracranial arteries in institutions with the required expertise.\(^6\) Current endovascular approaches include endovascular pharmacologic thrombolysis, manipulation of the clot with the use of a guidewire or microcatheter, mechanical and aspiration thrombectomy, and most recently, stent-retriever technology. The primary disadvantage of endovascular therapy is the delay in initiation of treatment because of the time required to mobilize the interventional team and, in many cases, the need to transfer the patient to another hospital.\(^7,8\) Other potential limitations include difficulty getting the catheter to the site of occlusion, damage to the arterial wall from devices, fragmentation and distal embolization of the thrombus, risks associated with general anesthesia (if used), and complications of systemic and cerebral hemorrhage.\(^7,9,10\) In the absence of data from a randomized trial, it is uncertain whether endovascular therapy, with or without the previous use of intravenous t-PA, is more effective than intravenous t-PA alone.

Intravenous t-PA followed by endovascular therapy combines the advantages of a rapid start of intravenous t-PA with a greater likelihood of early recanalization with the use of endovascular therapy in patients with persistent occlusion after treatment with intravenous t-PA. On the basis of preliminary work, first tested in the small, randomized Emergency Management of Stroke (EMS) trial during 1995 and 1996\(^11\) and consecutive single-group trials (the Interventional Management of Stroke [IMS] I and II trials),\(^12,13\) as well as the expanded clinical use of endovascular therapy after intravenous t-PA, the IMS III trial was organized to begin enrollment in 2006. In April 2012, after 656 of a planned 900 participants had undergone randomization, the data and safety monitoring board recommended to the sponsor (the National Institute of Neurological Disorders and Stroke) that enrollment be terminated owing to the crossing of the prespecified boundary for futility. Here we report the results of the prespecified primary efficacy and subgroup analyses and safety data through 90 days of follow-up.

**METHODS**

**TRIAL DESIGN**

We conducted the IMS III trial, an international, phase 3, randomized, open-label clinical trial with a blinded outcome, to test the approach of intravenous t-PA followed by protocol-approved endovascular treatment, as compared with standard intravenous t-PA. Intravenous t-PA was started within 3 hours after symptom onset in both groups. Details of the methods used in the trial have been published previously.\(^14\) The study protocol is available with the full text of this article at NEJM.org.

The design, analysis, and data collection for the IMS III trial, as well as the writing of the manuscript, were performed by members of the executive committee and investigators at the study sites (see the Supplementary Appendix, available at NEJM.org). These investigators vouch for the accuracy and completeness of the presented data and for the fidelity of this report to the study protocol. Genentech supplied t-PA for endovascular use, and EKOS, Concentric Medical, and Cordis Neurovascular supplied catheters; Genentech, EKOS, and Boehringer Ingelheim provided support for investigator meetings. None of the industry sponsors were involved in the study design, study conduct, manuscript review, or protocol review, except to make sure that the specified use of devices in the study followed the instructions for use approved by the Food and Drug Administration (FDA).

At the beginning of the trial, only a single thrombectomy device had been cleared for use
Endovascular Therapy after t-PA vs. t-PA Alone

by the FDA,15,16 and the trial leadership recognized that endovascular technology would continue to evolve. To keep the trial clinically relevant and optimize the endovascular approach, additional devices were allowed as they became cleared for clinical use by the regulatory authorities of participating countries, after approval by the executive committee of the IMS III trial.

At the beginning of the trial, CT angiography was used infrequently at participating hospitals to assess the presence of vascular occlusions in patients with acute stroke. Thus, the baseline National Institutes of Health Stroke Scale (NIHSS) score, a clinical measure of neurologic deficit with a range of 0 (no deficit) to 42 (maximum possible deficit), was used to identify patients with a score of 10 or more, who have a greater than 80% likelihood of a major arterial occlusion on subsequent angiography after intravenous t-PA.11,17,18 In amendment 3 to the protocol, after 284 participants had undergone randomization, identification of occlusion with the use of CT angiography was allowed to determine trial eligibility for patients with an NIHSS score of 8 or 9, because the routine use of CT angiography had increased rapidly during the early course of the study.19

To ensure that a similar, standard, FDA-approved total dose of t-PA (0.9 mg per kilogram of body weight administered over a 1-hour period; maximum dose, 90 mg) would be administered in patients assigned to endovascular therapy and those assigned to intravenous t-PA, the patients in the endovascular-therapy groups in the EMS and all IMS trials received only approximately two thirds of the standard dose of intravenous t-PA. Safety data on the standard dose of intravenous t-PA followed by additional intraarterial t-PA became available during the latter part of the IMS III trial, by which time this approach had become more common in clinical practice.20 Thus, the standard dose of intravenous t-PA was implemented in the endovascular-therapy group after the approval of amendment 5 to the protocol in June 2011.

PARTICIPANTS

We planned to enroll a maximum of 900 participants, 18 to 82 years of age, at 58 centers in the United States, Canada, Australia, and Europe. Eligibility criteria included receipt of intravenous t-PA within 3 hours after symptom onset and a moderate-to-severe neurologic deficit (defined as an NIHSS score ≥10 or, after approval of amendment 3, a score of 8 to 9 with CT angiographic evidence of an occlusion of the first segment of the middle cerebral artery [M1], internal carotid artery, or basilar artery at institutions where CT angiographic imaging at baseline was the standard of care for patients with acute stroke). Written informed consent was obtained from the patient or a legal representative before enrollment. Detailed inclusion and exclusion criteria are provided in Table 1 in the Supplementary Appendix.

TREATMENTS

All participants began receiving a standard dose of intravenous t-PA (0.9 mg per kilogram), with 10% as a bolus and the remainder infused over a 1-hour period (maximum dose, 90 mg). Throughout the trial, randomization was required within 40 minutes after the initiation of the infusion. The patients randomly assigned to the intravenous t-PA group received the remainder of the standard dose.

Participants randomly assigned to the endovascular-therapy group underwent angiography as soon as possible, either at the hospital that initiated treatment with intravenous t-PA or at another participating hospital. Participants who had no angiographic evidence of a treatable occlusion received no additional treatment, and those with a treatable vascular occlusion received endovascular intervention with an approach chosen by the site neurointerventionalist (i.e., thrombectomy with the Merci retriever [Concentric Medical], Penumbra System [Penumbra], or Solitaire FR revascularization device [Covidien], or endovascular delivery of t-PA by means of the MicroSonic SV infusion system [EKOS] or a standard microcatheter). The angiographic procedure had to begin within 5 hours and be completed within 7 hours after the onset of stroke. Heparin infusion was started intravenously with a 2000-unit bolus, followed by an infusion of 450 units per hour during endovascular therapy, and was discontinued at the end of the procedure.

CLINICAL ASSESSMENTS AND OUTCOMES

The primary outcome measure was a modified Rankin scale score of 2 or less (indicating functional independence) at 90 days. The modified Rankin score is a measure of disability and functional status after stroke that ranges from 0 (no
symptoms) to 5 (severe disability and bedridden) and 6 (death). All modified Rankin scale assessments at 90 days were to be performed by study investigators who were not involved in the treatment of the patient and who were unaware of the treatment assignment. The patient’s functional status before the qualifying stroke was assessed by means of a modified Rankin score already documented in the patient’s medical history.

CT was performed at baseline, at 24 hours (±6 hours), and if there was a neurologic decline. CT angiography was performed at baseline at those study sites that routinely included it in their baseline imaging protocol. CT angiography was planned for all participants at 24 hours to assess vascular patency. The Thrombolysis in Cerebral Infarction (TICI) score, which ranges from 0 (no reperfusion) to 3 (full reperfusion in the distribution of the occluded artery), was used to assess the angiographic outcome in the endovascular-therapy group, for both recanalization of the original primary occlusive lesion and reperfusion of the distal vasculature of the occluded artery on completion of the angiographic procedure (see Table 4 in the Supplementary Appendix for further descriptions).

**STATISTICAL ANALYSIS**

Participants were randomly assigned in a 2:1 ratio to endovascular therapy or intravenous t-PA alone with the use of an Internet-based, computerized algorithm of minimization and the biased-coin method, which accounted for two factors: clinical center and baseline NIHSS strata (scores of 8 to 19 vs. ≥20). We calculated that a sample of 900 patients would provide an effect size of 10 percentage points (the absolute difference between the endovascular-therapy and intravenous t-PA groups in the proportion of participants with a modified Rankin score of ≤2 at 90 days), assum-

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**Table 1. Characteristics of the Patients at Baseline.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Endovascular Therapy (N=434)</th>
<th>Intravenous t-PA Alone (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Range</td>
<td>23–89</td>
<td>23–84</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>218 (50.2)</td>
<td>122 (55.0)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>51 (11.8)</td>
<td>19 (8.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (2.5)</td>
<td>12 (5.4)</td>
</tr>
<tr>
<td>NIHSS score‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Range</td>
<td>7–40</td>
<td>8–30</td>
</tr>
<tr>
<td>ASPECTS of 8, 9, or 10 — no. (%)§</td>
<td>247 (56.9)</td>
<td>131 (59.0)</td>
</tr>
<tr>
<td>Presumptive location of stroke — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>224 (51.6)</td>
<td>106 (47.7)</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>197 (45.4)</td>
<td>109 (49.1)</td>
</tr>
<tr>
<td>Brain stem or cerebellum</td>
<td>10 (2.3)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Unknown or multiple locations</td>
<td>3 (0.7)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Atrial fibrillation — no. (%)</td>
<td>153 (35.3)</td>
<td>70 (31.5)</td>
</tr>
<tr>
<td>History of hypertension — no. (%)</td>
<td>319 (73.5)</td>
<td>171 (77.0)</td>
</tr>
<tr>
<td>History of diabetes — no. (%)</td>
<td>94 (21.7)</td>
<td>54 (24.3)</td>
</tr>
<tr>
<td>History of congestive heart failure — no. (%)</td>
<td>50 (11.5)</td>
<td>31 (14.0)</td>
</tr>
<tr>
<td>History of coronary artery disease — no. (%)</td>
<td>102 (23.5)</td>
<td>72 (32.4)</td>
</tr>
<tr>
<td>History of hyperlipidemia — no. (%)</td>
<td>215 (49.5)</td>
<td>112 (50.5)</td>
</tr>
<tr>
<td>Serum glucose — mmol/liter</td>
<td>7.4±2.9</td>
<td>7.6±3.1</td>
</tr>
<tr>
<td>Time from stroke onset to initiation of intravenous t-PA — min</td>
<td>122.4±33.7</td>
<td>121.2±33.8</td>
</tr>
</tbody>
</table>

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Endovascular Therapy after t-PA vs. t-PA Alone

**RESULTS**

**CHARACTERISTICS OF THE PARTICIPANTS**

A total of 656 participants underwent randomization (434 participants to endovascular therapy and 222 to intravenous t-PA alone) at 58 study centers between August 25, 2006, and April 17, 2012 in the United States (41 sites), Canada (7), Australia (4), and Europe (6) (see the Supplementary Appendix). Table 2 in the Supplementary Appendix lists reasons why screened patients did not undergo randomization.

Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Endovascular Therapy (N=434)</th>
<th>Intravenous t-PA Alone (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin scale score — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>379 (87.3)</td>
<td>197 (88.7)</td>
</tr>
<tr>
<td>1</td>
<td>35 (8.1)</td>
<td>21 (9.5)</td>
</tr>
<tr>
<td>2</td>
<td>19 (4.4)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>148±21.3</td>
<td>147.3±24</td>
</tr>
<tr>
<td>Current antiplatelet use — no. (%)</td>
<td>186 (42.9)</td>
<td>108 (48.6)</td>
</tr>
<tr>
<td>Current statin use — no. (%)</td>
<td>155 (35.7)</td>
<td>83 (37.4)</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Range</td>
<td>0.9–1.7</td>
<td>0.9–1.7</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant between-group differences, except for history of coronary artery disease (P=0.01). The abbreviation t-PA denotes tissue plasminogen activator.
† Race or ethnic group was self-reported.
‡ The National Institutes of Health Stroke Scale (NIHSS), a serial measure of neurologic deficit, is a 42-point scale that quantifies neurologic deficits in 11 categories, with 0 indicating normal function without neurologic deficit and higher scores indicating greater severity of deficit.
§ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) allows for the systematic assessment of 10 regions of the brain with the use of computed tomography, with a score of 1 indicating a normal region and 0 indicating a region showing signs of ischemia; total scores range from 10 (no evidence of early ischemia) to 0 (all 10 regions in the hemisphere show early ischemic changes).
¶ Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no substantial disability despite the presence of symptoms, 2 slight disability, and 3 moderate disability necessitating some help; a score of 6 indicates death. Persons with a score of 0, 1, or 2 are considered to be functionally independent.
not undergo randomization, and Figure 1 in the Supplementary Appendix shows the numbers of patients who underwent study interventions. An unfavorable imputation was applied for 27 participants (14 participants for whom the primary outcome was assessed outside the specified 30-day window and 13 for whom the primary outcome was not assessed).

The only baseline variable that differed significantly between the two treatment groups was the proportion of patients with a history of coronary artery disease (P=0.01) (Table 1). Data on the presence or absence of major arterial occlusions according to the NIHSS score for the 306 participants who underwent CT angiography at baseline are shown in Figure 2 in the Supplementary Appendix.

**PRIMARY OUTCOME**

The trial was stopped early because of futility, according to the prespecified rule. There was no significant difference between the endovascular-therapy and intravenous t-PA groups in the overall proportion of participants with a modified Rankin score of 2 or less (40.8% and 38.7%, respectively; absolute adjusted difference, 1.5 percentage points; 95% confidence interval [CI], −6.1 to 9.1, with adjustment for NIHSS strata) (Fig. 1). There was also no significant difference in the predefined subgroups of patients with an NIHSS score of 20 or more, indicating severe stroke (difference of 6.8 percentage points in favor of the endovascular-therapy group; 95% CI, −4.4 to 18.1), and patients with a score of 8 to 19, indicating moderately severe stroke (difference of −1.0 percentage point in favor of the intravenous t-PA group; 95% CI, −10.8 to 8.8) (Fig. 2).

**SECONDARY OUTCOMES**

Predefined secondary analyses showed no significant differences among the subgroups. The direction of effect favored better overall outcomes among participants in the endovascular-therapy group treated with intravenous t-PA within 2 hours after the onset of symptoms, as compared with those treated with intravenous t-PA alone within 2 hours after onset (Fig. 2, and Fig. 3 in the Supplementary Appendix), but the difference was not significant. There was a similar direction of effect toward better outcomes with a time from the start of intravenous t-PA to groin puncture of 90 minutes or less in the endovascular-therapy group, as compared with a procedure-initiation time of more than 90 minutes, but the difference was also not significant. Table 5 in the Supplementary Appendix provides details regarding the dosing of t-PA and treatment times.

**REPERFUSION RATES**

Reperfusion rates at angiography in the endovascular-therapy group, as measured according to TICI grades 2 or 3 (indicating partial or complete re-
Endovascular Therapy after t-PA vs. t-PA Alone

In the treatment group, reperfusion rates were 65% for occlusion in the internal carotid artery (65 patients), 81% for an M1 occlusion (135 patients), 70% for a single occlusion in the second division of the middle cerebral artery (M2) (61 patients), and 77% for multiple M2 occlusions (22 patients). Only 4 patients had basilar occlusions, and the TICI score was not used for this location. Data regarding results in other vessels with smaller numbers of patients are not shown. Reperfusion rates, as measured by a TICI score of 2b (partial reperfusion of half or more of the vascular distribution of the occluded artery) to 3, were 38% for an occlusion in the internal carotid artery, 44% for an occlusion in M1, 44% for a single M2 occlusion, and 23% for multiple M2 occlusions.

The proportion of patients with a modified Rankin score of 2 or less at 90 days (primary outcome) increased with greater reperfusion. The primary outcome occurred in 12.7% of the 55

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–19</td>
<td>452</td>
<td>1.01 (0.78–1.31)</td>
</tr>
<tr>
<td>≥20</td>
<td>204</td>
<td>1.37 (0.63–2.99)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–65 yr</td>
<td>270</td>
<td>1.07 (0.78–1.48)</td>
</tr>
<tr>
<td>≥66 yr</td>
<td>386</td>
<td>1.01 (0.69–1.50)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>316</td>
<td>0.90 (0.62–1.30)</td>
</tr>
<tr>
<td>Male</td>
<td>340</td>
<td>1.18 (0.83–1.65)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No or unknown</td>
<td>433</td>
<td>1.13 (0.84–1.52)</td>
</tr>
<tr>
<td>Yes</td>
<td>223</td>
<td>0.89 (0.56–1.39)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤120 min</td>
<td>345</td>
<td>1.24 (0.88–1.74)</td>
</tr>
<tr>
<td>&gt;120 min</td>
<td>310</td>
<td>0.88 (0.62–1.24)</td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–7</td>
<td>271</td>
<td>1.12 (0.67–1.87)</td>
</tr>
<tr>
<td>8–10</td>
<td>378</td>
<td>1.03 (0.79–1.34)</td>
</tr>
<tr>
<td>ICA, M1, or basilar occlusion</td>
<td></td>
<td>1.05 (0.67–1.64)</td>
</tr>
<tr>
<td>NIHSS score 8–19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>231</td>
<td>1.16 (0.81–1.68)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA &gt;120 min</td>
<td>221</td>
<td>0.88 (0.61–1.26)</td>
</tr>
<tr>
<td>NIHSS score ≥20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>114</td>
<td>1.77 (0.60–5.21)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA &gt;120 min</td>
<td>89</td>
<td>0.98 (0.28–3.39)</td>
</tr>
<tr>
<td>ICA, M1, or basilar occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>124</td>
<td>1.18 (0.66–2.10)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA &gt;120 min</td>
<td>96</td>
<td>0.86 (0.42–1.74)</td>
</tr>
</tbody>
</table>

Figure 2. Adjusted Relative Risk for Predefined Subgroups, as Assessed According to the Primary Outcome of a Modified Rankin Score of 0 to 2 at 90 Days.

Data were adjusted for age (continuous), baseline NIHSS strata, and time from onset to initiation of intravenous t-PA (continuous). The comparisons of baseline NIHSS strata were not adjusted for baseline NIHSS score, and the subgroups defined according to the baseline NIHSS strata and time from onset to intravenous t-PA were adjusted only for age. One patient who underwent randomization did not receive intravenous t-PA but was included in the intention-to-treat analysis. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) allows for the systematic assessment of 10 regions of the brain with the use of computed tomography (CT), with a score of 1 indicating a normal region and 0 indicating a region showing signs of ischemia; total scores range from 10 (no evidence of early ischemia) to 0 (all 10 regions in the hemisphere show early ischemic changes). Data on ASPECTS were obtained for patients who had original CT scans for comparison. A total of 220 participants had an occlusion of the internal carotid artery (ICA), middle cerebral artery (M1), or basilar artery, as determined by means of CT angiography prior to treatment with intravenous t-PA.
patients with a TICI score of 0, in 27.6% of the 29 patients with a TICI score of 1, in 34.3% of the 108 patients with a TICI score of 2a (partial perfusion of less than half the vascular distribution of the occluded artery), in 47.9% of the 119 patients with a TICI score of 2b, and in 71.4% of the 7 patients with a TICI score of 3 (P<0.001). Among patients with an occlusion of the internal carotid artery, M1, or both, reperfusion rates, as measured by a TICI score of 2 to 3, according to the various endovascular approaches, were 71% for intraarterial t-PA (51 patients), 71% for the MicroSonic SV infusion system with intraarterial t-PA (14 patients), 73% for the Merci retriever (77 patients), 85% for the Penumbra System (39 patients), and 75% for the Solitaire FR revascularization device (4 patients).

Among the 147 participants in the endovascular-therapy group for whom CT angiograms were obtained at both baseline and 24 hours, the rate of partial or complete recanalization at 24 hours was 81% for an occlusion in the internal carotid artery, 86% for an M1 occlusion, 88% for an M2 occlusion, and 100% for a basilar occlusion (only 1 patient had basilar occlusions). The rates in the intravenous t-PA group, among 69 patients with both sets of CT angiograms, were 35% for an occlusion in the internal carotid artery, 68% for an M1 occlusion, and 77% for an M2 occlusion.

SAFETY

Table 2 lists the predefined safety outcomes. There were no significant differences in mortality at 7 days or 90 days, in the rate of symptomatic intracerebral hemorrhage, or in the rate of parenchymal hematoma, although the rate of asymptomatic intracerebral hemorrhage was higher in the endovascular-therapy group than in the intravenous t-PA group (P=0.01) (see Table 6 in the Supplementary Appendix for a list of all serious adverse events).

DISCUSSION

The IMS III trial was stopped early because of futility, according to the prespecified rules, and failed to show a benefit in functional outcome with the use of additional endovascular therapy, as compared with the standard therapy of intravenous t-PA alone. The safety profiles were similar in the two treatment groups.

We designed a stratified analysis for the primary outcome, hypothesizing that the efficacy of endovascular therapy would be greater in participants with more severe stroke (NIHSS score ≥20), since such patients have the highest likelihood of occlusion in a major intracranial artery and the greatest volume of ischemic brain at risk. In this subgroup, the difference in the proportion of participants with a modified Rankin score of 2 or less at 90 days in the endovascular-therapy group, as compared with those treated with intravenous t-PA alone, was not significant (6.8 percentage points; 95% CI, −4.4 to 18.1), and a larger difference among patients with more severe deficits who were treated within 2 hours after the onset of stroke was also not significant (14.0 percentage points; 99% CI, −6.2 to 34.1).

Although an earlier time to endovascular therapy was hypothesized to be associated with greater benefit, the results of relevant prespecified subgroup analyses were not significant. Trials of acute myocardial infarction have shown increased efficacy of percutaneous coronary intervention, as compared with fibrin-specific thrombolysis (1 percentage point lower mortality with percutaneous coronary intervention); efficacy is strongly related to both the rapidity of initiation of treatment and the severity and extent of myocardial ischemia.

Given these data from trials of reperfusion in patients with myocardial infarction, the strong relationship between the time from symptom onset to the initiation of treatment and the clinical effectiveness of intravenous t-PA, and subgroup data from the IMS III trial, future trials of endovascular therapy should consider methods to minimize delays to the initiation of endovascular therapy. In addition, although we did not find a significant benefit of endovascular therapy in patients with severe stroke or occlusion of a large artery, a larger trial that is sufficiently powered to assess these subgroups might show efficacy.

Although successful revascularization in the IMS III trial was associated with better functional outcomes in the endovascular-therapy group, there are limitations of revascularization as a surrogate measure for differential efficacy between the two reperfusion therapies. In this trial, we observed partial or complete reperfusion in 81% of M1 occlusions, as compared with a reported rate of 40% recanalization for M1 occlusions as measured by means of transcranial Doppler ultrasonography and magnetic resonance angiography.
2 to 3 hours after treatment with intravenous t-PA alone.7,29,30 Thus, although the endovascular approach provides an estimated increase of 40 percentage points in revascularization after the procedure, as compared with intravenous t-PA alone, we observed no significant clinical benefit of endovascular therapy after intravenous t-PA.

The single-group IMS I and II trials and the RECANALISE study indicate that the link between reperfusion and outcome is rapidly attenuated with increasing time from the onset of symptoms to reperfusion; in the IMS I and II trials, a 30-minute delay was associated with a 10% decrease in the probability of functional independence (defined as a modified Rankin score of 0, 1, or 2).31,32 Despite a strong emphasis on rapid treatment, the time to endovascular treatment in the IMS III trial was 32 minutes longer than in the IMS I trial, which was a smaller, phase 2, single-group study conducted at 17 sites. This may be one important reason for the lack of clinical benefit, despite the finding of substantially better revascularization with endovascular therapy than with intravenous t-PA.

Two recent phase 2 trials that compared stent retrievers with the Merci retriever showed clear and substantial increases in reperfusion in favor of the stent retrievers.33,34 Stent retrievers were used in only a small number of patients in the IMS III trial before the study was halted because of futility. Hence, one limitation of our trial is that it did not compare the efficacy of the new stent retrievers with that of intravenous t-PA alone. However, our study highlights the finding that improved reperfusion is not a guarantee of clinical efficacy. The efficacy of these new devices, as compared with intravenous t-PA alone, remains to be demonstrated.

<table>
<thead>
<tr>
<th>Table 2. Primary and Secondary Safety End Points.</th>
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<tr>
<td><strong>End Point</strong></td>
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<tr>
<td>Death — no. (%)</td>
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<tr>
<td>Within 7 days</td>
</tr>
<tr>
<td>Within 90 days</td>
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<tr>
<td>Intracerebral hemorrhage within 30 hr — no. (%)</td>
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<tr>
<td>Symptomatic</td>
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<tr>
<td>Asymptomatic</td>
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<tr>
<td>Parenchymal hematoma identified within 30 hr — no./total no. (%)†</td>
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<tr>
<td>Type 2</td>
</tr>
<tr>
<td>Type 1</td>
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<tr>
<td>Hemorrhage — no./total no. (%)</td>
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<tr>
<td>Subarachnoid</td>
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<tr>
<td>Intraventricular</td>
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<tr>
<td>Major complication due to nonintracerebral bleeding within 5 days — no. (%)‡</td>
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<tr>
<td>Recurrent stroke within 90 days — no. (%)</td>
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<tr>
<td>Device or procedural complication — no. (%)‡</td>
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* Events occurred during specified periods after the administration of intravenous t-PA. P values were obtained with the use of the Cochran–Mantel–Haenszel test. Data for events identified with the use of computed tomography exclude 32 participants for whom a scan was not obtained within 24 hours after initiation of intravenous t-PA or a postbaseline safety scan was not obtained within the defined time window (i.e., participants who died, had care withdrawn at the request of the family, or underwent imaging after the 30-hour window).† Parenchymal hematoma type 2 was defined as a dense hematoma involving more than 30% of the infarcted area with substantial space-occupying effect or any hemorrhagic area outside the infarcted area, and type 1 as a hematoma involving 30% or less of the infarcted area.‡ Complications included groin hematoma, vessel dissection, vessel perforation, and emboli in a previously uninvolved territory, as identified by the site investigator or as assessed centrally.
The IMS III trial and other recent trials of endovascular therapy for acute ischemic stroke address the promise and limitations of endovascular therapy. The use of randomization in ongoing and future stroke trials, rather than the treatment of eligible patients with endovascular therapy outside any trial, and minimization of the time to treatment will be essential for assessing the potential benefit of endovascular therapy for acute ischemic stroke.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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8. Tonarelli SB, Tibbs M, Vazquez G,


Recanalisation success is associated with good clinical outcome despite advanced age and stroke severity in patients treated with the Solitaire stentriever

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\textbf{Abstract}
Intravenous recombinant tissue plasminogen activator is associated with significant recanalisation failure in the setting of large artery occlusion. Endovascular treatment by stentriever achieves improved rates of recanalisation but its impact on clinical outcomes remains unclear. We hypothesise that successful recanalisation, unattenuated by age and stroke severity, is associated with improved clinical outcomes in patients treated with the Solitaire stentriever (ev3 Endovascular, Plymouth, MN, USA). We conducted a retrospective study of 60 consecutive acute ischaemic stroke patients treated with the Solitaire stentriever. The data included demographics, vascular risk factors, ictal onset time, National Institutes of Health Stroke Scale (NIHSS) score at presentation, angiographic findings, post-procedure imaging, and clinical follow-up. Recanalisation success was defined as a thrombolysis in cerebral infarction score (TICI) $\geq 2b$. Good clinical outcome was defined as a modified Rankin Scale score (mRS) $\leq 2$ at 3 months. Of the 60 patients, the mean age was 64.1 (standard deviation 13.4) years and 68.3% were men. Median NIHSS score at presentation was 18 (interquartile range 14–22). Successful recanalisation (TICI $\geq 2b$) was achieved in 44 patients (73.3%). Of these 44 patients, 25 patients (56.8%) achieved mRS $\leq 2$ at 3 months. Multiple logistic regression showed significant association between recanalisation success and improved clinical outcome ($p = 0.019$). Of all patients, four (6.7%) developed symptomatic intracranial haemorrhage. Overall mortality was 28.3%. In conclusion, the Solitaire stentriever was associated with improved recanalisation rates. We showed that successful recanalisation is associated with good clinical outcomes after adjustments for age, sex and stroke severity.

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\subsection*{1. Introduction}
The use of intravenous recombinant tissue plasminogen activator (IV-rtPA) improves outcomes for acute ischaemic stroke. This was shown in a study by the National Institute of Neurological Disorders and Stroke\textsuperscript{1} when thrombolysis was administered within 3 hours and further studies showed sustained benefit up to 4.5 hours.\textsuperscript{2–4} It is on this basis that intravenous thrombolysis is offered as first line treatment for acute ischaemic stroke patients.

Rapid recanalisation appears to be the key to good clinical outcomes in acute stroke. However, recent studies showed poor recanalisation rates post IV-rtPA (46.2%)\textsuperscript{5} with consequent poor outcomes.\textsuperscript{6–9} Of note, occlusion of the distal internal carotid artery and proximal middle cerebral artery respond poorly to IV-rtPA.\textsuperscript{10–13} The recent development of devices for mechanical clot retrieval offer improved recanalisation rates of up to 69.5% for the MERCI device (Concentric Medical, Mountain View, CA, USA)\textsuperscript{14} 81.6% for Penumbra (Penumbra, Alameda, CA, USA)\textsuperscript{15} and 89.7–100% for the most recent Solitaire stentriever (ev3 Endovascular, Plymouth, MN, USA).\textsuperscript{16,17} There is emerging interest in the provision of mechanical clot retrieval as first line therapy or adjunct therapy to IV-rtPA.\textsuperscript{18} However, recent findings by investigators of Interventional Management of Stroke III,\textsuperscript{19} SYNTHESIS Expansion\textsuperscript{20} and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE)\textsuperscript{21} showed equivalent clinical outcomes comparing intra-arterial (IA) therapy with IV-rtPA alone. There was reasonable concern that these studies employed an older...
generation of IA strategies (such as the MERCI device) leading to lower recanalisation rates and consequent poorer clinical outcomes.

We hypothesise that, in patients with similar age and stroke severity, successful recanalisation (thrombolysis in cerebral infarction [TICI] score $>2b$) by Solitaire stentriever is associated with improved clinical outcomes. We report here our single centre experience with the Solitaire stentriever in 60 patients.

2. Methods

2.1. Data extraction

This study received approval from the Ethics Committee at our institution. Patients who underwent mechanical clot retrieval with the Solitaire stentriever were extracted from a prospectively maintained stroke database. Patient demographics, vascular risk factors (hypercholesterolaemia, diabetes, hypertension, atrial fibrillation and smoking), stroke symptom onset time, the National Institutes of Health Stroke Scale (NIHSS) score at presentation and modes of treatment were obtained from the database. Procedural data (site of occlusion, procedure timing, number of device passes, post-procedure arterial stenosis, TICI and presence of vessel perforation) and post-procedure CT brain scan findings were obtained from our institutional Picture Archiving and Communications System. Clinical data, including follow-up and outcomes (mortality at 30 days and modified Rankin scale [mRS] at 3 months), were obtained from patient medical records.

2.2. Imaging assessment

The duration of the procedure was determined by first and last angiographic times. This was combined with ictal onset time to determine the time from ictal onset to recanalisation. At completion, angiograms were rated for TICI score$^{22}$ by the performing neuro-interventionist (PJM, RJD or BY). The TICI perfusion categories were as follows:

Grade 0: No perfusion. No antegrade flow beyond the point of occlusion.

Grade 1: Penetration with minimal perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.

Grade 2: Partial perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, for example, the opposite cerebral artery or the arterial bed proximal to the obstruction.

Grade 2a: Partial filling ($<50\%$) of the entire vascular territory is visualized.

Grade 2b: Complete filling of all of the expected vascular territory is visualised, but the filling is slower than normal.

Grade 3: Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

Post-procedure CT scans of the brain at 24–36 hours were assessed by neuro-interventionists for presence of intracranial haemorrhage. Intracranial haemorrhagic transformation$^{23}$ were classified into four categories as follows. Haemorrhagic infarction type 1: small petechiae along the margins of the infarct; haemorrhagic infarction type 2: more confluent petechiae within the infarcted area but without space-occupying effect; parenchymal haemorrhage type 1: haematoma in $<30\%$ of the infarcted area with some slight space-occupying effect; and parenchymal haemorrhage type 2: dense haematoma in $>30\%$ of the infarcted area with substantial space-occupying effect or as any haemorrhagic lesion outside the infarcted area. Symptomatic intracranial haemorrhage was defined as parenchymal haemorrhage type 2 with neurological deficit.

2.3. Clinical assessment

All patients had clinical data (including stroke onset and risk factors) and NIHSS score determined and recorded at presentation as per our institutional guidelines. Unconscious patients were given an NIHSS score of 35.

Patients and/or records were reviewed for clinical outcome in terms of mortality at 30 days and mRS at 3 months. The mRS guidelines$^{24}$ are as follows. Grade 0: no symptoms at all; grade 1: no significant disability despite symptoms (able to carry out all usual duties and activities); grade 2: slight disability (unable to carry out all previous activities but able to look after own affairs without assistance); grade 3: moderate disability (requiring some help, but able to walk without assistance); grade 4: moderately severe disability (unable to walk without assistance, and unable to attend to own bodily needs without assistance); grade 5: severe disability (bedridden, incontinent, and requiring constant nursing care and attention); and grade 6: death. A good clinical outcome was defined as mRS $\leq 2$ and a poor clinical outcome was defined as mRS $>2$.

2.4. Treatment technique

All patients treated with the Solitaire stentriever had general anaesthesia. A balloon guide catheter is positioned near the thrombus site. With the aid of a rotating haemostatic valve (RHV), a guide wire is advanced just distal to the clot. The guide wire is then stabilised. The Rebar microcatheter (ev3 Endovascular) is then advanced just distal to the clot. After that, the guide wire is withdrawn and the microcatheter is stabilised by tightening the RHV. The Solitaire stentriever is then advanced to the tip of the microcatheter using fluoroscopy as guidance. The RHV is then loosened and the microcatheter is pulled back which will deploy the Solitaire stentriever. The RHV is tightened again. The balloon of the guide catheter is inflated proximal to the clot to occlude the vessel. After this, the clot is retrieved by withdrawing the microcatheter and Solitaire stentriever together while simultaneously applying aspiration through the guide catheter. When possible we prefer to use the 8 French balloon guide catheter with the balloon inflated to arrest flow and suction performed with 50 ml syringes. If this is not possible a smaller guide catheter is used (the 6 French Envoy [DePuy Synthes, West Chester, PA, USA]) with suction applied in a similar fashion.

2.5. Statistical analysis

Statistical analysis was performed using STATA version 12 (Stata Corp., College Station, TX, USA). Patient characteristics are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate for continuous variables and expressed as frequencies and percentages for categorical variables. The correlation between variables was assessed using the Spearman rank correlation coefficient. Univariate analysis comparing different patient characteristics between groups was performed.
using Wilcoxon–Mann–Whitney test and Pearson chi-squared test (or Fisher's exact test) as appropriate. Unadjusted association between recanalisation success (TICI) and clinical outcome (mRS) was investigated using Fisher's exact test. To investigate the association between recanalisation success and clinical outcome adjusted for age and stroke severity, an ordinal regression analysis (shift analysis) model was attempted, but could not be used due to the violation of underlying parallel regression assumption (a significant Brant test). A binary logistic regression analysis with mRS ≤ 2 as an outcome was subsequently performed for this purpose. A p value of less than 0.05 was considered indicative of a statistically significant result.

3. Results

From December 2009 to August 2012, 60 consecutive patients (41 men and 19 women) with a mean age of 64.13 (SD 13.41) years were treated with the Solitaire stentriever at The Royal Melbourne Hospital. NIHSS scores at presentation were available in all patients and the median NIHSS score was 18 (IQR 14–22; range, 2–35). Cardiovascular risk factors included diabetes (21.7%), hypertension (48.3%), hypercholesterolaemia (40.0%), smoking (28.3%) and atrial fibrillation (41.7%). These baseline patient characteristics are summarised in Table 1. Forty-eight patients (80.0%) had anterior circulation infarct and 12 (20.0%) had posterior circulation infarct. Occlusion of only the internal carotid artery occurred in 11 patients (18.3%). Occlusion of only the middle cerebral artery occurred in 27 patients (45.0%). Occlusion of both the internal carotid and middle cerebral arteries occurred in 10 patients (16.7%). Occlusion of only the basilar artery occurred in 11 patients (18.3%). Occlusion in both basilar artery and posterior cerebral artery occurred in one patient (1.7%). Out of the 60 patients, 47 patients (78.3%) were treated with the Solitaire stentriever without other endovascular treatment and 39 (65.0%) of them achieved successful recanalisation. The other 13 patients (21.7%) were treated with angioplasty, stenting and/or Penumbra in addition to the Solitaire stentriever. Twenty-seven (45.0%) patients received IV-rtPA prior to treatment with the Solitaire stentriever. Time to intervention, defined as the duration between the time of symptom onset and the start of angiography, was a median of 284 (IQR 219–353; range, 95–1725) minutes. The median duration of procedure was 72 (IQR 44–93; range, 17–216) minutes. The median total time taken from stroke onset until the end of the procedure was 361 (IQR 286–450; range, 142–1851) minutes. These angiographic data are summarised in Table 2.

Out of the 60 patients, 44 patients (73.3%) were classified as having successful recanalisation, defined as TICI ≥ 2b, and 16 patients (26.7%) were classified as having unsuccessful recanalisation, defined by TICI < 2b. The recanalisation success rate at each clot location is described in Table 3. All patients were followed-up at 3 months and the mRS score was obtained for each patient as shown in Table 4. Overall, 26 out of 60 patients (43.3%) achieved a good clinical outcome (one patient [6.25%] in the unsuccessful recanalisation group and 25 patients [56.6%] in the successful recanalisation group; Spearman rho = 0.45 [95% confidence interval (CI) 0.22–0.63]; Fisher's exact p < 0.0001). In terms of intracranial haemorrhage, 48 patients did not have any intracranial haemorrhage (80.0%), eight patients (13.3%) had asymptomatic intracranial haemorrhage and four patients (6.7%) had symptomatic intracranial haemorrhage. Other complications included vessel perforation in one patient (1.7%) and mortality within 30 days in 17 patients (28.3%).

Mortality at 3 months following clot retrieval is shown in Table 5. Overall 19 patients (31.7%) died. Out of the 44 patients with successful recanalisation, 10 patients (22.7%) died while out of the 16 patients with unsuccessful recanalisation, nine patients (56.3%) died (Spearman rho = –0.32 [95% CI –0.53 to –0.07]; Fisher’s exact p = 0.026). Table 6 presents a univariate comparison of patient characteristics between two recanalisation success groups. NIHSS score at presentation, sex and procedure duration were found to be statistically significantly different between two groups of patients. Fig. 1 shows the distribution of scores on the mRS with respect to recanalisation success.

As estimated by logistic regression, following successful recanalisation, the odds ratio (OR) for a favourable outcome, adjusted for age, stroke severity, as well as sex and procedure duration (due to the groups being significantly different with respect to these two variables), was 33.3 (95% CI 2.14–518.6; p = 0.012), while the OR

Using Wilcoxon–Mann–Whitney test and Pearson chi-squared test (or Fisher’s exact test) as appropriate. Unadjusted association between recanalisation success (TICI) and clinical outcome (mRS) was investigated using Fisher’s exact test. To investigate the association between recanalisation success and clinical outcome adjusted for age and stroke severity, an ordinal regression analysis (shift analysis) model was attempted, but could not be used due to the violation of underlying parallel regression assumption (a significant Brant test). A binary logistic regression analysis with mRS ≤ 2 as an outcome was subsequently performed for this purpose. A p value of less than 0.05 was considered indicative of a statistically significant result.

3. Results

From December 2009 to August 2012, 60 consecutive patients (41 men and 19 women) with a mean age of 64.13 (SD 13.41) years were treated with the Solitaire stentriever at The Royal Melbourne Hospital. NIHSS scores at presentation were available in all patients and the median NIHSS score was 18 (IQR 14–22; range, 2–35). Cardiovascular risk factors included diabetes (21.7%), hypertension (48.3%), hypercholesterolaemia (40.0%), smoking (28.3%) and atrial fibrillation (41.7%). These baseline patient characteristics are summarised in Table 1. Forty-eight patients (80.0%) had anterior circulation infarct and 12 (20.0%) had posterior circulation infarct. Occlusion of only the internal carotid artery occurred in 11 patients (18.3%). Occlusion of only the middle cerebral artery occurred in 27 patients (45.0%). Occlusion of both the internal carotid and middle cerebral arteries occurred in 10 patients (16.7%). Occlusion of only the basilar artery occurred in 11 patients (18.3%). Occlusion in both basilar artery and posterior cerebral artery occurred in one patient (1.7%). Out of the 60 patients, 47 patients (78.3%) were treated with the Solitaire stentriever without other endovascular treatment and 39 (65.0%) of them achieved successful recanalisation. The other 13 patients (21.7%) were treated with angioplasty, stenting and/or Penumbra in addition to the Solitaire stentriever. Twenty-seven (45.0%) patients received IV-rtPA prior to treatment with the Solitaire stentriever. Time to intervention, defined as the duration between the time of symptom onset and the start of angiography, was a median of 284 (IQR 219–353; range, 95–1725) minutes. The median duration of procedure was 72 (IQR 44–93; range, 17–216) minutes. The median total time taken from stroke onset until the end of the procedure was 361 (IQR 286–450; range, 142–1851) minutes. These angiographic data are summarised in Table 2.

Out of the 60 patients, 44 patients (73.3%) were classified as having successful recanalisation, defined as TICI ≥ 2b, and 16 patients (26.7%) were classified as having unsuccessful recanalisation, defined by TICI < 2b. The recanalisation success rate at each clot location is described in Table 3. All patients were followed-up at 3 months and the mRS score was obtained for each patient as shown in Table 4. Overall, 26 out of 60 patients (43.3%) achieved a good clinical outcome (one patient [6.25%] in the unsuccessful recanalisation group and 25 patients [56.6%] in the successful recanalisation group; Spearman rho = 0.45 [95% confidence interval (CI) 0.22–0.63]; Fisher’s exact p < 0.0001). In terms of intracranial haemorrhage, 48 patients did not have any intracranial haemorrhage (80.0%), eight patients (13.3%) had asymptomatic intracranial haemorrhage and four patients (6.7%) had symptomatic intracranial haemorrhage. Other complications included vessel perforation in one patient (1.7%) and mortality within 30 days in 17 patients (28.3%).

Mortality at 3 months following clot retrieval is shown in Table 5. Overall 19 patients (31.7%) died. Out of the 44 patients with successful recanalisation, 10 patients (22.7%) died while out of the 16 patients with unsuccessful recanalisation, nine patients (56.3%) died (Spearman rho = –0.32 [95% CI –0.53 to –0.07]; Fisher’s exact p = 0.026). Table 6 presents a univariate comparison of patient characteristics between two recanalisation success groups. NIHSS score at presentation, sex and procedure duration were found to be statistically significantly different between two groups of patients. Fig. 1 shows the distribution of scores on the mRS with respect to recanalisation success.

As estimated by logistic regression, following successful recanalisation, the odds ratio (OR) for a favourable outcome, adjusted for age, stroke severity, as well as sex and procedure duration (due to the groups being significantly different with respect to these two variables), was 33.3 (95% CI 2.14–518.6; p = 0.012), while the OR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
<th>Age at presentation (mean, SD [range]), years</th>
<th>Vascular risk factors</th>
<th>NIHSS at presentation (median, IQR [range])</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>60, 64.13, 13.41 (28–87)</td>
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<td>18, 14–22 (2–35)</td>
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<td>68.3 (41)</td>
<td>Hypertension</td>
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<td>Hypercholesterolaemia</td>
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<td>Smoking</td>
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<td></td>
<td></td>
<td></td>
<td>Atrial fibrillation</td>
<td></td>
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</tbody>
</table>

Data are presented as percentage (%) unless otherwise stated. IQR = interquartile range, NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation.

<table>
<thead>
<tr>
<th>Location of clot</th>
<th>Success rate (%)</th>
<th>Successful recanalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>10</td>
<td>90.9</td>
</tr>
<tr>
<td>MCA</td>
<td>17</td>
<td>63.0</td>
</tr>
<tr>
<td>ICA + MCA</td>
<td>7</td>
<td>70.0</td>
</tr>
<tr>
<td>Vertebrobasilar</td>
<td>10</td>
<td>83.3</td>
</tr>
</tbody>
</table>

ICA = internal carotid artery, MCA = middle cerebral artery.
For death was 0.14 (95% CI 0.019–0.985; p = 0.048). Despite standard collinearity assessment not indicating excessive collinearity in the model (variance inflation factor = 1.2), the procedure duration was significantly associated with the success of recanalisation (Spearman’s rho = –0.41, p = 0.001) and models without procedure duration were subsequently considered. This resulted in the OR for a favourable outcome following successful recanalisation of 39.7 (95% CI 2.72–577; p = 0.007) and the OR for death following successful recanalisation of 0.13 (95% CI 0.021–0.776; p = 0.026).

4. Discussion

We found that successful recanalisation (TICI ≥ 2b) was associated with improved outcomes in a population of patients treated with the Solitaire stentriever, independent of age, sex, stroke severity and procedure duration, with an OR of 33.3 (95% CI 2.14–518.6; p = 0.012). Mortality following successful recanalisation was also lower with an OR of 0.14 (95% CI 0.019–0.985; p = 0.048). The Solitaire stentriever achieved a high rate of recanalisation (73.3%) with a low rate of symptomatic haemorrhage (6.7%). The safety and efficacy of the device are consistent with several studies performed elsewhere.25,26

When compared to the Koh et al.27 meta-analysis our patient characteristics are comparable with similar age (64.13 years), stroke severity (NIHSS = 18.27), occlusion sites (middle cerebral artery = 45.6%) and number of passes of the device used. Furthermore, time to treatment and treatment time are not significantly different from the current study to those reported in the meta-analysis. Good functional outcomes were achieved in our group in 43.3% of patients treated, which was comparable to that reported in the meta-analysis of 50.8%. However, whilst symptomatic haemorrhage rates were also comparable (6.7% versus 6.8%) our patient population suffered from significantly higher mortality (28.3% versus 11.1%). This may relate to the inclusion of a significant number of severe posterior circulation strokes in the current study.

Subgroup analysis of patients who received IV-rtPA prior to endovascular intervention showed the recanalisation rate improved to 85%. It has previously been reported that patients with proximal occlusions are less likely to respond to IV-rtPA. Subgroup analysis of the EPITHET trial showed that patients with internal carotid artery occlusion were less likely to have a good clinical outcome when treated with IV-rtPA than those receiving placebo.8 Other groups have used trans-cranial Doppler to determine the site of occlusion as well as to monitor recanalisation in patients receiving IV-rtPA.7 This demonstrated decreasing rates of recanalisation moving distal to proximal with 44% of distal middle cerebral artery, 30% of proximal middle cerebral artery and 6% of terminal internal carotid artery occlusions resolving within 2 hours post IV-rtPA. Given these reports, a tendency towards more proximal occlusions may be expected in those patients who had failed intravenous thrombolysis on clinical grounds. However, no difference between this subgroup and the cohort as a whole was seen with isolated middle cerebral artery occlusion identified in 50% and 56% of patients, respectively.

In accordance with other trials, recanalisation was statistically significantly associated with outcome. Patients who failed to recanalise almost uniformly did poorly on functional outcomes (p < 0.001). In the sole patient who failed to recanalise, yet demonstrated good clinical outcome at 3 months, apparently spontaneous recanalisation was observed at repeat CT angiography 24 hours after failed endovascular therapy. It is unclear what role, if any,
the use of the Solitaire stentriever played in this patient. Whilst it might be expected that "pre-treatment" with IV-rtPA may increase the incidence of delayed recanalisation, this was not supported in our study, albeit with small numbers. The correlation between poor outcome and failed recanalisation with the Solitaire stentriever was stronger in the subgroup of patients who received IV-rtPA prior to endovascular therapy than in the cohort as a whole. No patients in this subgroup who failed to recanalise had a good functional outcome at 90 days (n = 4).

Not unexpectedly baseline NIHSS score was statistically significantly associated with functional outcomes. A statistically significantly lower baseline NIHSS score was seen in those patients who managed to recanalise (16.7 versus 22.9; p < 0.05). A difference in clot location may explain this finding; however no such difference was identified (p = 0.273). Bang and colleagues have previously shown that the quality of a patient’s collaterals impacts recanalisation by mechanisms that remain unclear.25 It would be expected that baseline NIHSS score would correlate with collateral flow and this may provide some explanation for this finding, however, our data lacks the numbers to investigate this further.

Patients were selected based on a significant clinical deficit and large vessel occlusion on CT angiography. However, we recognise the disadvantages of a single-centre, non-randomised retrospective study. In addition, the inclusion of significant proportion of posterior circulation strokes (20%) is noteworthy. This group is known to have a less favourable clinical course and may partially postulate a less successful recanalisation therapy.26 In keeping with that theory, a recent retrospective study, albeit with small numbers, demonstrated that baseline NIHSS score was statistically significant (p < 0.05). A difference in clot location may explain this finding; however no such difference was identified (p = 0.273). Bang and colleagues have previously shown that the quality of a patient’s collaterals impacts recanalisation by mechanisms that remain unclear.25 It would be expected that baseline NIHSS score would correlate with collateral flow and this may provide some explanation for this finding, however, our data lacks the numbers to investigate this further.

Our study adds to the evidence of the significant role that recanalisation impacts outcome in acute stroke treatment.27–29 However, what remains unclear is the variable clinical improvements in patients with successful recanalisation. This may be partially explained by the degree of collateral circulation until successful reperfusion is achieved. It has previously been shown that degree of collateral circulation affects outcomes, but also the success of recanalisation therapy.27 In keeping with that theory, a recent report by Turk and colleagues demonstrated comparable functional outcome results in patients treated up to and beyond 6 hours when CT perfusion was used as a measure of penumbral28

5. Conclusion

In conclusion, we showed a high rate of successful recanalisation using the Solitaire stentriever in acute ischaemic strokes. Recanalisation is a significant determinant of functional outcome, unattenuated by age, sex and stroke severity. However, data from randomised controlled studies are required to definitively demonstrate clinical benefit prior to recommending its general application to acute ischaemic stroke.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

Clinical Study

Recanalisation success is independent of ASPECTS in predicting outcomes after intra-arterial therapy for acute ischaemic stroke

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Thrombolysis in Cerebral Infarction

Abstract

Intra-arterial (IA) therapy for stroke is an increasingly utilised management approach for acute ischaemic stroke. We aimed to correlate radiological characteristics and recanalisation success with radiological and functional outcomes at 90 days in patients treated with IA therapy. This was a single centre, retrospective study investigating the correlation between pre-procedural Computed Tomography-Angiogram Source Image (CTA-SI) Alberta Stroke Program Early Computed Tomography Score (ASPECTS), recanalisation success, and functional outcome at 90 days in patients with an acute ischaemic stroke from 2007–2012. Outcome measures were pre-procedural non-contrast computed tomography (NCCT), CTA-SI, and post-procedural NCCT ASPECTS that were obtained and analysed by three blinded reviewers, recanalisation success (Thrombolysis in Cerebral Infarction [TICI] 2b–3) and favourable clinical outcome (90 day modified Rankin scale [mRS] score ≤2). Forty-four patients satisfied the inclusion criteria. The mean age was 64.2 years (standard deviation: 14.9; median: 66.5; interquartile range [IQR]: 54.5–76.5). The median National Institutes of Health Stroke Scale score was 17 (IQR: 13.5–20). Twenty-one (47.7%) patients achieved a mRS score ≤2. The 90 day mortality rate was 25.0% (n = 11). Of the patients who achieved TICI 2b–3, 65.5% (19/29) achieved mRS ≤2. There was a statistically significant association between recanalisation success (TICI ≥2b) and favourable neurological outcome at 90 days (odds ratio [OR] 25.22, 95% confidence interval [CI]: 2.86–222.37, p < 0.005). Patients with high pre-procedural CTA-SI ASPECTS are significantly more likely to have high post-procedural NCCT score (OR 23.36, 95% CI: 3.26–166.92, p = 0.002). Recanalisation success was strongly associated with good clinical outcome, unaffected by known predictive factors, which included age and stroke severity. This association was unattenuated by CTA-SI ASPECTS.

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1. Introduction

Intra-arterial (IA) therapy for stroke – a diverse group of endovascular therapies that includes thrombolysis, mechanical clot retrieval or both – is an increasingly utilised management approach for acute ischaemic stroke. In 2012, 10,000 to 12,000 IA stroke treatments were estimated to have been performed in the USA [1]. This emergence of IA therapy aims to treat patients at risk of recanalisation failure treated with intravenous tissue plasminogen activator (IV tPA) thrombolysis alone (that is, high clot burden, proximal occlusion) or those who are ineligible for IV tPA (symptom onset greater than 4.5 hours) [2,3]. Major international multi-centre trials demonstrate recanalisation rates of 57.3–85% with IA therapy [4–7].

An endovascular approach is highly targeted and reduces systemic exposure to tPA, however its correlation with clinical outcome as measured by modified Rankin Scale (mRS) at 3 months remains uncertain [5–8]. Several recently published randomised clinical trials did not demonstrate a significant difference in outcome between those treated with endovascular therapy either as an adjunct to IV tPA or with endovascular treatment alone, compared to IV tPA alone. IMS3 was a phase 3, randomised, open label clinical trial with a blinded outcome to test the approach of IV tPA followed by endovascular treatment (both IA thrombolysis and mechanical disruption). The study was stopped early after 656 patients had been randomised due to futility; there was no significant difference in the proportion of patients with mRS ≤2
at 90 days between the IV (tPA and endovascular groups (38.7% and 40.8%, respectively) [9]. Results were similar in the MR-RESCUE and SYNTHESIS trials [10,11]. This highlights the need for appropriate patient selection, especially based on neuroimaging, to identify those most likely to benefit from endovascular therapy and to ensure that benefits of the intervention outweigh the risks.

The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is well validated and correlates strongly with functional outcomes (mRS) after IV thrombolysis [12–15]. Computed Tomography Angiogram–Source Image (CTA-SI) ASPECTS is more sensitive than plain CT ASPECTS in predicting outcome in patients post IV thrombolysis [16–18]. However, its use in endovascular therapy alone is yet to be appropriately proven.

We proposed and tested the hypothesis that pre-procedural CTA-SI ASPECTS and recanalisation success correlate with post-procedural non-contrast computed tomography (NCCT) ASPECTS (as a marker for final infarct volume) and functional outcome at 90 days in patients treated with IA therapy. This is a retrospective study on IA therapy patients from a single tertiary centre.

2. Materials and methods

2.1. Patients

This was a single centre, retrospective study investigating the correlation between pre-procedural neuroimaging parameters and outcomes of patients treated with IA therapy from 2007–2012. CTA-SI ASPECTS and recanalisation success were correlated with post-procedural NCCT ASPECTS and the mRS at 3 months. Inclusion criteria were: anterior circulation infarct, presentation within 6 hours of stroke onset, treatment by IA therapy, and large artery occlusion (proximal or distal internal carotid artery [ICA], middle cerebral artery [MCA] M1 or M2 branches). Exclusion criteria included lack of pre-procedural CTA or follow up NCCT scan or MRI. Data collection included demographics, stroke severity, vascular risk factors, angiographic findings, and clinical outcomes. Clinical outcomes were mRS at 90 days, neurological decline with haemorrhagic transformation on follow up CT scan and 30 day mortality. mRS data were dichotimised and a score of ≤2 considered a favourable outcome.

2.2. Image acquisition

Axial, non-helical NCCT was performed using a Siemens Sensation 16 using parameters 120 kV, 320 mAs, 1.0 s rotation time, 4.5 mm slice thickness, and 12 × 0.75 mm detector combination (Siemens AG, Munich, Germany).

CTA was then performed with 90 mls contrast and a further 50 ml normal saline flush. Both were injected at 5 mls/s. Helical CTA images were acquired using parameters 100 kV, 200 mAs, 1.25 pitch, 0.5 s rotation time, slice thickness 0.75 mm, 16 × 0.75 mm detector configuration, and slice spacing 0.4 mm. Images were reformatted to 2.5–3.0 mm. Follow up brain NCCT was taken between 24–48 hours. MRI was substituted in one patient for whom there was no follow up brain NCCT.

2.3. Image analysis

Three experienced independent reviewers retrospectively assigned ASPECTS to patient images. The scans were anonymised and randomised for scoring. The three readers were blinded to clinical and imaging information (such as CTA-SI ASPECTS when reading NCCT ASPECTS and recanalisation success) when reading scans.

ASPECTS was assigned to pre-procedural brain NCCT and pre-procedural CTA and follow up brain NCCT. A parenchymal haemorrhage category 2 (PH2) transformation was defined as any haemorrhage on follow up occupying more than 30% of the initial infarct area with significant mass effect, or clot remote from the infarcted area [19].

Ten ASPECTS regions were scored, comprised of the subcortical areas (caudate nucleus, lentiform nucleus, internal capsule) and MCA cortical areas (M1 through to M6 and insular cortex). One point was removed from an initial score of 10 for any signs of parenchymal ischaemia over any two consecutive slices. NCCT ASPECTS was assigned using the following criteria: loss of grey-white differentiation and/or sulcal effacement and/or hypodenuation [20]. MRI diffusion weighted images were scored using a similar method. CTA ASPECTS was assigned with loss of parenchymal contrast uptake or reduced arterial filling. A single rater’s score was used; the scorer with the best inter-rater agreement (kappa) was taken as the standard ASPECTS for further statistical analysis.

Occlusion location and Thrombolysis in Cerebral Infarction (TICI) score categories were graded from 0 to 3. Grade 0 = no perfusion, Grade 1 = minimal perfusion, and Grade 2a = only partial perfusion (<two thirds), Grade 2b = complete filling of the expected vascular territory that is slower than normal, and Grade 3 = complete perfusion [21]. Successful recanalisation was taken as those patients achieving TICI 2b or 3.

2.4. Intervention

All patients were treated with differing IA therapies including clot retrieval and mechanical thrombectomy with the Solitaire AB Device (ev3 Neurovascular, Inc., Irvine, CA, USA), or the Merci Retrieval System (Concentric Medical, Inc. Hertogenbosch, The Netherlands), percutaneous transluminal angioplasty with the Gateway Balloon Catheter and Ultrafart (Boston Scientific Corporation, Natick, MA, USA) and IA thrombolysis (urokinase, dose ranges from 500,000 units to 1,000,000 units).

The use of the Solitaire AB device involved positioning of the delivery microcatheter distal to the thrombus (Rebar microcatheter, ev3 Neurovascular). The clot was removed by withdrawing the microcatheter and Solitaire AB together while simultaneously aspirating through the guide catheter. A similar procedure was used with the Merci Retrieval System.

Percutaneous transluminal angioplasty involved maneuvering the catheter within the clot then inflating under fluoroscopic guidance. IA thrombolysis was by the placement of a microcatheter within the clot itself and injection of urokinase.

2.5. Statistical analysis

Data analysis was performed using STATA12 (StataCorp, College Station, TX, USA). The value of p = 0.05 was selected as the threshold for statistical significance. Inter-rater agreement was assessed using a weighted kappa score with quadratic weights and further validated using intra-class correlation coefficient (ICC) and Lin’s concordance coefficient (LCC).

All ASPECTS and outcome measures were dichotimised to reflect the proportion of patients with a favourable score (ASPECTS > 7) or a good outcome respectively (mRS ≤2). This was done using receiver operating characteristic curve analysis.

McNemar’s test was used to investigate the association between pre-procedural CTA ASPECTS and post-procedural NCCT ASPECTS. Fisher’s exact testing was used to investigate the association between recanalisation success and post-procedural NCCT ASPECTS, as well as to investigate the association between good functional outcome at 90 days and each of pre-procedural CTA ASPECTS, recanalisation success, and post-procedural NCCT ASPECTS.
Effect sizes were reported as odds ratios (OR) to ensure consistency with multivariable analysis.

The Wilcoxon–Mann–Whitney rank sum test was used to investigate the differences in age and stroke severity between post-procedural NCCT ASPECTS positive and negative groups as well as between groups with and without good functional outcome. Corresponding effect sizes were estimated using Hodges-Lehmann median shift parameter.

To estimate the degree of adjusted association between the dichotomised post-procedural score and various patient characteristics (age, admission National Institutes of Health Stroke Scale (NIHSS) score, recanalisation success, pre-procedural CTA), a multiple binary logistic regression model was used. Three separate multiple logistic regression models were used in the assessment of the association between patient outcome (mRS) and patient characteristics (adjusted for age and NIHSS). These included models with CTA ASPECTS, without CTA ASPECTS, and a model with no ASPECTS at all.

Standard assessment of model collinearity was performed. Bayesian Information Criterion (BIC) was used to assess model fit [22]. The model with the smaller value of BIC is preferred. The strengths of evidence favouring a specific model is weak if the difference in BIC is 0–2, positive if BIC difference is 2–6, strong if BIC difference is 6–10, and very strong if BIC difference is >10.

3. Results

Over the period from January 2007 to January 2012, 44 patients met the inclusion criteria for this study. Table 1 describes the distribution of patients in this study. The mean age was 64.2 years (standard deviation [SD]: 14.9; median: 66.5; interquartile range [IQR]: 54.5–76.5) and there were 27 (61.4%) males. The median NIHSS was 17 (IQR: 13.5–20). Target vessel occlusions were in the ICA (n = 20, 45.5%); three recorded carotid T occlusions, 17 distal ICA) and MCA M1 and M2 segments (n = 24, 54.5%; 21 M1 and three M2). There were 25 (56.8%) right hemisphere infarcts and 19 (43.2%) left hemisphere infarcts. Mean onset-to-groin time was 259.9 (SD: 78.4) minutes and mean groin-to-recanalisation/discontinuation time was 70.9 (SD: 30.2) minutes. The rate of TICI 2b–3 revascularisation was 65.9% (n = 29) and 27.3% (n = 12) had a haemorrhagic transformation. Of these 2.3% (n = 1) had symptomatic decline with a PH2 haemorrhage. Twenty-one (47.7%) patients achieved a good 90 day outcome (mRS ≤ 2). Twelve (48%) of the right hemisphere infarcts and nine (47.4%) of the left hemisphere infarcts had a good functional outcome. Of the 12 patients with a right hemisphere infarct that had a favourable functional outcome, 66.7% (n = 8) had a poor post-procedural NCCT ASPECTS. This was higher than observed in the group of nine left hemisphere infarcts with a favourable functional outcome, 55.6% of whom had a poor post-procedural NCCT ASPECTS. Of those with a favourable functional outcome and post-procedural NCCT ASPECTS > 7, a higher proportion were left hemisphere infarcts (44.4% left versus 33.3% right). The median mRS was 3. The 30 day mortality rate was 20.5% (n = 9). The 90 day mortality rate was 25.0% (n = 11). Of the patients who achieved TICI 2b–3, 65.5% (19/29) achieved mRS ≤ 2.

The inter-rater agreement between scorers for the pre-procedural NCCT ASPECTS was fair (κ = 0.67, ICC = 0.70, LCC = 0.70) and strong for CTA ASPECTS (κ = 0.86, ICC = 0.86, LCC = 0.86). Inter-rater agreement between scorers in post-procedural NCCT was strong (κ = 0.91, ICC = 0.92, LCC = 0.91). Because of the low κ value for pre-procedural NCCT ASPECTS its use in further statistical analysis was not deemed to be reliable. Table 2 illustrates the spread of ASPECTS.

Multivariable logistic regression modelling indicated a statistically significant association between recanalisation success (TICI ≥ 2b) and favourable functional outcome at 90 days irrespective of pre-procedural CTA ASPECTS or post-procedural NCCT after adjusting for age and admission NIHSS. Patients with successful recanalisation had the odds of mRS ≤ 2 25.22 times higher (95% confidence interval [CI]: 2.86–222.37, p < 0.005) than those without successful recanalisation. Further results describing associations of recanalisation success and CTA-SI ASPECTS to outcome (mRS) are presented in Table 3. A comparison of models with and without CTA-SI ASPECTS and no ASPECTS at all indicated a positive association with models that do not include ASPECTS in the analysis. Models 1 and 2 have higher BIC values than model 3 where ASPECTS was removed from the analysis.

Additional modelling indicated a statistically significant association between pre-procedural CTA-SI ASPECTS and post-procedural NCCT ASPECTS. Specifically, adjusted for patient age, admission NIHSS, and successful post-procedural recanalisation status, patients with high pre-procedural CTA ASPECTS had the odds of high post-procedural NCCT score increased 23.36 times (95% CI: 3.26–166.92, p = 0.002) as compared with low pre-procedural CTA-SI ASPECTS patients (Table 4).

4. Discussion

Our study showed a significant correlation between recanalisation success (TICI ≥ 2b) and mRS at 90 days after adjusting for age and stroke severity. The proportion of patients who had TICI ≥ 2b...
and mRS ≤ 2 was 65.5% (19/29). Pre-procedural CTA-SI ASPECTS was strongly correlated with the post-procedural NCCT ASPECTS (OR 23.36, 95% CI: 3.26–166.92, p = 0.002, Table 1). In contrast to current literature a favourable pre-procedural CTA-SI ASPECTS was not associated with functional outcome at 90 days (OR 0.398, 95% CI: 0.044–3.629, p = 0.042, Table 1). In contrast to other studies, the poor inter-rater observability when scoring NCCT ASPECTS meant we were unable use it in further statistical analysis [20].

There were several limitations in this study. The small sample size reduces statistical power in our results. In addition, all the patients were from a single centre. The effect of selection bias for ASPECTS dichotomised at 7 [28]. This reflects the unreliability of NCCT ASPECTS in an emergent setting and has implications in its use for selection of patients for endovascular therapy.

There were several limitations in this study. The small sample size reduces statistical power in our results. In addition, all the patients were from a single centre. The effect of selection bias for ASPECTS dichotomised at 7 [28]. This reflects the unreliability of NCCT ASPECTS in an emergent setting and has implications in its use for selection of patients for endovascular therapy.

In our study, we showed that recanalisation success defined by TICI ≥ 2b was significantly associated with a mRS ≤ 2, a surrogate marker of good clinical outcome. We showed that recanalisation success was strongly associated with good clinical outcome, unaffected by known predictive factors, which included age and stroke severity. This association was unattenuated by CTA-SI ASPECTS. Further studies, with larger sample sizes, are needed to address CTA-SI ASPECTS as a selection tool in IA therapy.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References


Table 3

| Favourable neurological outcome (mRS ≤ 2) | Model 1 | | Model 2 | | Model 3 |
|---|---|---|---|---|---|---|
| | Adjusted OR | 95% CI | p value | Adjusted OR | 95% CI | p value | Adjusted OR | 95% CI | p value |
| Age (per extra year) | 0.94 | 0.89–0.10 | 0.043 | 0.94 | 0.89–0.10 | 0.042 | 0.94 | 0.89–0.10 | 0.047 |
| Admission NIHSS (per extra point) | 0.93 | 0.80–1.07 | 0.291 | 0.92 | 0.80–1.06 | 0.247 | 0.91 | 0.79–1.05 | 0.216 |
| Successful recanalisation (TICI 2b, 3) | 25.22 | 2.86–222.37 | 0.004 | 27.16 | 3.05–241.84 | 0.003 | 28.48 | 3.29–246.94 | 0.002 |
| Post-procedural CT ASPECTS > 7 | 2.76 | 0.28–26.88 | 0.383 | 1.51 | 0.29–7.97 | 0.626 | 1.65 | 0.28–9.81 | 0.600 |
| CTA-SI ASPECTS > 7 | 0.40 | 0.04–3.63 | 0.414 | NA | NA | NA | NA | NA | NA |
| BIC | 63.19 | 60.12 | 56.37 |

Table 4

<table>
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<tr>
<th>Post-procedural NCCT ASPECTS</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p value</th>
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<tr>
<td>Age (per extra year)</td>
<td>1.03</td>
<td>0.97–1.09</td>
<td>0.382</td>
</tr>
<tr>
<td>Admission NIHSS (per extra point)</td>
<td>0.87</td>
<td>0.73–1.04</td>
<td>0.118</td>
</tr>
<tr>
<td>CTA-SI ASPECTS &gt; 7</td>
<td>23.36</td>
<td>3.27–166.92</td>
<td>0.002</td>
</tr>
<tr>
<td>Successful recanalisation (TICI 2b, 3)</td>
<td>5.64</td>
<td>0.71–44.67</td>
<td>0.101</td>
</tr>
</tbody>
</table>

ASPECTS = Alberta Stroke Program Early CT-Score, BIC = Bayesian Information Criterion, CI = confidence interval, CTA-SI = computed tomography angiogram source image, mRS = modified Rankin scale, NA = not applicable, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, TICI = Thrombolysis in Cerebral Infarction.


Clinical Study

Shorter time to intervention improves recanalization success and clinical outcome post intra-arterial intervention for basilar artery thrombosis

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A R T I C L E   I N F O

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A B S T R A C T

Basilar artery thrombosis is associated with poor clinical outcomes and high mortality rate if untreated. Clinical outcome correlates with recanalization success. As arterial clot composition undergoes organization over time and may become more resistant to recanalization therapy, we postulate that recanalization success is time-dependent. We aim to investigate whether time to intervention predicts recanalization success leading to improved clinical outcomes. Forty-nine consecutive patients with basilar artery thrombosis treated with intra-arterial (IA) therapy between 1993 and 2011 were included. Patient demographics, clinical features, clot location, time to intervention and post-procedural thrombolysis in myocardial infarction (TIMI) scores were collected. Recanalization success was defined as a score of TIMI 2–3. Clinical outcome was measured using the 90-day modified Rankin Scale (mRS) score, with good neurological outcome defined as mRS 0–2. The mean patient age was 59.8 years ± 17.9 and 36.7% were females. IA therapy was commenced within 6 hours of stroke onset in 17/49 (34.7%) patients. Of this 6-hour onset group, 17/17 (100%) demonstrated recanalization success (TIMI 2–3) and 10/17 (58.8%) achieved good neurological outcome at 90-days. IA therapy was commenced after 6 hours of stroke onset in 32/49 (65.3%) patients, with 24/32 (75%) and 6/32 (18.75%) patients achieving recanalization success and good outcome, respectively. A shorter delay to IA therapy is significantly associated with recanalization success (p = 0.038) and good neurological outcome at 90 days (p = 0.009) in patients with acute basilar artery thrombosis. We recommend a systematic approach to minimize time delay to IA therapy for this condition.

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1. Introduction

Acute basilar artery thrombosis represents from 1% to 4% of all ischaemic strokes.1–3 It is a catastrophic subtype of posterior circulation ischaemic stroke which is associated with an 80% to 90% mortality rate in the absence of treatment.4–6 Successful recanalization of an occluded artery is associated with better outcomes.7,8 However, due to the low rates of successful recanalization of occluded basilar arteries by intravenous (IV) thrombolytics (30%),9 intra-arterial (IA) interventions are justified.4

IA interventions have been shown to be efficacious in their ability to achieve high recanalization rates,10,11 leading to lower mortality rates and better functional outcomes.12,13 Only one multicentre randomized controlled trial has assessed the efficacy of IA therapy for acute basilar thrombosis. The Australian Urokinase Stroke Trial (AUST) recruited 16 patients over 7 years, randomised into either the treatment or placebo group.14,15 Good neurological outcomes were more frequently observed in the treatment group (50%) than in the placebo group (12.5%).15 Independent variables affecting survival were shown to include collateral state and age,16 thrombus volume and pre-treatment morbidity,17 and Glasgow Coma Scale (GCS) score.18

The recanalization rate for individual patients is not uniform. It may be that the longer the delay to intervention from stroke onset, the lower the chances of achieving successful recanalization. However, this has yet to be validated. A theory has been proposed that the clot composition changes with time. Fresh newly formed clots are more red blood cell dominant and less resistant to thrombolysis, while older clots are more fibrin-rich and well-organized and hence more resistant to thrombolysis.19–22 Furthermore, shortening the delay to intervention is vital in ensuring the survival of penumbral tissue.23 Successful intervention to attenuate the growth of the ischaemic core positively contributes to good clinical outcomes.24–26 Survival of penumbral tissue relies on achieving
successful recanalization of occluded arteries, which may be limited by delay to initiation of IA intervention. In this study, we aim to determine if time to treatment is a predictor of recanalization success. We hypothesize that early intervention significantly improves recanalization success.

2. Methods

This is a retrospective single centre review of 49 consecutive patients with confirmed acute basilar artery thrombosis who received IA intervention between 1993 and 2011. Patients who presented within 24 hours of symptom onset were offered IA therapy following confirmation of basilar artery thrombosis by digital subtraction angiography (DSA). Exclusion criteria were: established extensive infarction on pre-operative CT scan, intracranial haemorrhage and patients presenting more than 24 hours post stroke. Study approval was granted by the local research and ethics committee.

Clinical parameters were identified through medical records review. Information on age, gender, vascular risk factors, clinical presentation and GCS score were collected. Time to intervention was defined as time from symptom onset or from when patient was last seen neurologically well to arterial puncture time. In the subgroup of patients presenting with a stuttering clinical course followed by sudden onset of decrease in conscious state, time of symptom onset was defined from the sudden deterioration in clinical state.

Angiograms were reviewed by three neuro-interventionists (BY, PJM, RJD), with consensus opinion reached on clot location, collateral supply, post procedural thrombolysis in myocardial infarction (TIMI) score and procedure time.

The TIMI grading system was used to grade recanalization success irrespective of vessel. TIMI grade 0 is defined as no recanalization, TIMI grade 1 as recanalization past the initial occlusion but no distal branch filling, TIMI grade 2 as recanalization with incomplete or slow distal branch filling and TIMI grade 3 as full recanalization with filling of all distal branches. Successful recanalization was defined as TIMI grade 2 or 3.

Diagnostic angiography was performed to confirm location of thrombosis. A 6F femoral sheath was inserted into the common femoral artery, followed by selective catheterization of the vertebral arteries and subsequent confirmation of basilar artery thrombosis. Intra-arterial intervention required the placement of an Envoy 6F guide catheter (Codman and Shurtleff, Raynham, MA, USA) into the vertebral artery that allowed the passage of a Renegade microcatheter (Boston Scientific, Natick, MA, USA). Once intra-thermous placement of the micro-catheter was achieved, an initial 200,000 units of urokinase was injected, followed by pulsed hand injections of further urokinase (maximum 1000,000 units). Alternatively, IA tissue plasminogen activator (IA-tPA) was given (10 mg/hour: 20 mg total infused). Repeat selective angiography was conducted in 15-minute (min) intervals to assess for recanalization. If flow disruption or occlusion persisted at 30 min since the start of intervention, attempts to recanalize using a Penumbra Device (Penumbra, Alameda, CA, USA), Solitaire Device (ev3 Neurovascular, Irvine, CA, USA) or angioplasty were conducted. Mechanical thrombectomy with Concentric Merci (Concentric Medical, Mountain View, CA, USA) or the Solitaire Device was used at the discretion of the neurointerventionists. Heparin infusion was continued post-operatively for 24 hours, aiming for an activated partial thromboplastin time of 60–65, unless there was evidence of significant infarction or haemorrhage.

Patients underwent a standardized clinical neurological evaluation, with clinical outcome graded according to the 90-day mRS score. Good neurological outcome was defined as mRS ≤ 2.

Statistical analysis was performed by the Clinical Epidemiology and Health Services Evaluation Unit at the Royal Melbourne Hospital, using STATA10 (StataCorp, College Station, TX, USA). A p-value < 0.05 was considered to be statistically significant. Fisher’s exact test was used to determine the correlation between categorical variables and outcome variables. Multivariate logistic regression was used to find predictors of good neurological outcome.

3. Results

Of the 49 patients, the mean age was 59.8 years ± 17.9, 36.7% were females and mean GCS score was 9.5 ± 4.4. Baseline characteristics, vascular risk factors, clinical presentation and key angiographic and clinical data are presented in Table 1.

3.1. Recanalization success

IA intervention included IA urokinase (89.8%), angioplasty (34.7%), stent insertion (24.5%), mechanical embolectomy with the Concentric MERCI device (8.2%), Solitaire device (4.1%), and IA-tPA (2.0%) (Table 2). The mean urokinase dose was 752,000 units. Successful recanalization (TIMI 2–3) was achieved in: 37/49 (84.1%) patients treated with IA Urokinase; 14/17 (82.4%) treated with angioplasty; 11/12 (91.7%) with stent insertion; 2/4 (50%) with a MERCI device; and 2/2 (100%) with a Solitaire device. A total of 41/49 (83.7%) patients achieved successful recanalization. Of 49 patients, TIMI 3 was achieved in 34 (69.4%) patients, TIMI 2 in seven (14.3%) patients, TIMI 1 in three (6.1%) patients and TIMI 0 in five (10.2%) patients. The mean time to intervention was 10.81 hours ± 7.646. Patients were dichotomised into those treated ≤6 hours and >6 hours after symptom onset as similar to previous reports. All 17 (100%) patients with treatment initiated within 6 hours from stroke onset achieved successful recanalization (TIMI 2–3). The association between time to intervention and Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics, vascular risk factors, clinical presentation and key angiographic and clinical data of patients treated with intra-arterial intervention for basilar artery thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Total (n = 49)</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (36.7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.8 ± 17.9</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disorder</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (55.1)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>16 (32.7)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>5 (10.2)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>8 (16.3)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>GCS score</td>
<td>9.5 ± 4.4</td>
</tr>
<tr>
<td>Hemiaparesis</td>
<td>21 (42.9)</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>11 (22.4)</td>
</tr>
<tr>
<td>Quadruparesis</td>
<td>4 (8.2)</td>
</tr>
<tr>
<td>Quadraplegia</td>
<td>4 (8.2)</td>
</tr>
<tr>
<td>Locked-in</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Ocular motor dysfunction</td>
<td>31 (63.3)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>26 (53.1)</td>
</tr>
<tr>
<td>Seizure</td>
<td>6 (12.2)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Time to intervention</td>
<td></td>
</tr>
<tr>
<td>≤6 hours</td>
<td>17 (34.7)</td>
</tr>
<tr>
<td>&gt;6 hours</td>
<td>32 (65.3)</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or number (%). GCS = Glasgow Coma Scale score.
recanalization success (TIMI 2–3) was statistically significant \((p = 0.038)\). Key angiographic data and clinical outcome with TIMI scores are presented in Table 4.

### 3.2. Time to clinical outcome

Of 49 patients, 16 (32.7%) achieved a good neurological recovery (mRS 0–2), while 17 (34.7%) patients had moderate to severe disability (mRS 3–5). The 90-day mortality rate (mRS = 6) was 32.7%. Of 16 patients who died, eight (50%) were due to basilar artery thrombosis, two (12.5%) to vessel perforations as a result of an intra-operative complication and six (37.5%) due to intracranial haemorrhagic conversion. Dichotomisation of patients using a cut-off point of 6 hours post-stroke onset revealed that of 17 patients, 10 (58.8%) and seven (41.2%) patients who received IA intervention ≤6 hours post stroke onset achieved good (mRS 0–2) and poor (mRS 3–6) neurological recovery at 90 days post-stroke respectively. Fisher’s exact test revealed statistically significant association between time to intervention and the 90-day mRS scores \((p = 0.009)\). Key angiographic and clinical data and treatment outcome information with 90-day mRS scores are presented in Table 5.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Intra-arterial (IA) intervention with time to intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA intervention</td>
<td>Time to intervention</td>
</tr>
<tr>
<td>≤6 hours ((n = 17))</td>
<td>&gt;6 hours ((n = 32))</td>
</tr>
<tr>
<td>Urokinase</td>
<td>15 (88.2)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Stent</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>MERCI</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Solitaire</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>tPA</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are number (%). tPA = tissue plasminogen activator, MERCI = Concentric Merci Device (Concentric Medical, Mountain View, CA, USA), Solitaire = Solitaire Device (ev3, Irvine, CA, USA).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Key angiographic data for patients treated with intra-arterial intervention for basilar artery thrombosis and clinical outcome with TIMI scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>TIMI 0–1 ((n = 8))</td>
</tr>
<tr>
<td>Time to intervention</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>8 (25)</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>mRS 3–6</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>5 (31.3)</td>
</tr>
</tbody>
</table>

Data are number (%). TIMI = thrombolysis in myocardial infarction, mRS = modified Rankin Scale.

There were six intra-operative complications – three vessel perforations, two groin complications and one arterial dissection. Of three vessel perforations, two (66.7%) were guide wire perforations while one (33.3%) was a MERCI device related perforation. The arterial dissection was caused by the placement of a guidewire catheter into the parent artery. Nine of 49 patients (18.4%) had complicating intracranial haemorrhagic conversion, and six (66.7%) of these patients died within 90 days.

Multivariate logistic regression of the association between mRS and time to intervention demonstrated that time to intervention is a significant predictor \((p = 0.007)\) for good neurological outcome with an odds ratio of 0.159 (95% confidence interval: 0.042–0.599), adjusting for age (Table 5).

### 4. Discussion

The natural history of acute basilar artery thrombosis managed with antiplatelet and/or anticoagulant therapy is poor.\(^5,30\) Hacke et al. reported a mortality rate of 86% in a cohort of 22 patients who received antiplatelet or anticoagulant therapy, while Schonewille et al. reported a mortality rate of 40% in a cohort of 82 patients and a dependency rate (mRS 4–5) of 65% in a similar subgroup of patients.\(^{30}\)Coupled with the low spontaneous recanalization rate in patients with acute basilar thrombosis, a more aggressive approach of IA intervention is justified.\(^4\) IA interventions such as IA urokinase, mechanical thrombectomy with Concentric Merci, Penumbra or Solitaire Devices, angioplasty and stent placement may provide high recanalization rates, which are significantly associated with a greater than 50% decrease in mortality rate.\(^6\) The preferred method is mechanical recanalization, with the Solitaire Device shown to achieve a recanalization rate of 89%\(^,31\) and the Penumbra Device a 100% recanalization rate.\(^,32\) However, failed recanalization with IA intervention is not uncommon.\(^,10\) Our study suggests time to intervention, defined with a relatively strict time window of 6-hours, is a predictor of recanalization success in basilar artery thrombosis. It is possible that the changes in clot composition over time result in older fibrin-rich clots to be more organized and hence more resistant to thrombolysis, decreasing the likelihood for the occluded arteries to be recanalized.\(^19–22\)

Recanalization is associated with a significant survival benefit.\(^,7,8\) Our study showed that 30/41 (73.2%) patients who were recanalized survived at 90 days, compared to 3/8 (37.5%) non-recanalized patients \((p = 0.094)\). This compares to findings from Eckert et al. that showed a reduction in mortality rate from 72% to 54% with recanalization \((p = 0.118).\(^,24\) In our study, 15/41 (36.6%) recanalized patients achieved a good neurological outcome (mRS 0–2), compared to 1/8 (12.5%) if recanalization did not occur \((p = 0.245)\).

Furthermore, our study found that early time to successful recanalization (TIMI 2–3) is significantly associated with good clinical outcome. Thus, 10/17 (58.8%) patients who achieved successful recanalization within 6-hours from stroke onset developed favourable clinical outcomes, while 5/24 (20.8%) patients successfully recanalized beyond 6-hours from stroke onset developed poor clinical outcomes (mRS 3–6) \((p = 0.021)\). Eckert et al. found similar
findings, reporting that 16/54 (30%) successfully recanalized patients achieved a favourable outcome at 90-days (Barthel index > 90), while 3/30 (10%) non-recanalized patients survived with a favourable outcome.28 They also showed no association between recanalization success and favourable outcome at 90 days (p = 0.125).28 However, despite similar results in both studies, classification systems used to define recanalization success and favourable clinical outcome differs, with Eckert et al defining recanalization success as a fully visible basilar artery with filling of the posterior cerebral artery (PCA) and failure of recanalization as no changes or only little improvement of basilar artery opacification without filling of the basilar tip.26 Eckert et al also used the Barthel index to investigate clinical outcome, instead of the mRS scoring system used in this study.26

We found a significant correlation between earlier treatment and good neurological recovery (58.8% if treated <6 hours compared to 18.8% if treated >6 hours; p = 0.009). Eckert et al also reported a significant improvement in neurological outcome (Barthel index > 90) if treatment could be initiated within 6-hours (36% if treated <6 hours compared to 7% if treated >6 hours; p = 0.005), concluding that early treatment is the most important factor for successful endovascular therapy in acute vertebrobasilar occlusion.28 There are several limitations to our study. This is a retrospective single-centre study of consecutive patients that, however, may lead to selection bias. The number of patients reviewed is also small. However, despite these limitations, findings from this study highlight the need for system implementations, with the aim of increasing patient awareness to stroke symptoms,33 and introducing protocols aimed at minimizing door to needle time.34 These protocols can be in the form of a “Code Stroke” protocol that expressly avoids some elements of clinical evaluation that is believed to contribute little to the management of stroke patients, thereby preventing any time delays in treatment.34

5. Conclusion

Our study suggests that early intervention improves the likelihood of achieving recanalization success and good clinical outcome post IA intervention in basilar artery thrombosis. We propose a need for hospital system implementations to minimize the delay to treatment.

Conflict of interest/disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

Efficacy and safety of different doses of intravenous tissue plasminogen activator in Chinese patients with ischemic stroke

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1. Introduction

Stroke is one of the leading causes of disability and death in both developing and developed countries. In China, stroke, with an annual incidence of 219 people per 100,000 in a population of approximately 1.3 billion, is the second commonest cause of death and is a huge societal challenge. Intravenous thrombolysis with tissue plasminogen activator (tPA) is effective in the treatment of patients with acute stroke. Pooled meta-analysis has indicated that tPA for acute ischemic stroke is one of the most powerful treatments in clinical practice. In the National Institute of Neurological Disorders and Stroke (NINDS), Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) and the European Cooperative Acute Stroke Study (ECASS) 3 trials, the standard dose of tPA was 50 mg. However, multivariate analyses were not performed to account for potential confounding factors. In the Chinese Stroke Registry, a 0.6 mg/kg dose of tPA has become the standard dose.11

The dose response to tPA may be different in Chinese patients compared with Western populations, but this has not been systematically examined. We aimed to compare the efficacy and safety of different doses of tPA in Chinese stroke patients. We included all acute ischemic stroke patients treated with tPA within 4.5 hours of onset. Patients were treated with three dose regimens of tPA (0.6–0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg). The following data were collected: patient demographics; vascular risk factors; neuroimaging results; time of tPA administration; clinical assessment before treatment, at 24 hours and 3 months; and modified Rankin Scale (mRS) score at 3 months. A total of 105 patients with stroke of Han Chinese origin were included in the study. The baseline characteristics of the three dose groups were well matched. In the 0.9 mg/kg group (n = 31), 51.1% had favorable outcome at 3 months, compared with 38.7% of patients in the 0.8 mg/kg group (n = 31) (odds ratio [OR] to 0.9 mg/kg group, 0.57; 95% CI, 0.19–1.73; p = 0.32) and 34.8% in the 0.6–0.7 mg/kg group (n = 23) (OR to 0.9 mg/kg group, 0.31; 95% CI, 0.08–1.16; p = 0.08). There were no statistically significant differences in the incidence of symptomatic intracerebral hemorrhage and mortality rate. There was a higher proportion of patients with good functional outcomes in the 0.9 mg/kg group. Although not significant, these results strongly support the feasibility and urgent need for a dose ranging trial to establish an optimal tPA dose in Chinese stroke patients.

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regime was 0.9 mg/kg, chiefly Caucasian patients were enrolled and the trial did not take into account any differences in ethnicity. There has been no randomized controlled tPA trial in Chinese patients. Hence, there is no existing agreement on the optimal dose of tPA in China for acute ischemic stroke. As a result, the dose regimens of tPA used in Chinese stroke patients varies between 0.6 mg/kg and 0.9 mg/kg and the practice of acute stroke management deviates significantly from established international guidelines. In this context, we performed a retrospective study in a major Chinese University Hospital, to examine the efficacy and safety of different doses of tPA in Chinese stroke patients.

2. Patients and methods

We retrospectively included 105 consecutive patients with acute stroke who received tPA at the Branch of Shanghai Jiao Tong University Affiliated First People’s Hospital from 1998 to 2008. Ethics approval for this project was granted by the hospital ethics committee.

The following clinical parameters at presentation were recorded: age, gender, vascular risk factors, stroke onset, National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS) score and neuroimaging results. Patients who fulfilled the inclusion criteria described below for thrombolysis were given intravenous (iv.) tPA (alteplase; Boehringer Ingelheim, Ingelheim, Germany). Three different doses of tPA were administered (0.6 mg–0.7 mg/kg, 0.8 mg/kg and 0.9 mg/kg). The decisions to allocate patients to different dose groups were based partly on financial constraints, without standardized selection criteria. The funding arrangements of hospitals in China were such that patients would have to bear the costs of medical services and medications. Of note, patients who were allocated to the 0.6 mg/kg group only required one ampoule of tPA (50 mg) which resulted in a 50% reduction in costs. Of the total tPA dose, 10% was administered as a bolus in 2 minutes, and the remainder was given by continuous iv. infusion over 60 minutes, usually in the Emergency Department. The following parameters were monitored: neurological deterioration, vital signs and bleeding complications. All patients were transferred to the stroke unit as soon as possible. Antiplatelet agents and anticoagulation were withheld for the first 24 hours. A CT brain scan was repeated at 24 hours or at the time of any suspected intracerebral hemorrhage.

2.1 Inclusion and exclusion criteria

All acute ischemic stroke patients who were given tPA within 4.5 hours were included in the study. Inclusion criteria and exclusion criteria were otherwise as outlined in the NINDS trial.3

2.2. Outcome measures

The efficacy outcome variable was the percentage of patients with a favorable outcome at 3 months, defined as a mRS score of 0 or 1. The safety outcome parameters included mortality rate at 3 months and symptomatic intracerebral hemorrhage (sICH); the sICH was determined according to NINDS criteria and ECASS 3 criteria.5

2.3. Statistical analysis

Clinical data were collected and entered separately by two neurologists (J.D.Y. and J.S.Y.) using the Epidata system (The EpiData Association; Odense, Denmark). The system allowed for verification of data entry accuracy. The Statistical Package for the Social Sciences (release 16.0.0) (SPSS; Chicago, IL, USA) was used to perform the statistical analysis. Tests of significance were conducted at the p = 0.05 level of significance. Differences of baseline characteristics between the three dose groups were determined by using the analysis of variance (ANOVA) for continuous variables (age, NIHSS, systolic pressure, diastolic pressure and time to treatment) and a chi-squared ($\chi^2$) test for categorical variables (gender, hypertension, diabetes and atrial fibrillation). The difference in the efficacies of different dose groups was calculated with the use of the chi-squared test of proportions. Binary logistic regression was used to test the statistical significance of the effect of dose on functional recovery at 3 months, adjusted for potential confounding prognostic factors such as age, baseline NIHSS, time to treatment, diabetes, gender and systolic blood pressure. The Fisher’s exact test was used to compare the differences in the incidence of sICH and mortality at 3 months.

3. Results

The baseline characteristics were well matched in the three treatment groups. These included age, NIHSS, time to treatment and vascular risk factors. A total of 105 patients of Chinese origin were included in this study. Demographic characteristics and baseline clinical characteristics were calculated separately for the three tPA dose groups and are shown in Table 1. Statistically significant baseline differences were observed in gender ($p < 0.001$) and systolic blood pressure ($p = 0.04$) between the dosage groups. In the 0.6–0.7 mg/kg group, 87% of patients were male compared to less than 50% in the other two dosage groups; patients in the 0.8 mg/kg dose group had higher systolic blood pressure than the other groups on average. No statistically significant group differences were observed in terms of important clinical characteristics such as age, NIHSS at onset and time to treatment.

3.1. Clinical efficacy

Of the patients in the 0.9 mg/kg group, 51.1% achieved a favorable clinical outcome (mRS score 0, 1) at 3 months, compared with 38.7% patients in the 0.8 mg/kg group and 34.8% patients in the 0.6–0.7 mg/kg group. Binary logistic regression analyses adjusted for the known confounding variables that included age, baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0.6–0.7 mg/kg (n = 23)</th>
<th>0.8 mg/kg (n = 31)</th>
<th>0.9 mg/kg (n = 51)</th>
<th>p value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>69.8 ± 8.6</td>
<td>72.9 ± 8.7</td>
<td>72.7 ± 10.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Gender (male%)</td>
<td>87%</td>
<td>48.4%</td>
<td>37.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS (mean)</td>
<td>12.6 ± 6.8</td>
<td>12.7 ± 5.0</td>
<td>13.0 ± 6.3</td>
<td>0.96</td>
</tr>
<tr>
<td>Systolic pressure (mmHg) (mean ± SD)</td>
<td>146.5 ± 22.3</td>
<td>156.1 ± 19.9</td>
<td>143.8 ± 21.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg) (mean ± SD)</td>
<td>82.8 ± 13.8</td>
<td>83.8 ± 10.7</td>
<td>82.8 ± 10.8</td>
<td>0.92</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>52.2%</td>
<td>64.5%</td>
<td>64.7%</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>17.4%</td>
<td>9.7%</td>
<td>19.6%</td>
<td>0.73</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>13%</td>
<td>32.3%</td>
<td>29.4%</td>
<td>0.23</td>
</tr>
<tr>
<td>Time to treatment (minutes) (mean ± SD)</td>
<td>170.3 ± 43.9</td>
<td>174.3 ± 45.2</td>
<td>153.5 ± 53.0</td>
<td>0.14</td>
</tr>
</tbody>
</table>

SD = standard deviation, NIHSS = National Institutes of Health Stroke Scale.

*p values represent the statistical significance of comparisons between the three dose groups. Continuous variables (age, NIHSS, systolic pressure, time to treatment) were analyzed by using the analysis of variance. Categorical variables (gender, hypertension, diabetes and atrial fibrillation) were analyzed by using the chi-squared test of proportion.
However, the differences did not reach statistical significance (4.3% in 0.6–0.7 mg/kg, 9.7% in 0.8 mg/kg and 9.8% in 0.9 mg/kg). Inversely, the application of the NINDS criteria showed a trend to versus increasing rate of symptomatic ICH in higher doses of tPA.

According to the ECASS 3 criteria, the proportion of patients who developed sICH was similar in each dose group: 4.3% in 0.6–0.7 mg/kg, 3.2% in 0.8 mg/kg and 3.9% in 0.9 mg/kg. (Table 2). Conversely, the application of the NINDS criteria showed a trend towards increasing rate of symptomatic ICH in higher doses of tPA (4.3% in 0.6–0.7 mg/kg, 9.7% in 0.8 mg/kg and 9.8% in 0.9 mg/kg). However, the differences did not reach statistical significance (p = 0.81). A total of 15 patients died, including four patients in the 0.6–0.7 mg/kg group, 0.31; 95% CI, 0.08–1.16; adjusted p = 0.32, OR 0.6–0.7 mg/kg group to 0.9 mg/kg group, 0.57; 95% CI, 0.19–1.73; adjusted p = 0.08) (Table 2).

The overall distribution of points on the mRS is shown in Fig. 1. Finally, a dichotomization of 51 patients in the 0.9 mg/kg group compared to 54 pooled patients with lower doses (0.6–0.8 mg/kg) indicated no difference (p = 0.17) (Table 3).

Using this trend to better outcomes in the higher dose group, a power calculation indicated that a sample size of 200 patients randomized to 0.6 mg/kg and to 0.9 mg/kg would be required to provide 80% power to identify a 20% difference in favorable outcome (p < 0.05) in the different dose groups.

### 3.2. Safety results

According to the ECASS 3 criteria, the proportion of patients who developed sICH was similar in each dose group: 4.3% in 0.6–0.7 mg/kg, 3.2% in 0.8 mg/kg and 3.9% in 0.9 mg/kg. (Table 4). Conversely, the application of the NINDS criteria showed a trend towards increasing rate of symptomatic ICH in higher doses of tPA (4.3% in 0.6–0.7 mg/kg, 9.7% in 0.8 mg/kg and 9.8% in 0.9 mg/kg). However, the differences did not reach statistical significance (p = 0.81). A total of 15 patients died, including four patients in the 0.6–0.7 mg/kg group, 0.31; 95% CI, 0.08–1.16; adjusted p = 0.32, OR 0.6–0.7 mg/kg group to 0.9 mg/kg group, 0.57; 95% CI, 0.19–1.73; adjusted p = 0.08) (Table 2). The overall distribution of points on the mRS is shown in Fig. 1. Finally, a dichotomization of 51 patients in the 0.9 mg/kg group compared to 54 pooled patients with lower doses (0.6–0.8 mg/kg) indicated no difference (p = 0.17) (Table 3).

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### 4. Discussion

There is emerging interest in the differing responses to tPA therapy in different racial groups. In comparison with Western patients, patients of Asian origin have lower plasma concentration of fibrinogen, lower plasminogen activator inhibitor-I levels and lower factor XIII activity.18–20 This led to the hypothesis that Asian patients are more responsive than their Western counterparts to thrombolytic treatment with tPA in both the coronary and cerebral circulations. Some clinical studies showed that lower dose tPA demonstrated similar clinical effects for Japanese and Chinese pa-
tients with AMI.8-10 Tending weight to the existence of differing responses to thrombolysis in Asian patients. In ischemic stroke, the Japanese Thrombolysis Study Group studied the effects of 20 mega-international units (MIU) duteplase (a recombinant tissue plasminogen activator similar to tPA; 20 MIU duteplase is equivalent to 0.6 mg/kg tPA) and showed similar arterial recanalization rate and clinical improvement when compared with 30 MIU duteplase (equivalent to 0.9 mg/kg tPA). Of note, the lower dose duteplase was associated with fewer severe intracerebral hemorrhagic events.11,21,22 Moreover, the Japan Alteplase Clinical Trial (J-ACT) trial concluded that for Japanese stroke patients, 0.6 mg/kg tPA may offer a similar clinical efficacy and safety profile to those reported in NINDS.11 However, the J-ACT trial was an open label study, rather than a randomized controlled trial.

Apart from potential differences in the hemostatic profile of Asian patients, there are well-documented differences in the pattern of cerebrovascular disease. In Chinese patients and other Asian groups, there is a greater incidence of small vessel disease and intracranial large vessel stenosis.2,3 This has also led to the speculation that there may be differing dosing requirements in Asia.

Based on the clinical trials and meta-analysis,5-7 North American and European stroke guidelines have recommended tPA 0.9 mg/kg as the standard dose.5-15 However, 0.9 mg/kg was the dose chosen in NINDS based on safety rather than clinical efficacy.7 In small dose-ranging studies conducted by the NINDS investigators, various doses were tested in small cohorts, from 0.35 mg/kg to 1.08 mg/kg. Safety analysis demonstrated that symptomatic ICH seldom occurred in doses of 0.85 mg/kg or lower.22,23 Furthermore, another pilot study concurred with the safety profile of 0.85 mg/kg tPA in stroke patients.24 The efficacy of different doses of tPA has never been formally tested in a randomized controlled trial.

Recent studies in China suggested that lower dose tPA (0.6-0.8 mg/kg) had the same efficacy and safety as standard dose tPA.12,13 In contrast, a very small study suggested that standard dose tPA was more effective than lower dose tPA (0.6-0.8 mg/kg) in Chinese stroke patients. There was no increase in the rate of sICH with the standard dose tPA, but the study only included 30 patients.25 Therefore, the optimal dose of tPA in Chinese stroke patients remains unresolved.

Our study of Chinese stroke patients treated with different doses of tPA (0.6 mg/kg to 0.9 mg/kg) suggested the possibility of a gradient of clinical efficacy favoring higher doses, but the differences were not significant. However, based on the findings, a randomised controlled clinical trial could be performed in China to address the dose controversy, with a sample size of 200 patients randomized between 0.6 mg/kg and 0.9 mg/kg (100 per group) providing 80% power in detecting a 20% difference in favorable clinical outcome at a p value of <0.05. Using either the ECASS 3 or NINDS definition of sICH, there was no difference between the three groups.

Our study has limitations. This was an observational retrospective study, without randomization and the numbers in each group are relatively small. Furthermore, the sample sizes were unequal in the three dose groups. The 0.9 mg/kg group included 51 patients while there were 21 patients in the 0.6-0.7 mg/kg group. This led to wide confidence intervals in determining the difference in favorable clinical outcome and the risks of symptomatic intracerebral hemorrhage. There is a significant likelihood of type 2 error. Of interest, the clinical outcome in the 0.6-0.7 mg/kg group was comparable with J-ACT.11 We recognize that the selection of doses used in our study was arbitrary and reflected the lack of clinical consensus in China, together with cost factors. Although statistical adjustments were performed to minimize the impact of baseline confounding factors, the significance of the results remained uncertain.

Stroke is a massive health problem in China and there is increasing use of thrombolytic therapy. Given the possibility that efficacy is optimized using the standard Western dose of 0.9 mg/kg tPA, a randomized dose-comparison study is an important research priority, to establish the optimal tPA dose in Chinese stroke patients.

Acknowledgments

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Single-center experience with TruFill platinum coils for the embolization of cerebral aneurysms

Abstract Endovascular coiling has become a powerful alternative to neurosurgical clipping of cerebral aneurysms. Apart from the Guglielmi Detachable Coil (GDC) (Boston Scientific, Galway, Ireland), there is limited published data about the newer generation of detachable platinum coils, e.g., TruFill (Cordis, Johnson and Johnson, Miami, Fl.). We report our initial clinical experience with the embolization of aneurysms by TruFill coils. Included in this retrospective study were 26 patients (age 55.4 ± 14.5 years; 9 male, 17 female) with 28 aneurysms, 21 ruptured and 7 unruptured. All patients were treated exclusively by embolization with TruFill platinum coils. Immediate angiographic and 6-month angiographic follow-up results were documented. Acute clinical outcome was recorded. Of the 28 aneurysms, 16 (57%) were completely occluded by TruFill embolization, 11 (39%) were incompletely occluded with residual necks, and 1 (4%) was partially occluded as residual aneurysm. There were no aneurysmal ruptures during the procedures. Follow-up at 6 months after the procedure was available in 18 patients and 19 aneurysms. Of the 19 aneurysms, 2 of 12 initially completely occluded aneurysms (17%) and 1 of 7 aneurysms with initial residual necks (14%) showed recanalization at the 6-month follow-up. One recanalized aneurysm was subsequently recoiled with consequent residual neck and remained unchanged at the 1-year follow-up. Embolization by TruFill platinum coils has a comparable total aneurysmal occlusion rate to that with GDC. The mid-term reintervention rate is low, and will require verification by future long-term studies.

Keywords Aneurysm • Coiling • GDC • TruFill • Subarachnoid • Embolization

Introduction

Guglielmi Detachable Coil (GDC) for endovascular embolization of cerebral aneurysms has been investigated extensively since its development [1] and is now accepted as the gold standard for aneurysm coiling. However, it is not a panacea for all aneurysms of different shapes and sizes [2]. Furthermore, inadequate “packing” of the aneurysmal sac is associated with aneurysm recanalization [3]. It has been demonstrated that additional techniques such as stenting of the parent artery and balloon remodeling are required in difficult cases, especially in aneurysms with wide necks [4]. The disadvantage of deploying stents and balloons is that it entails a higher risk of periprocedural complications and requires prolonged administration of antiplatelet agents [5]. Therefore, coils of different mechanical characteristics to that of GDC have been developed in an attempt to circumvent the need for stents and balloons in technically challenging cases, and to achieve dense packing without free spaces in the aneurysmal sac.

The TruFill platinum coil has recently received FDA approval for use in cerebral aneurysm embolization. In
contrast to GDC which uses an electrolytic mechanism for coil detachment, TruFill employs a hydraulic coil detachment system [6]. More importantly, the TruFill coil is softer. In addition, based on our own experience, the TruFill 3-D versions (complex shaped coils) have less circular memory and may be more conformable to the inner lumen of complex aneurysms and to the gaps within the coil package than GDC.

In view of the possible morphological advantages of the TruFill coil, we have decided to embolize exclusively with TruFill in aneurysm cases where stent-assisted or balloon remodeling techniques are not indicated. We have performed a retrospective analysis of all patients at our institute who received treatment by TruFill embolization. We report our experience with the use of the coil and, in particular, on the immediate and follow-up angiographic results.

Methods

From May 2002 to November 2003, 26 patients (9 male, 17 female; mean age 55.4 years) with 28 aneurysms were treated exclusively by endovascular embolization with TruFill platinum coils at the Institute of Neuroradiology, Johann Wolfgang Goethe University Hospital, Frankfurt am Main, Germany. All patients in the study presented to our institute with either ruptured (n=21) or unruptured (n=7) cerebral aneurysms.

The 26 patients underwent diagnostic cerebral angiography and three-dimensional rotational angiography (3DRA) whereby the location, size and shape of the aneurysms were evaluated by an expert panel of interventional neuroradiologists (J.B., R.D.) and a vascular neurosurgeon (A.R.). The decision regarding treatment by endovascular coiling was reached by consensus.

We placed a 5 F sheath in the femoral artery of the patient. A guide catheter (Envoy, Cordis, Johnson and Johnson, Miami, Fl.) was placed in the high cervical or petrous internal carotid artery or the proximal V2 segment of the vertebral artery (proximal to C1-C2 loop). Bolus intravenous (IV) heparin was administered with the dosage guided by regular activated clotting time (ACT) measurements (ACT >240 s). The “working projection” with the best view of the aneurysm and anatomical relationship to its parent vessels was chosen after repeat diagnostic angiogram and 3DRA. A microcatheter (Tracker SL10, Boston Scientific, Natick, Mass., or Prowler 14, Cordis, Johnson and Johnson) was passed coaxially through the guide catheter and placed in the inner lumen of the aneurysm under Roadmap guidance. TruFill platinum coils were introduced into the aneurysmal sac via the microcatheter. The endpoint for additional coil placement was reached when either the aneurysm had been densely packed or no further coils could be safely deployed. Repeat angiograms were performed in both the “working projection” and the standard views (anterior–posterior and lateral) to assess the degree of aneurysmal exclusion from the parent vessels and to check for possible complications such as thromboembolism.

The grading of aneurysm packing followed the system described by Raymond and Roy [2]. “Complete occlusion” was defined as complete obliteration of the aneurysmal sac including the neck region. “Residual neck” was defined as the persistence of any portion of the original defect of the arterial wall as seen on any single projection but without opacification of the aneurysmal sac. “Residual aneurysm” was defined as any opacification of the aneurysmal sac [2].

All patients received IV heparin for 48 h (target PTT 1.5 to 2 times normal). Patients with wide-neck aneurysms (neck width >3 mm; n=17) or with coil loops protruding into the parent vessel (n=1) were placed on aspirin 100 mg for 3 months. Repeat angiography was performed at a 6-month follow-up. Acute clinical outcome (within 30 days of endovascular coiling) was documented.

Results

Of 28 aneurysms, 17 (61%) were located in the anterior circulation and 11 (39%) in the posterior circulation. The most frequent location in the anterior circulation was the
anterior communicating artery (21%), and in the posterior circulation the basilar artery (29%).

The mean size of all aneurysms was 8.1±3.8 mm. The width of all aneurysmal necks had a mean of 4.7±2.1 mm with a consequent mean dome-to-neck ratio of 1.7±0.4. Subgroup analysis showed that anterior communicating artery aneurysms had a mean size of 8.5±3.6 mm with a mean dome-to-neck ratio of 1.54±0.1, while aneurysms located in the basilar artery had a mean size of 10.0±4.9 mm and mean dome-to-neck ratio of 1.7±0.3 (Table 1). Aneurysms were also subdivided into three groups: small aneurysms (<11 mm) with small necks (<3 mm), small aneurysms with wide necks (>3 mm), and large aneurysms (11 to 25 mm) (Table 2).

Immediate angiographic studies following aneurysm embolization showed that 16 out of 28 aneurysms (57%) were completely occluded (Fig. 1), 11 aneurysms (39%) were incompletely occluded with residual necks, and 1 aneurysm (4%) was partially occluded and defined as residual aneurysm. Of the aneurysms located in the anterior communicating artery (n=6), three were completely occluded, two had residual necks and one was a residual aneurysm. Of the basilar artery aneurysms (n=8), six were completely occluded and two had residual necks.

Of note, there were no aneurysmal ruptures during the embolization procedure. There were two deaths (8%) from delayed recurrent subarachnoid hemorrhage in patients with incompletely coiled large aneurysms. One aneurysm was 15 mm with a 10-mm neck (residual aneurysm) and the other was 10 mm with a 7-mm neck (residual neck). Patients with aneurysms less than 10 mm showed no procedure-related morbidity or mortality. There were two incidents of coils being stretched. Both cases occurred during deployment of the last and the second to last coil, respectively, prior to completion of the two procedures. Both “stretched” coils were retrieved by the gooseneck snare device without further events—neither thromboembolic complications nor inadvertent coil package removal.

Six-month angiographic follow-up was available in 18 patients with 19 aneurysms. Eight patients were lost to follow-up. Six patients refused follow-up cerebral angiography and two patients died. Of all the aneurysms (n=19) available for follow-up, 16 remained unchanged (84%). Of 12 aneurysms which were completely occluded following initial embolization, 10 (83%) remained unchanged at the 6-month follow-up. Of 7 aneurysms which had initial residual neck, 6 (86%) remained unchanged at follow-up. Of 12 completely occluded aneurysms and 7 aneurysms with residual necks, 2 (17%) and 1 (14%), respectively, showed recanalization at the 6-month follow-up (Figs. 2 and 3).

Our longest follow-up was in a patient with a recanalized aneurysm (residual aneurysm) which was subsequently recoiled with consequent residual neck and remained unchanged at the 1-year follow-up.

Discussion

As far as we are aware, our study is the first to be reported on the immediate and mid-term angiographic results of
Six-month angiographic follow up post coiling

![Graph showing angiographic follow-up post coiling](image)

**Fig. 3** Six-month angiographic follow-up after coiling

aneurysms treated exclusively by embolization with the TruFill platinum coil to be reported. Our results showed that the rates of immediate aneurysm occlusion (57%) and of mid-term recanalization (16%) were comparable to that of embolization by GDC. GDC series have shown aneurysm occlusion rates of 55% to 79% [7, 8] and recanalization rates of 14% to 33% [9–11].

In our series, we did not experience intraoperative thromboembolic events or aneurysmal ruptures. This was mildly surprising given that rates of thromboembolic complications range from 1% to 31% in published case series [7, 8, 12]. Furthermore, aneurysm perforation occurs at a rate of 3% with embolization by GDC [7]. This result could be explained by the relatively small number in our series or by the inherent mechanical advantages of the TruFill coil. In our experience the TruFill coil is softer than GDC, and some authors have suggested that the risk of intraoperative aneurysmal rupture is proportional to the stiffness of the coil [13]. However, a larger study is required to address this question more fully.

The 30-day mortality rate was 8% in our patients. The larger series with GDC have shown similar short-term mortality rates ranging from 4% to 8% [7, 14]. In our series, recurrent subarachnoid hemorrhage was the cause of death in both patients. It is important to note that recurrent hemorrhage occurred in the postoperative period and that both patients had suboptimally packed large aneurysms with wide necks. Incomplete occlusion has been reported as an important contributory factor for recurrent subarachnoid hemorrhage [10].

From a technical point of view, we have found that the detachment of TruFill coils driven by a hydraulic device is reliable and faster than the GDC electrolytic detachment system. The possible advantage of speedier detachment is that in emergency situations where intraoperative complications require fast packing, time is of the essence. On the other hand, we have also observed that the TruFill coil is possibly more prone to being “stretched”. We have noted two cases of “stretched coils” in two of our patients whereby the coils were not excessively manipulated. After these experiences, we believe that the repositioning of the microcatheter over the coil immediately before retrieval is a risk factor for coil stretching. Fortunately, both “stretched coils” were retrieved by the gooseneck snare device.

Apart from the small number of patients, another weakness in our study is the exclusion of patients in whom additional techniques such as balloon remodeling and stent-assisted coiling were considered necessary. This would have created a selection bias whereby the true occlusion rate of the TruFill coil could not be tested. Another limitation of our study was the relatively short 6-month follow-up. It has gradually become clear that a percentage of aneurysms, whether surgically clipped or coiled, undergo recanalization. The rate of recanalization with GDC has been reported in one long-term study to be 14% [11]. The time course of recanalization is poorly understood, and to characterize more definitively the specific recanalization of aneurysms coiled by TruFill would require a future study with a longer follow-up.

The pathophysiological basis for recanalization is complex. A recent study by Tamatani et al. [3] correlated the recurrence of aneurysms and the packing “volume” of coils within the aneurysmal sac. The study showed significant correlation between embolized volume and the stability of embolized aneurysm [3]. This added strength to the currently held view that loosely packed aneurysms are associated with a higher risk of recanalization. Clearly, the strategy is to increase the density of the coil package within the aneurysmal sac. An experimental in vitro study of coiling by Piotin et al. [15] compared the density of coil packing of helical coils and complex shaped coils (TruFill, Cordis). The study concluded that complex shaped coils achieve a significantly increased density of coil packing as compared to helical coils. This is in agreement with our own experience that TruFill coils are more conformable and, in certain aneurysmal anatomies, may be able to achieve denser packing than GDC.

In conclusion, in comparison with GDC, embolization by TruFill platinum coils gives a comparable total aneurysmal occlusion rate of 57%. The mid-term recanalization rate in our series was 17% in initially completely occluded aneurysms and 14% in aneurysms with initial residual necks. We believe that TruFill coils constitute a viable alternative to GDC. However, the long-term recanalization rate is unclear and requires further study.
References

Section 6 Additional papers contributing to the knowledge of cerebrovascular diseases

I am presenting 114 peer reviewed papers which may cover areas beyond what is comprised in the first 5 sections. For these papers I was not senior author and the collaborators and topics covered range widely. The important aspects are exploration of factors affecting stroke other than those conventionally regarded as major. Studies of other diseases such as demyelination, non-organic seizures, tremors, special engineering advances leading developments of devices such as catheters to be employed in the specialty of stroke.

List of publications


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