Clinical and Imaging Correlates of Outcome after Intracerebral Haemorrhage

By

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Dedication

For my late father Dr Shun-Liang Wu, and mother Hsiu-Hua Wu.

For the unconditional love and support from my wife Sharon,
children Theo, Thomas and Zach.
Abstract

Intracerebral haemorrhage (ICH) results from rupture of an intracranial blood vessel and contributes to 10-15% of all strokes. Despite being a relatively uncommon presentation of stroke it contributes to 50% mortality and two thirds of the disability adjusted life years lost caused by stroke worldwide and there is currently no effective acute intervention. Brain injury after ICH results from mechanical disruption of the brain substance leading to ischaemic injury and increased intracranial pressure. Intervention trials focused on limiting impact of primary injury have been negative. Secondary brain injury can also ensue from peri-haematoma oedema and toxic by-products of haematoma degradation and inflammation. Although the mechanisms contributing to this secondary process remain poorly understood, strategies to limit impact of secondary injury may provide additional management targets in ICH.

This thesis examines the different clinical and imaging factors associated with ICH outcome. Patient data were predominately derived from the Helsinki Intracerebral Haemorrhage Study containing comprehensive clinical, laboratory and mortality data for 1013 patients. The Helsinki data was also pooled with the Virtual International Stroke Trials Archive – Intracerebral Haemorrhage (VISTA-ICH) and Royal Melbourne Hospital intracerebral haemorrhage registry for analysis, while imaging data from the Salford Royal Hospital intracerebral haemorrhage registry was used in a validation study. All analyses were planned a priori and performed by the writer of the thesis. All multivariable logistic regression analyses were adjusted for known predictors of outcome, including patient age, baseline National Institutes of Health Stroke Scale, Glasgow Coma Scale score, male sex, previous warfarin use, baseline ICH volume, ventricular extension and infratentorial location.

The methodological study examined the best practice method for deriving haematoma and oedema volumes following planimetric segmentation, given the volume dependent effect of haemorrhage on outcome. The analysis found volume reported by software outputs underestimated true volume by up to 41% in images with variable slice thickness due to an inherent technical error that assumes a uniform slice
thickness for the entire series. An in-house plugin to perform this correction for the software Osirix was made available for public download with the published results.

This study highlights the critical impact the method of volume calculation can have on results, which may impact heavily on outcome analysis of clinical studies.

The first clinical study examined the aetiology and outcome of 85 (5.9%) patients with simultaneous multiple ICHs (SMICH) in the pooled cohort (n=1452) of patients from Helsinki and Melbourne ICH studies. These patients had less hypertensive aetiology (20% vs 37%, p=0.001) and more systemic coagulopathy (12% vs 3%, p<0.001) when compared to patients with single intracerebral haemorrhage. Although simultaneous intracerebral haemorrhages occurred ~1 in 20 patients, its presence was not associated with increased mortality on univariate (p=0.610) or multivariable (OR 0.760 95% CI 0.401-1.529, p=0.473) analyses. These findings suggest that management of SMICH should follow the routine management practice of ICH patients in general.

The second clinical study assessed the impact of pre-stroke use of metformin and sulphonylurea on outcome of diabetic ICH patients. The study was driven by the observation that oral antidiabetic medication use was associated with improved outcome in ischaemic stroke. The patients (n=374) were pooled from Helsinki and Royal Melbourne ICH studies and VISTA-ICH. In the multivariable analysis pre-stroke metformin use was associated with reduced 90-day mortality (OR 0.50 95% CI 0.25-0.99, p=0.047) while no association was noted with sulphonylurea (OR 0.96 95% CI 0.49-1.88, p=0.906). There was no association between use of antidiabetic medications and oedema at baseline or at 72 hours.

The natural history of peri-haematoma oedema was studied in the third clinical study using data from 861 patients from the Helsinki ICH Study. Only non-operative supratentorial ICH patients were included. Average oedema growth rate was calculated for each scan to derive an oedema growth trajectory for the whole cohort. The oedema growth trajectory demonstrates 60% of the expected oedema growth in the first 3 weeks was reached within the first 24 hours, followed by a slower subacute stage of growth. Oedema volume at 72 hours was associated with increased 6-month
mortality (OR 1.60 95% CI 1.04 – 2.46, p=0.032) in the multivariable analysis. Larger baseline haematoma volume and higher baseline glucose were associated with increased oedema growth. This study highlights the emerging importance of peri-haematomal oedema as a prognostic indicator and potential target for management.

The final study in this thesis examined the relationship between persistent hyperglycemia with mortality and oedema growth. Patients were included if they had documented glucose measurements within 0-24 hours and 24-72 hours, and considered persistently hyperglycemic if glucose remained ≥8mMol/L in both epochs. Baseline hyperglycaemia was noted in 318/576 (55%) patients, and 53% (167) remained persistently hyperglycaemic. In the multivariable analysis, persistent (OR 3.68 95% CI 1.99-6.79, p<0.001) but not transient (OR 1.29 95% CI 0.66-2.54, p=0.50) hyperglycaemia, was associated with 6-month mortality. However persistent hyperglycaemia was not associated with 72-hour oedema (p=0.493). Previous studies associating hyperglycaemia and outcome have reported association based on single glucose measurement. The results of this study highlight the prognostic impact only remained if the hyperglycaemia is persistent. A clinical trial investigating impact of glycaemic control after intracerebral haemorrhage is needed.

This thesis has outlined several clinical and imaging prognostic indicators of outcome in ICH. The evolving factors of brain injury after ICH are complex, dynamic and remain incompletely understood. Further research into modifiable factors influencing oedema and patient outcome will generate hypotheses for translational targets. The future approach to ICH management is likely to require a multi-prong approach targeting both primary and secondary injury.
Declaration

This is to certify that

i) This Thesis comprises only my original work except where indicated in the preface

ii) Due acknowledgement has been made in the preface and text to all other material used

iii) This Thesis is less than 100,000 words, exclusive of tables, bibliographies, appendices and footnotes.

Dr Teddy Wu

August 2017
Acknowledgements

The studies presented were conceived and conducted by myself under the supervision and mentoring of A/Prof Atte Meretoja. My other supervisors Prof Stephen Davis, Prof Patricia Desmond and A/Prof Bruce Campbell also contributed significantly to my PhD supervision. I like to thank all the supervisors for their generous and valuable time and direction throughout the PhD. It was a privilege to be part of such a productive and world-class research infrastructure.

I like to thank the collaborators from Helsinki University Hospital for collecting the data for the Helsinki Intracerebral Haemorrhage Study. It was a privilege to be granted access to this valuable dataset. I like to thank in addition to A/Prof Meretoja for access to the database, the other senior collaborators Professor Turgut Tatlisumak, A/Prof Jukka Putaala and A/Prof Daniel Strbian for their contribution and invaluable comments on the manuscripts and revisions.

A special thanks to A/Prof Atte Meretoja for his continual support and supervision of my PhD even after he had returned to Finland to assume a busy executive role. I am grateful for the extra hours he spent with me reviewing study hypotheses and analysis plans and the countless hours going over my manuscripts and input during the revision process. I have learned a lot from Atte’s work ethics and approach to scientific research which have provided me with a solid foundation for my future research aspirations.

I like to thank the generous financial support provided to my by the Neurological Foundation of New Zealand in my first two years of PhD and also the Royal Melbourne Hospital Neuroscience Foundation for funding support throughout.

Without your support my PhD studies and conference attendances would not have been possible.

The Royal Melbourne Hospital stroke data was derived from the prospectively stroke database collected by Ms Louise Weir, Stroke Nurse Practitioner. I thank her for the endless hours she has spent on ensuring the data is up to date and accurate.

I also like to thank collaborators from the School of Medical Sciences, University of Manchester lead by Dr Adrian Parry-Jones for contributing data to the study performed in Chapter III. I am grateful also to Dr Seun Sobowale and Dr Robert
Hurford for their efforts in learning planimetric segmentation together and in putting a revision together for a paper at short notice on top of their busy clinical duties.

I also received generous technical support throughout the PhD from the Imaging Laboratory headed by Mr Gagan Sharma. Gagan has been instrumental in providing technical assistance in scripting and sorting of the innumerable images used for the entire PhD. I also like to thank Dr Søren Christensen from Stanford University for his technical assistance in creating the software plugin that will help others derive accurate volume output. I like also to thank Dr Nawaf Yassi and Associate Professor Bernard Yan from the Royal Melbourne Hospital and Dr Minmin Ma from Jinling Hospital, Nanjing, China for their input into the paper presented in Chapter IV.

I like to especially acknowledge the friendship and collegial support from Dr Yassi. I have learnt a lot from your own approach to completing your PhD studies and from observing your clinical skills at code strokes. The training runs for the Melbourne half marathon (2016) also provided me with required time out to recharge my batteries, even though you were the eventual winner by 2 seconds.

Last but not the least of all, I want to thank my family for their unconditional love. To my sons, Theo, Thomas and Zach, your smiles provided invaluable energy and motivation throughout this journey. You remind me of the small things that matter in life and keep my feet grounded. To my wife Sharon, your insurmountable love and support to me for more than a decade, especially the last three years, have been inspirational. You have supported me through my entire medical career, nursed me through the troughs and rejoiced in my success. Thank you for inspiring me to be the person that I am today and I look forward to many years of love and quality time together.
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Preface

The work presented in this thesis was performed in the Department of Medicine, the University of Melbourne in association with the Department of Neurology and Radiology, The Royal Melbourne Hospital. This work was carried out under the supervision of Associate Professor Atte Meretoja, from Department of Medicine, the University of Melbourne, and Department of Neurology, Helsinki University Hospital, Helsinki, Finland. This work was also co-supervised by Professor Stephen Davis, Associate Professor Bruce Campbell both from Department of Medicine, University of Melbourne and Department of Neurology, the Royal Melbourne Hospital, and also by Professor Patricia Desmond, Department of Radiology, the Royal Melbourne Hospital.

This thesis has five main results chapters, all of which have been submitted to peer reviewed international journals with 5 published papers. The papers have been listed below as publications and conferences proceedings where abstracts were presented.

I was responsible for the study conception, design, statistical analysis, manuscript drafting, communication between co-authors, submission preparation and revision of all the papers presented in this thesis, under supervision of Associate Professor Atte Meretoja. I collected imaging data for the Helsinki ICH study by performing planimetric segmentation of oedema, haematoma and ventricular haemorrhage on all available CT scans (>2000) from the dataset. I also contributed additionally to the Royal Melbourne Hospital dataset by updating clinical information and outcome data.

All the other authors listed in the papers also contributed to the intellectual content and revision of papers. The following passages list and describe the contribution of
authors to the chapters.

Associate Professor Atte Meretoja:

- Involved in overall supervision of all the projects, provided intellectual input into study conception, study design, statistical analysis and manuscript preparation.
- Participated in the design, data collection and publication of the Helsinki Intracerebral Haemorrhage Study.

Professor Stephen Davis:

- Provided intellectual input into study design, result analysis and manuscript preparation for all studies

Professor Patricia Desmond:

- Provided intellectual input into study results and manuscript preparation for studies presented in Chapters III, IV and VI

Associate Professor Bruce Campbell

- Provided intellectual input into study design, result analysis and manuscript preparation for studies presented in Chapters III, IV and V.

Dr Nawaf Yassi:

- Acted as the second rater for selection of patients into study presented in Chapter IV.
- Provided intellectual input into study design, result analysis and manuscript preparation for studies presented in Chapters III, IV and V

Professor Turgut Tatlisumak:

- Provided intellectual input into study result and manuscript preparation for studies presented in Chapters III, IV, V, VI and VII
- Participated in the design, data collection and publication of the Helsinki Intracerebral Haemorrhage Study.

Associate Professor Daniel Strbian:

- Provided intellectual input into study result and manuscript preparation for studies presented in Chapters IV, V, VI and VII
- Participated in the design, data collection and publication of the Helsinki Intracerebral Haemorrhage Study.

Associate Professor Jukka Putaala:
• Provided intellectual input into study result and manuscript preparation for studies presented in Chapters IV, V, VI and VII
• Participated in the design, data collection and publication of the Helsinki Intracerebral Haemorrhage Study.

Mr Gagan Sharma:
• Provided technical assistance in obtaining planimetric volumes after segmentation and the creation of the software plugin for Osirix.
• Provided intellectual input into study result and manuscript preparation for studies presented in Chapters III, IV, VI and VII

Dr Søren Christensen:
• Assisted in creation of software plugin for Osirix
• Provided intellectual input into study result and manuscript preparation in Chapter III.

Dr Adrian Parry-Jones:
• Provided intellectual input into study conception, design, analysis and manuscript preparation in Chapter III.

Dr Oluwaseun Sobowale:
• One of the raters involved in planimetric segmentation in the study presented Chapter III. Also provided intellectual input into study design, study results, manuscript preparation in Chapter III.

Dr Robert Hurford:
• One of the raters involved in planimetric segmentation in the study presented Chapter III. Also provided intellectual input into study design, study results, manuscript preparation in Chapter III.

Dr Minmin Ma:
• Assisted in data collection, provided intellectual input into study results and manuscript preparation in Chapter V.

Dr Dharshan Shah:
• Assisted in data collection, provided intellectual input into study results and manuscript preparation in Chapter V.

Associate Professor Bernard Yan:
• Assisted in data collection, provided intellectual input into study results and manuscript preparation in Chapter V.

Publications arising from this Thesis


Other collaborative publications


Peer-reviewed abstracts


## List of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>APO</td>
<td>Apolipoprotein</td>
</tr>
<tr>
<td>ATACH</td>
<td>Antihypertensive Treatment of Acute Cerebral Hemorrhage</td>
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<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
</tr>
<tr>
<td>AVF</td>
<td>Arterio-venous Fistula</td>
</tr>
<tr>
<td>AVM</td>
<td>Arterio-venous Malformation</td>
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<tr>
<td>CAPRIE</td>
<td>Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events</td>
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<tr>
<td>CCM</td>
<td>Cerebral Cavernous Malformation</td>
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<tr>
<td>CLEAR</td>
<td>Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage</td>
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<tr>
<td>CTA</td>
<td>Computed Tomography Angiography</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DHC</td>
<td>Decompressive Hemicranieotomy</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
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<tr>
<td>DSA</td>
<td>Digital Subtraction Angiography</td>
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<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
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<tr>
<td>EVD</td>
<td>External Ventricular Drain</td>
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<tr>
<td>GAMES-RP</td>
<td>Glyburide Advantage in Malignant Edema and Stroke</td>
</tr>
<tr>
<td>GBD</td>
<td>Global Burden of Diseases Study</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>GIST-UK</td>
<td>United Kingdom Glucose Insulin in Stroke Trial</td>
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<tr>
<td>GRE</td>
<td>Gradient Recalled Echo</td>
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<tr>
<td>GUSTO</td>
<td>Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries</td>
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<tr>
<td>HI-DEF</td>
<td>High-Dose Deferoxamine in Intracerebral Hemorrhage</td>
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<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
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<tr>
<td>HU</td>
<td>Hounsfield Unit</td>
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ICH - Intracerebral Haemorrhage
ICH-ADAPT - Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial
IHD - Ischaemic Heart Disease
INR - International Normalised Ratio
INTERACT - The Intensive Blood Pressure Reduction In Acute Intracerebral Haemorrhage Trial
IVH - Intraventricular Haemorrhage
LDL - Low Density Lipoprotein
MISTIE - Minimally Invasive Surgery plus Recombinant Tissue-type Plasminogen Activator
MRA - Magnetic Resonance Angiography
MRI - Magnetic Resonance Imaging
mRS - Modified Rankin Scale
NF-κB - Nuclear Factor Kappa-light-chain-enhancer of Activated B cells
NIHSS - National Institutes of Health Stroke Scale
NIfTI - Neuroimaging Informatics Technology Initiative
DOAC - Direct Oral Anticoagulant
OR - Odds Ratio
PATCH - Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated with Antiplatelet Therapy
PREDICT - Prediction of Haematoma Growth and Outcome in Patients with Intracerebral Haemorrhage Using the CT-Angiography Spot Sign
QASC - Quality in Acute Stroke Care
ROI - Region Of Interest
SD - Standard Deviation
SAH - Subarachnoid Haemorrhage
SMICH - Simultaneous Intracerebral Haemorrhages
SPARCL - Stroke Prevention by Aggressive Reduction in Cholesterol Levels
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>STICH</td>
<td>International Surgical Trial in Intracerebral Haemorrhage</td>
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Chapter I: Literature review

1.1 Introduction:
Intracerebral haemorrhage (ICH) contributes to 10 to 15% of strokes (Qureshi et al., 2001). In Australia and Finland, the proportional contribution is ~11% and 14% respectively (Meretoja et al., 2010; Leyden et al., 2013). Globally in 2015, ICH was responsible for 3.3 million deaths (6% of any cause) and 73 million (3% of any cause) disability adjusted life years lost (Kassebaum et al., 2016; Wang et al., 2016b). Despite advancement in treatment for acute ischaemic stroke, (Goyal et al., 2016) there remains no effective treatment for ICH (Steiner et al., 2014; Hemphill et al., 2015).

This literature review aims to provide a global overview of intracerebral haemorrhage and will first discuss the definition of stroke from intracerebral haemorrhage, its epidemiology and impact on global health. This is followed by expanded discussion on risk factors, pathophysiology, evolution of injurious processes and prognostic indicators. Finally a broad discussion on management strategies in ICH will conclude this chapter followed by general aims of this dissertation.
1.2 Definition of stroke and intracerebral haemorrhage

Stroke is defined by the World Health Organization as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” (Aho et al., 1980). The definition was originally developed in 1970 (WHO, 1971) and the duration of symptoms for clinical determination of stroke was somewhat arbitrary. Subarachnoid haemorrhage was considered under umbrella definition of stroke and could cause ‘“Global” disturbances of cerebral function,, without focal neurological deficits’ (Aho et al., 1980).

A later definition published in 1989 defined stroke as “an acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain” again with transient ischaemic attack being defined by symptoms lasting less than 24 hours in duration (Goldstein et al., 1989). In this definition subarachnoid haemorrhage was excluded from definition of stroke if there was no damage to the brain and the authors specifically defined intracerebral haemorrhage as being “spontaneous…due to the rupture of an abnormal artery (aneurysm or AVM) or arteriole in the brain parenchyma.” (Goldstein et al., 1989). The authors suggested several clinical features such as headache with nausea at onset, persistent disturbance of consciousness and combined global motor-sensory involvement with altered consciousness as more likely to result from ICH than infarction.

This definition was proposed prior to widespread using of neuroimaging for diagnostic evaluation of stroke. It is now well known that in patients with cerebral ischaemia that permanent infarction can occur with clinical duration lasting less than 24 hours (Oppenheim et al., 2006). Likewise patients with ICH may not necessary present with focal neurological symptoms with headache being the only recognised symptoms in up to about 20% of all ICH presentations (Kleindorfer et al., 2007). It is not possible to clinically distinguish between ischaemic stroke and ICH and ante-mortem diagnosis of ICH requires diagnostic neuroimaging.
In 2013 the American Heart Association / American Stroke Association proposed an updated definition of stroke. Ischaemic stroke was defined as an “episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction” with infarction requiring objective evidence of cell death from “pathological, imaging… objective evidence of... focal ischemic injury in a defined vascular distribution” or “clinical evidence of cerebral… ischemic injury based on symptoms persisting ≥24 hours” (Sacco et al., 2013). This updated definition introduced a tissue-based definition for defining ischaemic stroke even if symptoms were less than 24 hours in duration, which would have been classified as transient ischaemic attack based on prior definitions.

For ICH, the updated stroke definition noted “Hemorrhages in the CNS should be classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages should not be characterized as stroke.” (Sacco et al., 2013). In this definition, stroke caused by ICH is “Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma”. This definition requires imaging identification of haemorrhage within the brain parenchymal or ventricular system. Although the definition excludes traumatic intraparenchymal haemorrhage, clinically it may be difficult to distinguish as there may be lack of superficial signs of injury or history. Conversely in a patient with a fall and ICH, it may be difficult to distinguish as to whether the stroke caused the fall or the fall resulted in traumatic haemorrhage. Coup contrecoup pattern of ICH or multiple haemorrhages on imaging may provide diagnostic clues to trauma being the cause (Sacco et al., 2013).

Subdural and extradural haematomas, which are often result of trauma are excluded from definition of stroke from ICH. Although subarachnoid haemorrhage was classified as a subtype of stroke it caused “Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma”, in Australia and New Zealand subarachnoid haemorrhage is commonly managed by neurosurgeons rather than stroke
neurologists/physicians. For the purpose of this thesis only stroke resulting from parenchymal haemorrhage or intraventricular haemorrhage is considered under the term “ICH”.

1.3 Classification of intracerebral haemorrhage

Stroke from ICH is often referred to as ‘spontaneous’. The term ‘spontaneous’ is slightly misleading as it suggests a lack of underlying cause. There are a number of causes for non-traumatic ICH, with different clinical risk factors, imaging and pathological findings, management strategies and prognosis (Qureshi et al., 2001; Al-Shahi Salman et al., 2009). Previous epidemiological studies have different selection criteria for stroke due to ICH. Some studies considered ICH secondary to vascular malformation (cavernoma and arterio-venous malformation) as ‘secondary’ ICH, (Fogelholm et al., 1992; Inagawa et al., 2003; Labovitz et al., 2005; Bejot et al., 2013) and were excluded from analysis, while others included all types of non-traumatic, non-tumour related ICH (Anderson et al., 1994; Thrift et al., 2001; Kubo et al., 2003; Zhang et al., 2003; Lavados et al., 2005; Lovelock et al., 2007; Gattellari et al., 2014).

Despite differences in the selection of ICH patients by cause in epidemiology studies, understanding ICH pathogenesis is important to guide subsequent investigation, patient prognostication and clinical management. Pathologies such as cerebral amyloid angiopathy and hypertensive angiopathy require brain tissue for definitive diagnosis (Fisher 1971; Knudsen et al., 2001) but surgery with biopsy is not routinely performed, particularly in haemorrhages located in the deep part of the brain. The haemorrhage location, however, can suggest underlying pathogenesis, which is one common approach to ICH classification.

1.3.1 Anatomical classification

In general, haematoma location can be classified into lobar or non-lobar (deep or infratentorial) (Samarasekera et al., 2015; Rannikmae et al., 2016; Charidimou et al., 2017b). The premise for this simplified classification is that hypertensive angiopathy causes deep haemorrhages while cerebral amyloid angiopathy results in lobar haemorrhages. A number of different approaches comprising of different anatomical categories have been reported (Rannikmae et al., 2016; Charidimou et al., 2017b). In
general, the lobar haemorrhages have been grouped into a general ‘lobar’ category while some authors have further classified deep structures into distinct categories of ‘deep’ haemorrhages (Charidimou et al., 2017b). A recently proposed CHARTS anatomical classification system divides the lobar category into 5 distinct categories based on the location of haemorrhage epicenter (frontal, parietal, temporal, occipital and insula) (Charidimou et al., 2017b).

However, the main limitation of the anatomical classification is that it may over-simplify the presumptive cause of ICH. For example, lobar haemorrhage suggests underlying cerebral amyloid angiopathy and deep haemorrhages hypertensive angiopathy. The main limitation with this is that not all deep haemorrhages are the result of hypertensive angiopathy and likewise not all lobar haemorrhages result from cerebral amyloid angiopathy as these conditions can often co-exist (Charidimou et al., 2012).

1.3.2 Classification by pathogenesis

A recently proposed ICH classification system, the SMASH-U system, (Meretoja et al., 2012) systematically classifies ICH into 6 different pathologies and the following passages outline the pathogenesis classified by the SMASH-U system.

1.3.2a Cerebral amyloid angiopathy

Cerebral amyloid angiopathy is characterised by deposition of amyloid protein within the small to medium arteries of the brain, cortical veins and leptomeninges (Vinters and Gilbert 1983). ICH related to cerebral amyloid angiopathy typically occurs in elderly patients presenting with ICH located in the lobar region. Other associated findings are cortical microhaemorrhages and convexal subarachnoid haemorrhage (SAH) (Greenberg et al., 1993; Linn et al., 2010). Lobar ICH is typically associated with clinical stroke symptoms while microhaemorrhages and convexal SAH can be asymptomatic or present with transient neurological symptoms due to focal epileptic seizures that can mimic transient ischaemic attack. Definite diagnosis of cerebral amyloid angiopathy requires neuropathological evidence of vascular amyloid deposition (Knudsen et al., 2001). In patients over 55 years of age with either multiple or single lobar, cortical, or corticosubcortical ICH, and absence of another ICH cause, ‘probable’ and ‘possible’ cerebral amyloid angiopathy can be diagnosed based on the Boston Criteria (Knudsen et al., 2001).
The incidence of cerebral amyloid angiopathy in ICH studies varies across different ethnicities. In general, studies involving predominately European patients utilising the Boston Criteria classified cerebral amyloid angiopathy in approximately one third of all ICH patients (Jamieson et al., 2012; Meretoja et al., 2012; Palm et al., 2013; Marti-Fabregas et al., 2014). In a Taiwanese study of nearly 4000 patients, cerebral amyloid angiopathy accounted for only 12% of the ICH population (Yeh et al., 2014). In other studies where ICH aetiology was not classified, Asian (Inagawa et al., 2003; Wang et al., 2015a) patients had lower proportion (15-21%) of lobar ICH when compared with European populations (Nilsson et al., 2002; Tetri et al., 2009; Samarasekera et al., 2015) (25-52%), suggesting lower incidence of cerebral amyloid angiopathy in Asian patients. Reported rates of cerebral amyloid angiopathy are significantly lower in studies that required pathological confirmation for diagnosis (Yen et al., 2005; Petridis et al., 2008).

1.3.2b Hypertensive angiopathy
Hypertension-related ICH is postulated to result from rupture of small deep penetrating arteries (Qureshi et al., 2009). As a result of effects of chronic hypertension, the arteries undergo degeneration, fragmentation and fibrinoid necrosis (Fisher 1971) and are prone to rupture. Charcot-Bouchard microaneurysms of between 100 to 600 μm in diameter can also be found in patients with chronic hypertension and are believed to be responsible for hypertension related ICH (Challa et al., 1992; Qureshi et al., 2009). Hypertension related ICH is usually located in the deep white matter structures or the brainstem and the cerebellum.

The incidence of hypertension related ICH also varies, likely due to differences in prevalence of hypertension and compliance with medical management across different ethnicities. Yeh et al reported hypertension caused 55% of 4000 Taiwanese patients (Yeh et al., 2014) in contrast to the Helsinki ICH study by Meretoja et al in which hypertension related ICH accounted for 35% of 1013 ICH patients (Meretoja et al., 2012). Similarly in studies that reported location without specifying aetiology, non-white populations have higher proportion of deeply located ICH (Nilsson et al., 2002; Inagawa et al., 2003; Wang et al., 2015a) and increased prevalence of hypertension as a risk factor (Burt et al., 1995; Wong 1999; Chen et al., 2011a).
1.3.2c Structural vascular lesions
Vascular malformations contribute to less than 10% of all patients presenting with ICH (Meretoja et al., 2012; Yeh et al., 2014) and are an important cause of ICH in young patients without history of hypertension (Ruiz-Sandoval et al., 1999; Koivunen et al., 2014). Vascular malformations can be classified into high or low flow lesions. High flow lesions result from abnormal connection between the arterial and venous vessels. High flow abnormalities include arterio-venous malformation (AVM) with a nidus of vessels between the arterial feeder and the venous drainage system while direct connection between artery and vein is referred to as dural arterio-venous fistula (AVF) (Geibprasert et al., 2010). Low flow vascular malformations include cerebral cavernous malformation (CCM), cerebral telangiectasia and developmental venous anomalies. Almost all ICH from low flow lesions are due to CCMs, which are pockets of vascular anomaly lined by a thin layer or endothelium without contribution from arterial bed (Tu et al., 2005).
Vascular malformations are predominately located near the cortical regions while CCMs can also be found in deep white matter (Aiba et al., 1995; Geibprasert et al., 2010; Gross et al., 2011). The age of presentation of ICH from vascular malformation typically is in the 2nd to 5th decade of life (Cordonnier et al., 2008). Dural AVF and AVM result in medium to large size ICH while ICH from CCMs is usually small volume haemorrhage due to the difference in flow state (Cordonnier et al., 2008).

1.3.2d Medication related ICH
ICH in the setting of anticoagulation use or systemic thrombolysis constitutes up to 25% of ICH patients (Meretoja et al., 2012; Schols et al., 2014; Yeh et al., 2014). The incidence of anticoagulation associated ICH is increasing due to the ageing population (Bejot et al., 2013). Elderly anticoagulated patients often have multiple comorbidities and co-existence of hypertensive and/or amyloid angiopathy is common.

1.3.2e Other and undetermined aetiologies
Less common causes of ICH include vasculitis, cerebral reperfusion injury (after carotid or intracranial revascularization), reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, Moyamoya Disease, liver cirrhosis, systemic coagulopathy and drug induced (Meretoja et al., 2012). In approximately 10 to 20% of ICH patients who do not have a vascular lesion, or fulfill
criteria for hypertensive ICH or cerebral amyloid angiopathy, the aetiology is undetermined (Meretoja et al., 2012; Yeh et al., 2014).

1.3.2f. Limitations of SMASH-U classification system

The major limitation of the SMASH-U classification system is that it classifies aetiology into the most likely pathogenesis based on clinical and radiological information (Meretoja et al., 2012) without the need for pathological determination. It is likely that a proportion of patients would be mis-classified when compared with pathological diagnosis, for example not all patients ≥55 years of age with lobar, cortical or cortico-subcortical ICH with full negative workup would have cerebral amyloid angiopathy. Similarly patients classified with anticoagulant associated ICH may have an underlying hypertensive angiopathy or cerebral amyloid angiopathy that triggered the haemorrhage. The results of studies utilising the SMASH-U classification system therefore need to be interpreted in the setting of these limitations.

1.4 Incidence and burden of intracerebral haemorrhage

Intracerebral haemorrhage contributes to 10-20% of all strokes, although the proportional contribution to stroke subtypes is higher in non-European populations (Saposnik et al., 2000; Zhang et al., 2003). The crude incidence rate of ICH varies between ethnic origins, between 10-30 per 100,000/year in European, Indian, Hispanic and Black populations (Feigin et al., 2006; van Asch et al., 2010; Tveiten et al., 2012; Bejot et al., 2013; Hilmarsson et al., 2013; Gattellari et al., 2014) and about 50 per 100,000/year in people of South East Asian descent. Within ethnic groups there are also regional variations, with higher crude incidence of ICH in Northern Manhattan Blacks (49.5/100,000) (Labovitz et al., 2005) than in South London (14.9/100,000) (Smeeton et al., 2007) and Barbados (17.6/100,000) (Corbin et al., 2004). Similarly Asian immigrants in Auckland, New Zealand have a similar incidence to Europeans (20.7 vs 18.6 per 100,000) (van Asch et al., 2010) and lower ICH rates when compared to studies from Japan (52/100,000) (Inagawa et al., 2003; Kubo et al., 2003), Taiwan or China (92-328/100,000, age adjusted rate to world population) (Tsai et al., 2013). The differences in incidence likely reflect the ethnic and environmental differences in risk factors for ICH.
In Australia, ICH incidence rates were reported in community based studies from North East Melbourne (1996-1997), Perth (1989-1990), New South Wales (2001-2009) and Adelaide (2009-2010). The crude incidence rates per 100,000 population/year were 35 in Perth, 30 in North East Melbourne, 25.2 in New South Wales and 18 in Adelaide (Anderson et al., 1994; Thrift et al., 2001; Leyden et al., 2013; Gattellari et al., 2014). In Finland, a study from the Jyvaskyla region in south central Finland reported crude incidence rate of 31/100,000/year over a 4-year period (1985-1989) (Fogelholm et al., 1992). The results of the Finnish Heart Association study (FHA 89-91) reported ICH rate of 23.7/100,000/year in 4 regions in mid to lower South of Finland (Numminen et al., 1996).

Community based registries from the UK and Europe have indicated stable rates of ICH in the past 3 decades (Lovelock et al., 2007; Bejot et al., 2013). The FINSTROKE (1983-1997) (Sivenius et al., 2004) also noted stable ICH incidence rates while the Australian studies suggested a declining ICH rate in studies published after 2000 (Leyden et al., 2013; Gattellari et al., 2014) compared to earlier decades (Anderson et al., 1994; Thrift et al., 2001).

A systematic review of 47 population-based studies from 28 countries from 1970 to 2006 demonstrated no change in the rates of ICH (Feigin et al., 2009). In the Dijon registry, the incidence of ICH between the epochs 1985-1993 and 2001-2008 reduced by 50% in patients < 60 years of age but there was an increase of 80% in those ≥75 years of age (Bejot et al., 2013). Similar findings were reported in the Oxfordshire community based studies, where the incidence of ICH was compared between two time epochs (The Oxford Community Stroke Project - 1981-1986 and Oxford Vascular Study 2002-2006). The authors noted a near 50% reduction in number of ICHs in the <75 year age group but an increase in crude number of cases in patients ≥75 years of age (Lovelock et al., 2007). These data suggest that reduction in ICH rates in the young is offset by an increase in ICH in the older population. The reduction in ICH incidence in the young is likely due to improved control of hypertension while increased anticoagulant use in the elderly likely accounts for increasing rates of ICH.

Although ICH constitutes a small proportion of all strokes, according to the Global Burden of Diseases study 2015 it is responsible for 50% mortality and two-thirds disability-adjusted life years lost due to stroke. In 2015 ICH caused 3.3 million
stroke-related deaths (6% of any cause of death globally) and 73 million (3% of any cause of disability globally) stroke-related disability adjusted life years lost (Kassebaum et al., 2016; Wang et al., 2016b). This is compared with 2.9 million deaths and 45 million disability-adjusted life years lost caused by ischaemic stroke. The impact of ICH was greater in developing countries than developed countries. In the 2 decades between 1990 and 2013 there was an increasing proportional contribution of disability-adjusted life years lost (2.14% in 1990 vs 2.79% in 2013) and deaths (5.22% in 1990 vs 6.40% in 2013) due to ICH to all diseases in the developing countries compared to a trend towards reduction in the developed countries (Feigin et al., 2015). The global death and disability-adjusted life years lost due to stroke is projected to increase to 7.8 million and 60.9 million respectively in 2030 with most of the increase expected to come from the developing countries (Mathers and Loncar 2006).

1.5 Risk factors for intracerebral haemorrhage

There are a number of modifiable and non-modifiable risk factors for ICH with some common risk factors for ischaemic stroke such as age and hypertension. The INTERSTROKE analysis measured the relative importance of several ICH risk factors in hypertension, current smoking, waist-to-hip ratio, diet, physical activity, alcohol use, apolipoproteins, diabetes mellitus, psychosocial factors and cardiac disease (O'Donnell et al., 2016). The INTERSTROKE analysis reported that hypertension was the most importance ICH risk factor with population attributable risk (PAR) of 56.4%, followed by psychosocial stress (PAR 24.8%) and alcohol (PAR 9.8%) (O'Donnell et al., 2016). Conversely, regular physical activity was associated with a substantial reduction in the risk of ICH (OR 0.63 95% CI 0.48-0.81), an observation likely accounted for by improved blood pressure control and general cardiovascular health (Fagard and Cornelissen 2007). The following passages expand on the discussion on ICH risk factors.

1.5.1 Non-modifiable factors

1.5.1a Genetic risk factors

The most well known genetic association with ICH is the Apolipoprotein (APO) E gene. The APOE gene is located on chromosome 19 and is responsible for lipid
transport and cell membrane maintenance (Zhang et al., 2014). There are 3 alleles to the APOE genes, termed epsilon (ε) 2, ε3 and ε4 and each isoform has specific antioxidant and neurotrophic function (Zhang et al., 2014). Each individual has two alleles of the APOE in different combinations. The ε4 allele is associated with late onset Alzheimer’s Disease (Corder et al., 1994) and development of cerebral amyloid angiopathy (Rannikmae et al., 2013), both conditions are associated with deposition of Aβ peptide in the cerebral vessels. A large-scale genome wide association study with 2189 cases and 4041 controls associated APOE ε4 not only with lobar ICH but also with deep ICH (Biffi et al., 2010b). The risk of recurrence in both lobar (O’Donnell et al., 2000) and non-lobar (Raffeld et al., 2015) ICH is also increased in carriers of APOE ε4.

APOE ε2 in contrast to ε4 occurs in significantly lower frequency in patients with Alzheimer’s Disease compared to controls suggesting a protective effect (Corder et al., 1994; Nicoll et al., 1997). Despite this APOE ε2 was shown in a meta-analysis to be significantly associated with cerebral amyloid angiopathy (Rannikmae et al., 2013) and other studies have associated it with risk of lobar ICH and its recurrence but not with deeply located ICH (O’Donnell et al., 2000; Biffi et al., 2010b). APOE ε3 is the most common allele but it has not been associated with risk of ICH (Zhang et al., 2014; Carpenter et al., 2016). The exact mechanism through which APOE ε2 and ε4 increase risk of ICH is uncertain but likely involves a combination of increase vessel fragility through amyloid deposition and accelerated vessel stress through association with hypertension and hypercholesterolaemia (Carpenter et al., 2016).

1.5.1b Age
In case-controlled studies, increasing age was associated with increased risk of ICH. Every decade increase in age was associated with a two-fold increase in risk (Ariesen et al., 2003). Age of ICH onset, however, differs between ethnicities with median age of onset in studies involving predominately European ancestry in the 7th decade of life (Feigin et al., 2006; Meretoja et al., 2012) while in Asians (Yeh et al., 2014; Sun et al., 2016) and blacks (Smeeton et al., 2007; Xian et al., 2014) the age of onset is up to a decade earlier.
1.5.1c Sex
Male sex was associated with increased risk of ICH compared to women in a meta-analysis of 9 studies (Arieseen et al., 2003). ICH studies also indicated a male preponderance (Smeeton et al., 2007; Meretoja et al., 2012; Xian et al., 2014), particularly in Asian patients (Yeh et al., 2014; Sun et al., 2016), which likely results from the increased incidence of hypertension in men and the Asian population.

1.5.1d Cerebral microbleeds
Cerebral microbleeds are small rounded or ovoid hypointense lesions seen on specific magnetic resonance imaging (MRI) sequences such as T2* gradient recalled echo (GRE) imaging or susceptibility weighted imaging (SWI; discussed later) (Wang et al., 2014b). These are thought to represent regions of extravasation from small blood vessels. Cerebral microbleeds can be located either in the lobar or deep regions of the brain. Cerebral microbleeds in the lobar location suggest underlying cerebral amyloid angiopathy while deep microbleeds suggest hypertensive cause, although the two can co-exist and a mixed pattern of microbleeds can be seen (Wilson and Werring, 2017). In general, the presence of cerebral microbleeds is associated with risk of ICH occurrence in patients with or without history of stroke. In the population-based Rotterdam study (n=4759, age ≥45 years, mean follow up 4.9 years) where 99.2% of participants had no history of stroke, the presence of cerebral microbleed on MRI, irrespective of location was associated with risk of ICH (lobar microbleeds adjusted HR 5.32 95% CI 1.39-20.37, p=0.016; deep microbleeds adjusted HR 5.98 95% CI 1.08-33.16, p=0.044) (Akoudad et al., 2015). In patients with history of ICH, the presence and number of lobar microbleeds also predicted future ICH recurrence. In a cohort study of 94 patients with probable cerebral amyloid angiopathy, the 3-year cumulative risk of recurrent symptomatic ICH was 14% for 1 microbleed, increasing to 51% for patients with ≥6 microbleeds at baseline (Greenberg et al., 2004). A subsequent analysis of the expanded cohort reported risk of recurrent ICH was highest in those with ≥5 (HR 4.12 95% CI 1.6-9.3) compared to those with between 2-4 microbleeds (HR 2.93 95% CI 1.3-4.0) (Biffi et al., 2010a). Resumption of antiplatelet or anticoagulant medication after ICH for a separate indication appears also to be associated with increased risk of ICH recurrence particularly in cerebral amyloid angiopathy. In one study of ICH patients with cerebral amyloid angiopathy (n=104, 60.1% had ≥cerebral microbleed), the resumption of aspirin after ICH was
independently associated risk of ICH recurrence (HR 3.95 95% CI 1.6-8.3, p=0.021) (Biffi et al., 2010a). In a recent meta-analysis of 4 studies with 990 ischaemic stroke patients with atrial fibrillation, with majority of patients on warfarin treatment, the presence of cerebral microbleed was associated with increased risk of symptomatic ICH on follow up (OR 4.16 95% CI 1.54-11.24, p=0.005) (Charidimou et al., 2017a). However, there may be a differential ICH risk for deeply located microbleeds associated with hypertensive angiopathy despite the findings in the Rotterdam study. In a Japanese study (n=807, 188 (23.3%) had ICH as index event, 142 (76%) were deep ICH), the use of either aspirin or warfarin after index stroke was not independently associated with occurrence of deep ICH (with aspirin HR 2.03 95% CI 0.67-6.20, p=0.21; with warfarin 2.47 95% CI 0.62-9.90, p=0.20) (Imaizumi et al., 2013). Future research is required to clarify potential differential ICH risk in the location of microbleed to guide decision making in antithrombotic therapy in patients with cerebral microbleed.

1.5.2 Modifiable risk factors

1.5.2a Hypertension
Chronic hypertension results in deposition of lipid hyaline (lipohyalinosis) within the walls of small blood vessels, resulting in weakening of vessels walls and formation of microaneurysms within the deep or brainstem regions of the brain (Fisher 1971, 1972). Intracerebral haemorrhage is presumed to result from microaneurysm rupture. In the INTERSTROKE study, hypertension emerged as the strongest independent risk factor for ICH (OR 4.69 99% CI 3.51-4.77), with population attributed risk of 56% (O'Donnell et al., 2016). Covariates adjusted in the multivariable analysis for in the INTERSTROKE study for ICH were hypertension, current smoking, waist-to-hip ratio, diet, regular physical activity, alcohol intake, apolipoproteins B/A1, diabetes mellitus, psychosocial factors and cardiac causes. An earlier meta-analysis of 11 cohort studies also reported hypertension as an important risk factor (OR 3.68 95% CI 2.52-5.38) (Ariesen et al., 2003).

1.5.2b Diabetes mellitus
Diabetes mellitus is an important risk factor for ischaemic stroke and ischaemic heart disease through accelerated atherosclerosis, mediated by increased vascular inflammation resulting from advanced glycation end products associated with
hyperglycaemia (Basta et al., 2004). A systematic review of 9 studies assessing risk of ICH with diabetes published in 2003 demonstrated diabetes to be a relatively weak independent risk factor (RR 1.30 95% CI 1.02-1.67) (Ariesen et al., 2003). The Emerging Risk Factors Collaboration, a meta-analysis of individual patient data from 102 prospective studies on vascular risk factors including nearly 700,000 patients also indicated diabetes to be a modest independent risk factor (HR 1.56 95% CI 1.19-2.05, adjusted for age, smoking status, body mass index, systolic blood pressure) (Sarwar et al., 2010). In contrast to these reports, the results of the INTERSTROKE collaboration indicated that diabetes mellitus was associated with reduced risk of ICH (OR 0.72 99% CI 0.60-0.87) (O'Donnell et al., 2016).

1.5.2c Smoking
Smoking accelerates atherosclerosis and is a major risk factor for ischaemic stroke. Three prospective longitudinal cohort studies reported contrasting results for ICH risk. In the Physician’s Health Study involving 22,022 US male physicians with nearly 18 years of follow up, ≥20 cigarettes/day of smoking was independently associated with a more than 2-fold increase in ICH risk (RR 2.08 95% CI 1.05-4.13) (Kurth et al., 2003b). The Women’s Health Study involving nearly 40,000 US women with 9 years’ of follow up data also associated current smoking of ≥15 cigarettes/day independently with increased risk of ICH (adjusted RR 2.15 95% CI 0.62-7.43) (Kurth et al., 2003a). However, the pooled cohort from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study (median follow-up time 13.5 years for patients without ICH and 8.0 years for patient experiencing ICH) demonstrated no association between smoking and incident ICH (adjusted RR 1.29 95% CI 0.82-2.03) (Sturgeon et al., 2007). A meta-analysis by Ariesen et al (RR 1.06 95% CI 0.89-1.26) and the INTERSTROKE study (OR 1.14 99% CI 0.95-1.36) also did not find smoking to be significantly associated of ICH risk (Ariesen et al., 2003; O'Donnell et al., 2016).

1.5.2d Alcohol
Alcohol consumption is associated with increased blood pressure in normotensive and hypertensive subjects (Puddey et al., 1985; Puddey et al., 1987), possibly due to pressure effects of alcohol on the cardiovascular system (Potter and Beevers 1984). Likely as a result of this association with hypertension, alcohol has been associated
with increased risk of ICH in a meta-analysis by Ariesen (OR 3.36 95% CI 2.21-5.12) (Ariesen et al., 2003) as well as the INTERSTROKE analysis (OR 2.09 99% CI 1.4-2.67) (O'Donnell et al., 2016).

1.5.2e Lipids
Cholesterol is an important part of the cell membrane and removal of cholesterol results in increased membrane permeability and increased risk of haemorrhage in small arteries (Wieberdink et al., 2011). The post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed an increased rate of ICH in atorvastatin treated patients (HR 1.68 95% CI 1.09-2.59) (Amarenco et al., 2006). However further analysis of the SPARCL trial indicated that ICH at entry into the study was the strongest predictor of subsequent ICH (HR 5.65 95% CI 2.81-11.30), while serum cholesterol levels were not significantly associated with risk of subsequent ICH (Goldstein et al., 2008). The Cholesterol Treatment Trialist Collaborators performed a meta-analysis on 14 lipid lowering randomised controlled trials (n=90,056) and demonstrated no association between low density lipoprotein (LDL) lowering and risk of ICH (RR 1.05 99% CI 1.05-0.78 - 1.41) (Baigent et al., 2005). In contrast to the community based Rotterdam Study (n=9,068), the level of triglyceride was associated with reduced ICH risk (HR for highest quartile vs lower quartile, 0.20 95% CI 0.06-0.69), while no significant association was found for high density lipoprotein (HDL) or LDL cholesterol (Wieberdink et al., 2011). A single centre study (n=513; 212 ICH and 301 control patients) analysed the longitudinal trend of serum lipid profiles in the 2 years leading up to ICH. There was a significant decline in serum LDL cholesterol (-0.63 mMol/L, p=0.001) and triglyceride (-0.76 mMol/L, p=0.0038) levels in the 6 months leading to ICH compared to control patients (Phuah et al., 2016). The role of lipid profile in ICH pathogenesis remains controversial and further studies are required to assess the link between serum lipid profile and ICH.

1.5.3f Antiplatelet and anticoagulant use
Antiplatelets are used for primary and secondary prevention of ischaemic heart disease and ischaemic stroke in the absence of atrial fibrillation or other indication for anticoagulation. Anticoagulants are also used for the prevention and treatment of venous thromboembolism. The Clopidogrel versus Aspirin in Patients at Risk of
Ischaemic Events (CAPRIE) study randomised 19,185 patients to either clopidogrel (75mg, n=9599) or aspirin (325mg, n=9586) with a mean follow up of nearly 2 years. CAPRIE demonstrated a low risk for ICH (clopidogrel 37 (0.39%) vs aspirin 51 (0.53%) patients) (CAPRIE Steering Committee 1996). Data from the UK medical research database – The Health Improvement Network (THIN) assessed the risk of ICH with antiplatelet use compared to non-users and demonstrated that single agent antiplatelet use was not associated with increased risk of ICH with aspirin (OR 1.06 95% CI 0.93-1.21) or clopidogrel (OR 0.91 95% CI 0.64-1.31) but that risk was increased with dipyridamole (OR 2.35 95% CI 1.60-3.44). The latter finding was attributed to dipyridamole use in patients with conditions predisposing them to risk of ICH and, in a subgroup analysis of patients with cerebrovascular disease, the use of dipyridamole was not associated with increased risk of ICH (OR 0.71 95% CI 0.30-1.68) (Garcia-Rodriguez et al., 2013). The study also reported no increased risk of ICH with combination aspirin/clopidogrel use (OR 1.18 95% CI 1.03-1.37) but risk was increased with aspirin/dipyridamole (OR 2.97 95% CI 1.80-4.90) (Garcia-Rodriguez et al., 2013). Interestingly, the Danish national registry data (n=82,854) on anti-platelet and warfarin prescription in patients surviving hospitalisation with atrial fibrillation demonstrated comparable risk of ICH in patients taking dual antiplatelet (0.8% per year), triple therapy (warfarin and dual antiplatelets, 1% per year) or warfarin monotherapy (0.6% per year) (Hansen et al., 2010). Data from the THIN database demonstrated warfarin use was associated with nearly 3-fold increase in risk of ICH (OR 2.82 95% CI 2.26-3.53) and risk further increases with concurrent use of warfarin with multiple antiplatelet agents (OR 6.98 95% CI 1.25-39.12) (Garcia-Rodriguez et al., 2013). Several direct oral anticoagulants (DOACs) have been made available in the past decade including the direct thrombin inhibitor dabigatran and factor Xa inhibitors apixaban and rivaroxaban. In general, the novel anticoagulants have been associated with reduced risk of intracranial haemorrhage compared with warfarin. Results from the major randomised trials for these drugs demonstrated low annual intracranial haemorrhage risk for all the DOACs (Dabigatran 0.3% p.a., apixaban 0.24-0.3% p.a. and rivaroxaban 0.5% p.a.) (Connolly et al., 2011; Granger et al., 2011; Patel et al., 2011; Hart et al., 2012). A subsequent meta-analysis of all the DOAC trials demonstrated significantly reduced risk of intracranial haemorrhage
when compared with warfarin use (OR 0.49, 95% CI 0.36-0.65) with no significant difference in risk between each of the three DOACs (Chatterjee et al., 2013).
1.6 Diagnosis of intracerebral haemorrhage

Prior to widespread availability of neuroimaging, ante-mortem diagnosis of ICH relied on electroencephalographic abnormalities in patients with clinical stroke symptoms and catheter angiogram. On angiography, the haematoma can be identified by displacement of blood vessels or active extravasation of contrast (figure 1) (Lazorthes 1959; Hoeffer et al., 2012). Intrathecal injection of air for pneumoencephalogram was used to improve delineation and location of the haematoma (Lazorthes 1959). These approaches were less sensitive when the haematoma was in a deep location.

Figure 1. Catheter angiogram demonstrating parieto-occipital haematoma with extravasation (arrow), from Lazorthes 1959 (Lazorthes 1959).

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With the advent of CT and MRI imaging, ICH can be rapidly diagnosed using these imaging modalities. Although some clinical features such as headache, vomiting, neck stiffness, severe hypertension and altered conscious state increase the probability of
ICH versus ischaemic stroke (Lovelock et al., 2010), clinically ICH can not be reliably distinguished from acute ischaemic stroke on clinical grounds alone (Runchey and McGee 2010). Cerebral imaging is therefore indicated for rapid diagnostic evaluation as well as ascertaining the cause of the ICH.

1.6.1 Computed tomography

Acute ICH on CT is represented by regions of increased attenuation with an accepted Hounsfield Unit (HU) range of between 44 and 100 (Parizel et al., 2001). The degree of attenuation is influenced by the protein content (haemoglobin) and the haematocrit, time from ictus and degree of active bleeding (New and Aronow 1976; Barras et al., 2009; Barras et al., 2013). Immediately after ictus, the haematoma can appear heterogeneous in density due to admixture of white cells, platelet clumps and protein rich serum into the haematoma complex (Parizel et al., 2001). In the hours to days following ICH the HU increases, predominately due to clot retraction which increases the haematocrit and the blood protein component present in the haematoma (Parizel et al., 2001). In the days to weeks following ICH, haematoma is degraded and slowly absorbed, correlating with reduction in HU intensity by approximately 1 HU per day (Dolinskas et al., 1977). Persistent mass effect can be present despite haematoma resolution due to the developing rim of peri-haematomal oedema. It may take several weeks to months before resolution of the haematoma and mass effect, resulting in a slit like cavity or region of gliosis.

1.6.2 Volume estimation

Obtaining an accurate haematoma volume estimation is important clinically for patient prognostication (discussed later in chapter) and in the clinical trial setting to accurately determine the effect of an intervention. A simple to use formula for volume estimation is the ABC/2 method (figure 2) (Beslow et al., 2010). A is the largest diameter on the axial CT slice with the largest volume haematoma, and B measures the largest diameter in a line perpendicular to A, C is the number of slices containing haematoma multiplied by slice thickness (mm).
Figure 2. The ABC/2 method of estimating haematoma volume (Beslow et al., 2010).

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ABC/2 represents a practical and easy to use bedside tool for evaluating ICH volume in the emergency department. The major limitation with the ABC/2 method is that it assumes an ellipsoid shape and is operator dependent in measuring the dimensions. Haematoma volume can also be determined using manual segmentation of the haematoma region and the volume derived by multiplying the sum of the area segmented by slice thickness or using automated computer-generated volume. A range of softwares is available including the open source freeware Osirix (Piximeo, Geneva, Switzerland) or Analyze (Biomedical Imaging Resource, Mayo Clinic). In general, ABC/2 overestimates volumes when compared to manual tracing (Huttner et al., 2006; Kosior et al., 2011) particularly in larger haematomas. More recently a semi-automated method utilising HU thresholds has been proposed for segmentation of both haematoma and oedema (discussed later in this chapter) (Volbers et al., 2011). For haematoma the HU is fixed between 44-100, while for oedema a fixed lower threshold of 5 HU is used in combination with a flexible upper threshold (maximum 33 HU, figure 3). The computer software automatically segments the region that fulfills the HU requirement for either haemorrhage or oedema and calculates the volume based on the area of the segmented regions and slice thickness. Other threshold methods have also been proposed including a lower threshold for oedema and segmentation without setting a HU limit (McCourt et al., 2014; Urday et al., 2015a). Regardless of the method used, a threshold-based approach generates more consistent volumes with better reliability when compared to manual segmentation.
1.6.3 Contrast enhanced imaging - angiography

Angiography can be performed non-invasively with CT or MRI, primarily to assess for underlying vascular malformations. A Cochrane review of retrospective studies assessed the diagnostic accuracy of acute CT angiogram (CTA) (8 studies, n=526) and MR angiogram (MRA) (3 studies, n=401) in diagnosing macrovascular malformations when compared with digital subtraction angiography (DSA) following acute intracerebral haemorrhage (Josephson et al., 2014). The authors found high sensitivity (CTA 0.95, MRA 0.98) and specificity (CTA 0.99, MRA 0.99) for both modalities in diagnosis of macrovascular malformations without a statistical significance in the accuracy between CTA and MRA (p=0.6).

MRA in patients with negative CTA may provide additional yield for detection of vascular malformation (van Asch et al., 2015) but catheter DSA should be performed in young patients (age <55) with lobar haemorrhage and without history of hypertension according to US guidelines (Wong et al., 2011; Hemphill et al., 2015). Magnetic resonance or CT venography can be performed in patients with suspected venous sinus thrombosis.

1.6.4 Contrast enhanced imaging – contrast extravasation

Following contrast administration, regions of contrast enhancement may be observed within the haematoma which represent active bleeding. This is referred to as the CTA ‘spot sign’ (figure 4) (Goldstein et al., 2007; Wada et al., 2007; Demchuk et al.,...
2012). A spot sign is noted in approximately one third of patients with acute ICH imaged with static CTA and can be singular or multiple (Goldstein et al., 2007; Wada et al., 2007; Brouwers et al., 2012; Demchuk et al., 2012). In general, the spot sign is defined by the presence of intra-haematoma contrast extravasation which is 1) serpiginous or spot-like without a connection to an outside vessel; 2) Hounsfield Unit must be at least double that of background haematoma; 3) No corresponding hyperdensity on non-contrast CT (Thompson et al., 2009; Demchuk et al., 2012; Meretoja et al., 2014). In the Prediction of Haematoma Growth and Outcome in Patients with Intracerebral Haemorrhage using the CT-angiography spot sign (PREDICT) definition, a size criteria of greater than 1.5mm was also required in defining the CTA spot sign (Demchuk et al., 2012).

The presence of the CT spot sign is a strong independent predictor of subsequent haematoma expansion (Goldstein et al., 2007), one of the most power prognostic markers of ICH outcome (Davis et al., 2006). In the PREDICT study (n=268), the spot sign was present in 51% of patients with haematoma expansion with a positive predictor value of 61% and negative predictive value of 71% (Demchuk et al., 2012). The predictive value of the CTA spot sign for haematoma expansion has been shown to be independent of the time from onset (Goldstein et al., 2007; Brouwers et al., 2012).
The major limitation of the CTA spot sign is the relative insensitivity of static CTA acquisitions. It has been demonstrated that multi-phase CT, delayed/venous phase CTA (Rodriguez-Luna et al., 2014) and also source images from CT perfusion (Wang et al., 2016a) could increase the detection rate of the spot sign. However, certain characteristics of the spot sign itself may influence the association with haematoma growth. In a post-hoc analysis of the PREDICT study (n=371) CTA acquired in the venous phase resulted in higher detection of spot sign when compared to arterial phase CTA (39% vs 27.3%, p=0.041). However, total absolute haematoma growth was less in the venous phase spot sign positive patients compared with the arterial phase (5.2–5.9 mL vs 17.1–17.8 mL, p=0.019) (Rodriguez-Luna et al., 2014). In the CT perfusion and detection of spot sign study by Wang et al (Wang et al., 2016a) early onset spot sign (detected before 23 seconds) was an independent predictor of haematoma growth (OR 28.84 95% CI 6.96-119.46, p<0.001) and also 3-month mortality (OR 22.37 95% CI 1.77-272.33, p=0.016). In this study the early onset spot sign had a sensitivity of 0.72 and specificity of 0.91 for ICH expansion. When the analysis included presence of spot sign at any time during CT perfusion acquisition the sensitivity for ICH expansion increased to 0.80 with a corresponding reduction in specificity to 0.74 (Wang et al., 2016a). Another study (n=162) examined the rate of

Figure 4. Hyperacute haematoma (90 minutes from onset, left image), CTA spot sign (centre) and subsequent haematoma growth (right image)
contrast extravasation within the spot sign and found it to be independently associated with haematoma expansion (OR 1.03 95% CI 1.01-1.08, p=0.047) and 90-day mortality (OR 1.15 95% CI 1.08-1.27, p=0.0004). Faster rate of spot sign enlargement was observed in patients with haematoma expansion (0.30mL/min vs 0.07mL/min, p=0.16) and 90-day mortality (0.27mL/min vs 0.04mL/min, p<0.0001) (Brouwers et al., 2015). These results suggest that not all spot signs have equal clinical relevance in predicting haematoma growth. Spot sign that appears early with faster rate of enlargement are more likely to be associated with ICH expansion due to faster rate of active extravasation. Conversely late appearing spot sign may indicate slower rate of contrast extravasation and may not necessarily influence haematoma growth and patient outcome.

1.6.5 Magnetic resonance imaging

The appearances of haemorrhage on MRI are more complex and determined by the age of the haematoma and influenced by the metabolic processing of extravasated blood (table 1). The signal intensity changes on both T1, T2 and SWI sequences relate to the paramagnetic effect of red cell components, specifically iron. Immediately after ictus (minutes to hours), oxygenated haemoglobin and protein rich serum predominate within the haematoma. In the early subacute (hours to days) stage, the haemoglobin becomes deoxygenated but is still compartmentalised within the red cell. In the late subacute stage (days to weeks) deoxyhaemoglobin is oxidised to methaemoglobin and is contained in the extracellular space following red cell lysis (Gomori and Grossman 1988; Parizel et al., 2001). In the chronic stage (months), macrophages clear up red cell degradation products leading to deposition of crystalline haemosiderin and insoluble ferritin and leaving behind a gliotic cavity filled with proteinacious fluid (Gomori and Grossman 1988; Parizel et al., 2001).

SWI is a high-resolution 3D GRE MRI technique that accentuates the paramagnetic properties of blood products and structures containing blood including haematoma and blood vessels appear as loss of signal (Tong et al., 2008). Due to its higher resolution and improved signal to noise ratio, SWI images are more sensitive for detection of haemorrhagic lesions than T2* GRE particularly when the lesions are small such as cerebral microhaemorrhages (Cheng et al., 2013).
It may be difficult, however, to determine the age of the haemorrhage without clinical information or information from other MRI sequences. In T1 sequences, the signal intensity is isointense or hypointense within the first hours to two days following ICH. In the subacute stage in the days to weeks after ictus, T1 signal becomes hyperintense due to the paramagnetic properties of the unpaired electrons in both deoxyhaemoglobin and methaemoglobin. In the chronic stage where haemosiderin forms the remnant of the haematoma and does not cause T1 shortening, it becomes iso-intense with grey matter (Grossman et al., 1988; Parizel et al., 2001; Macellari et al., 2014).

Haematoma on T2 sequences also undergo chronological changes. In the hyperacute stage after ICH, the haematoma is hyperintense on T2 due to significant amount of water content and the appearance is indistinguishable from fluid collection. In subacute phase T2 sequences become progressively hypointense due to paramagnetic properties of deoxyhaemoglobin and methaemoglobin. There is a surrounding region of increased intensity from peri-haematomal oedema. In the late subacute stage (days to weeks), the T2 signal becomes hyperintense again due to red cell lysis and increased water content. The overall region of increased intensity continues to regress due to resorption of peri-haematomal oedema. In the chronic stage, the region of gliosis is hyperintense while the rim of haemosiderin becomes hypointense (Grossman et al., 1988; Parizel et al., 2001; Macellari et al., 2014).

In summary, information gathered from T1, T2 and SWI sequences enable determination of the age of the haemorrhage. Changes on T1 are important for distinguishing between hyperacute to acute stage of ICH while T2 sequences assist in differentiation between subacute to late stage of ICH. Table 1 summarises the changes seen on each of these sequences after ICH.

Table 1. Stages of red cell metabolism and changes on CT and MRI sequences. Reproduced from Marcellari et al (Macellari et al., 2014).

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1.7 Mechanism of brain injury after intracerebral haemorrhage

1.7.1 Primary Injury – haematoma volume and haematoma expansion

1.7.1a The haematoma

Primary injury occurs due to mechanical disruption from the haematoma itself. It causes mechanical injury and can lead to significant mass effect resulting in secondary oligaemia, midline shift and transtentorial herniation. Pre-stroke warfarin use may influence baseline haematoma volume. Ma et al reported in 404 consecutive ICH patients that pre-ICH use of warfarin was significantly associated with larger baseline haematoma volume on univariate analysis (23.9 vs 14.2 mL, p=0.046), although the intensity of the anticoagulation did not influence the haematoma volume (Ma et al., 2013). In a report by Flaherty et al (n=258), pre-ICH warfarin use was also associated with baseline haematoma volume (22.1 vs 11.9 mL, p=0.03). In multivariable generalised linear model, patients with International Normalised Ratio (INR) >3.0 was significantly associated with baseline haematoma volume (p=0.02) but not when INR was less than 3 (Flaherty et al., 2008). Other studies have also associated larger baseline haematoma volume in patients treated with warfarin (Cucchiara et al., 2008; Kuwashiro et al., 2010; Chen et al., 2013; Curtze et al., 2014), although some studies have also reported lack of association (Flibotte et al., 2004; Sheth et al., 2010; Horstmann et al., 2013). The radiological characteristics of DOAC associated ICH are not well understood but, with the increasing use of DOACs in place of warfarin, it is expected that DOAC associated ICH will increase. In an international multi-centre study of 500 patients with anticoagulant related ICH (403 warfarin, 97 DOAC), there was no difference in the baseline ICH volume between DOAC-ICH and warfarin-ICH (14.4mL vs 10.6mL, p=0.78) (Wilson et al., 2017).

ICH volume is smaller in deep and infratentorial regions when compared with lobar location (Flaherty et al., 2008; Samarasekera et al., 2015). ICH volume may however impact outcome differently at different locations, for example a small brainstem haemorrhage or moderate size cerebellar haemorrhage may result in severe neurological deficit or obstructive hydrocephalus and herniation. Patients with lobar located haemorrhage may be protected from the mass effect of the haematoma due to
pre-existing cerebral atrophy in patients with cerebral amyloid angiopathy, which is the most common cause of lobar haemorrhage.

1.7.1b Haematoma expansion
Most patients with ICH undergo haematoma expansion which can result in increased mass effect, mechanical injury and risk for herniation and is a strong prognostic factor of outcome (discussed further later) (Davis et al., 2006). However, patients with smaller degree of haematoma expansion may not experience neurological deterioration. Therefore various definitions for significant haematoma expansion have been used in both absolute (>6mL, (Demchuk et al., 2012) >12.5mL, (Kazui et al., 1996) >20mL, (Fujii et al., 1998)) or relative terms (>33%, (Brott et al., 1997) >40%, (Kazui et al., 1996) >50% (Fujii et al., 1998)). The most commonly used definition in recent and ongoing trials of haemostatic agents combines absolute and relative growth criteria and dichotomizes the outcome as “>33% relative growth or absolute growth of >6mL” (Flaherty 2008; Meretoja et al., 2014). Approximately one-third of ICH patients will experience significant haematoma expansion from admission within 24 hours according to this definition (Dowlatshahi et al., 2011).

1.7.1c Predictors of haematoma expansion
The CTA spot sign discussed earlier in the Chapter is currently accepted as the most reliable predictor of haematoma expansion. The limitation of the CTA spot sign is that it is relatively insensitive in patients with haematoma expansion and requires use of intravenous contrast which may not be routinely performed in clinical practice. Other non-spot predictors of haematoma have been identified and are discussed below.

1.7.1d Shape and haematoma density
The association of active extravasation with regions of heterogeneous density was first observed in patients with acute traumatic extradural haematomas in the 1980s (Palmieri 1981; Zimmerman and Bilaniuk 1982), the so-called ‘swirl sign’. In ICH, the swirl sign is identified in between 15-46% of patients and was associated with haematoma expansion (Kim et al., 2008; Selariu et al., 2012). Other potential novel predictors of haematoma expansion on non-contrast CT include the ‘blend sign’ and the ‘black hole sign’ (Li et al., 2015; Li et al., 2016). The ‘blend sign’ is defined as ‘blending’ of adjacent hypoattenuating and hyperattenuating regions within the
haematoma differentiated by a clear margin, and with \( \geq 18 \) HU difference in measured density between the two regions (figure 5). The prevalence of the blend sign is between 17% and 20% of unselected ICH patients (Li et al., 2015; Sporns et al., 2017). There was excellent inter-observer reliability in the identification of the blend sign, which was independently associated with haematoma expansion (\( n=172, \text{OR} \quad 20.23 \quad 95\% \text{ CI} \quad 5.13-79.77, \text{p}<0.001 \)) in one study (Li et al., 2015) and secondary neurological deterioration in another study (\( n=182, \text{OR} \quad 11.47 \quad 95\% \text{ CI} \quad 3.70-35.58, \text{p}<0.001 \)) (Sporns et al., 2017).

**Figure 5. The 'blend sign', from Li et al (Li et al., 2015).**

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The black hole sign (figure 6) is defined as a region of relative hypoattenuation encapsulated within the haematoma with \( \geq 28 \) HU difference between the hypoattenuated region and the haematoma. The black hole sign was present in 15% and 23% of unselected ICH patients and was independently associated with haematoma expansion in two studies (\( n=206, \text{OR} \quad 4.12 \quad 95\% \text{ CI} \quad 1.44-11.77, \text{p}=0.008 \) by Li et al; \( n=128, \text{OR} \quad 4.09 \quad 95\% \text{ CI} \quad 1.52-11.00, \text{p}=0.005 \) by Yu et al) (Li et al., 2016; Yu et al., 2017).
The swirl, blend and black hole signs are mostly based on qualitative identification of hypoattenuating regions in the haematoma. Quantitative CT densitometry has been analysed by Barras in placebo treated patients of the Phase IIb trial of recombinant activated Factor VII in ICH (Mayer et al., 2005b) with available baseline CT <3 hours from ictus. The presence of heterogeneous density identified on CT was significantly associated with haematoma growth (Barras et al., 2009; Barras et al., 2013). Irregular shaped haematoma margins have also been associated with haematoma expansion. Barras et al devised a 5-point visual scoring system for irregularity of the haematoma but the authors were unable to demonstrate an association with haematoma expansion (Barras et al., 2009). Analysis from the PREDICT registry demonstrated an association with haematoma growth with irregularly shaped haematoma (Blacquiere et al., 2015).

Figure 6. The black hole sign, from Li et al (Li et al., 2016).

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1.8 Secondary injury after intracerebral haemorrhage

1.8.1 Secondary ischaemic injury

1.8.1a Hypoperfusion
A number of reports have used advanced imaging to assess whether perfusion changes after ICH may cause secondary ischaemia and exacerbate neuronal injury. A study using single photon emission CT (SPECT) demonstrated reduction in peri-haematomal blood flow in 23 patients imaged within 18 hours from onset, which significantly improved at 72 hours (Mayer et al., 1998). Other studies using CT or MRI perfusion have demonstrated reduced perfusion in the peri-haematomal region as indicated by increased mean transit time, time to peak of residual function (Tmax), reduced relative cerebral blood volume and relative cerebral blood flow in ICH patients imaged within 24 hours of onset (Kidwell et al., 2001; Schellinger et al., 2003; Herweh et al., 2010; Etminan et al., 2012; McCourt et al., 2014). A small study using MRI perfusion demonstrated mild global hypoperfusion in the hemisphere ipsilateral to the ICH when compared to the contralateral hemisphere (Kidwell et al., 2001). However none of the perfusion abnormalities reached thresholds considered to represent penumbral tissue based on definitions derived for ischaemic stroke.

Although peri-haematomal cytotoxic oedema as defined by reduced apparent diffusion coefficient can be observed in some ICH patients, there was no correlation between the presence of cytotoxicity and Tmax delay in 14 ICH patients from one study (Olivot et al., 2010). In another study (n=21) despite the presence of peri-haematomal reduction in perfusion there was no corresponding cytotoxic oedema or reduction in apparent diffusion coefficient (Butcher et al., 2004) (see also discussion in section 1.8 regarding cytotoxic oedema). Furthermore in a positron emission tomography study of 19 acute ICH patients (imaged <22 hours from onset), the peri-haematomal cerebral metabolic rate of oxygen and oxygen extraction fraction were reduced in the setting of reduced cerebral blood flow (Zazulia et al., 2001). In the post hoc analysis of Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH-ADAPT, n=67) there were relative reductions of cerebral blood volume and cerebral blood flow in the peri-haematomal oedema when compared to the contralateral brain region (McCourt et al., 2014). These findings suggest reduced metabolic demand rather than ischaemia is associated with increased oxygen
extraction fraction. A study of peri-haematomal brain tissue obtained during surgery (n=6) demonstrated progressive reduction of mitochondrial function as demonstrated by oxygen consumption when compared to control patients undergoing lobectomy for epilepsy (Kim-Han et al., 2006).

1.8.1b Remote ischaemia

In patients with brain MRI performed days following ICH onset, remote lesions on diffusion weighted imaging (DWI) can be observed. A number of studies have reported prevalence of remote DWI lesions in between 13% to 41% of ICH patients (Prabhakaran and Naidech 2012; Gioia et al., 2015). The presence of remote ischaemic lesions has been associated with worse functional outcome at 3 months and 1 year and increased risk of long term occurrence of ischaemic stroke and combined endpoint of cerebrovascular disease and vascular death (Prabhakaran and Naidech 2012). The presence of remote ischaemic lesions has been associated with leukoaraiosis, cerebral microbleeds and baseline haematoma volume (Gregoire et al., 2011; Kang et al., 2012; Menon et al., 2012). The contribution of blood pressure lowering is controversial with some authors reporting an association between blood pressure lowering and remote ischaemic lesions while others did not find this association (Garg et al., 2012; Menon et al., 2012; Gioia et al., 2015). The pathogenesis of remote ischaemic lesion is uncertain but likely resulting from changes in cerebral autoregulation, blood pressure fluctuations and elevated intracranial pressure in precipitating ischaemic lesions in patients with pre-existing microangiopathy from chronic effects of hypertension and cerebral amyloid angiopathy (Prabhakaran and Naidech 2012).
1.8.2 Peri-haematomal oedema

A rim of peri-haematomal oedema develops after ICH (Figure 7). Unlike oedema associated with ischaemic stroke which usually peaks 3-5 days after stroke onset (Simard et al., 2007), oedema after ICH evolves over a longer period and usually peaks during week 2 after ICH onset (Staykov et al., 2011; Venkatasubramanian et al., 2011). It is generally accepted that oedema progresses through two stages. In the hyperacute stage this is mediated by hydrostatic pressure and clot retraction resulting in oedema rich in ionic constituents with relatively intact blood-brain-barrier (Urday et al., 2015b). In the subacute stage disruption of the blood-brain-barrier leads to vasogenic oedema (Urday et al., 2015b).

Figure 7. Progression of peri-haematomal oedema after intracerebral haemorrhage resulting in delayed mass effect.

1.8.3 Hyperacute oedema formation

1.8.3a Clot retraction

Although the mechanisms behind early oedema development remain speculative, they are likely multi-factorial. Firstly, clot retraction, a process that occurs in response to haemostatic activation in order to limit primary injury at site of bleeding can cause transudation of plasma due to increased intraclot pressure (Majidi et al., 2016).
Additional hydrostatic pressure during expanding haematoma in the early stages following ictus can also contribute to transudation of serum into the interstitium. In a human cadaveric ICH model, clot retraction resulted in near 50% reduction in haematoma volume after single injection of blood (Majidi et al., 2016). In a non-collagenase pig model of ICH where blood was injected into the white matter there was accumulation of water rich in protein content in the peri-haematomal region without evidence for blood-brain-barrier disruption when the brain was examined up to 8 hours after ICH induction (Wagner et al., 1996).

1.8.3b Early cytotoxic oedema

Early cytotoxic oedema can develop in the peri-haematoma region after ICH (Olivot et al., 2010; Li et al., 2013b). Under normal conditions (figure 8A), the intracellular environment is sodium poor (~5 mMol/L) while the extracellular and intravascular space is high in sodium concentration (~140 mMol/L). The Na-K-Cl (NKCC1) co-transporter in the cell membrane enables sodium ions to move intracellularly via the concentration gradient. The concentration gradient between the intracellular and extracellular space is maintained by the energy dependent Na-K-Adenosine-Triphosphatase (ATPase) pump. Under ischaemic condition, as occurs during cerebral ischaemia or following ICH, there is progressive activation of the NKCC1 co-transporter induced by neurotransmitter glutamate and the inflammatory cytokine interleukin-6 (Castillo et al., 2002; Dziedzic et al., 2002; Simard et al., 2010a). This process allows for sodium ions to enter the intracellular space, which is accompanied by chloride and water (Figure 8B). In addition, there is expression of the SUR1-TRPM4 channel in both the neuronal and endothelium cell membrane. The channel is expressed in the neurovascular unit following cerebral injury including ICH (Simard et al., 2012). SUR1-TRPM4 channel is then activated by depletion of ATP, allowing for further movement of sodium, chloride and water intracellularly. With progressive failure of the Na-K-ATPase pump, there is progressive cell swelling resulting in cytotoxic oedema.

The SUR1-TRPM4 channel has been a target of interest in management of acute ischaemic stroke. In pre-clinical models inhibition of SUR1-TRPM4 with intravenous glyburide resulted in reduced oedema and improved clinical outcome (Simard et al., 2012). In a phase II study - Glyburide Advantage in Malignant Oedema and Stroke (GAMES-RP, n=86) treatment with intravenous glyburide for patients with large
volume ischaemic stroke was safe and resulted in reduced midline shift compared to placebo (4.6 vs 8.5mm, p=0.0006) (Sheth et al., 2016). The reduction in brain swelling with glyburide may account for the observation in ischaemic stroke that pre-stroke use of glyburide was associated with improved outcome after ischaemic stroke (Kunte et al., 2007; Kunte et al., 2012). In one rat ICH model SUR1-TRPM4 channel was expressed within the peri-haematoma region in the neurons and the endothelial cells and peak expression was reached within 24 hours after ICH onset. Treatment with intravenous glyburide resulted in significantly reduced brain water content, blood-brain-barrier breakdown and improved neurological function (Jiang et al., 2017). There are no observational studies associating pre-stroke use of glyburide and outcome after ICH.

The presence of cytotoxic oedema has been assessed in human ICH studies. In a MRI study of 59 ICH patients, the presence of peri-haematoma cytotoxic oedema, defined as increased DWI-b1000 signal and reduced apparent diffusion coefficient by >10% compared to the contralateral normal mirror region, was detected in 36 (61%) patients on day 3 MRI (Li et al., 2013a). In another MRI study peri-haematoma cytotoxic oedema was present in 10/20 (45%) at 24 hours, and in the 10 patients with serial MRI scans at 24 hours, days 3 and 7 after ICH onset, the degree of cytotoxic oedema was greatest on day 3 and began to reverse at day 7 (Li et al., 2013b). Early cytotoxic oedema was associated with larger peri-haematoma oedema volume and oedema growth on day 1 (Li et al., 2013b). However, other MRI studies found increased rather than reduced apparent diffusion coefficient in the peri-haematoma region early ICH reflecting presence of early vasogenic oedema. Butcher et al demonstrated increased peri-haematoma apparent diffusion coefficient in 21 patients imaged within 110 hours of ICH onset, including 6 patients scanned within 6 hours of ictus (Butcher et al., 2004). Other studies have reported mixed presence of reduced and increased apparent diffusion coefficient in the peri-haematoma region when ICH patients were imaged acutely (<6 hours from ictus) (Schellinger et al., 2003) and up to 3 days from ictus (Olivot et al., 2010). These results demonstrate the complex evolving peri-haematoma metabolic profile contributing to oedema formation.
1.8.3c Ionic oedema formation
Neuronal cytotoxic oedema results in relative depletion of sodium in the interstitial space (figure 8B). This creates an ionic gradient between the interstitium and intravascular space. The expression and activation of NKCCL1 on the luminal side of the endothelial cell membrane and SUR1-TRPM4 on the interstitial side of the cellular membrane coupled with the ionic gradient results in movement of sodium from the intravascular space to the interstitial space (Urday et al., 2015b). Chloride follows to maintain electrochemical neutrality and water follows as both chloride and sodium are osmotically active. This shift of fluid into the interstitial space is termed ‘ionic oedema’ as the composition of the fluid is protein poor due to relatively intact blood-brain-barrier but rich in ions and is postulated to occur within hours of ICH onset.

1.8.3d Vasogenic oedema resulting from localised blood-brain-barrier dysfunction
Cytotoxic oedema also occurs in the vascular endothelium resulting in cellular swelling and alteration of the tight junction architecture. This process enables serum to move across the blood-brain-barrier and this fluid is termed vasogenic oedema (Urday et al., 2015b) (figure 8C). Vasogenic oedema is essentially an ultrafiltrate of blood.

In addition to endothelial swelling, localised inflammation is also believed to contribute significantly to blood-brain-barrier disruption. Neuro-inflammation begins early after ICH onset with release of thrombin. Thrombin induces an inflammatory response by stimulating leucocytes to the site of the haemorrhage, which in turn releases inflammatory cytokines and chemokines as well as reactive oxygen species resulting in oxidative damage and opening of the blood-brain-barrier (Urday et al., 2015b). Secondly, thrombin acts directly on the endothelial tight junctions by increasing the contractility of the actin cytoskeleton resulting in gaps in the tight junction (Satpathy et al., 2004).

The second major stimulator of inflammation is haemoglobin. Red cell lysis begins within 24 hour after ICH and components of the red cell including haemoglobin and its degradation products are released into the brain issue (Aronowski and Zhao 2011). Preclinical evidence suggests haemoglobin induces inflammation via induction of toll-like receptors 2 and 4 which, in turn, activates Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB activation results in transcription of
genes that translate inflammatory cytokines, chemokines and metalloproteinases (Wang et al., 2014a). Metalloproteinases are a class of proteolytic enzyme that can directly distort the integrity of the blood-brain-barrier and increased levels have been associated with increased peri-haematomal oedema and poor outcome in human ICH (Li et al., 2013a).

Iron is also released into the extracellular space following degradation of haemoglobin. Free iron induces a series of reactions leading to production of toxic free radicals resulting oxidative stress and cell death. Strongest evidence for role of iron in oedema formation comes from animal ICH models where iron chelation resulted in reduced oedema formation and neuronal cell death (Gu et al., 2009; Okauchi et al., 2010).

The complement cascade is also activated by the presence of thrombin by cleavage of C3 which result in formation of anaphylatoxin and membrane attacking complexes. Anaphylactoxin activates microglia and induces infiltration of granulocytes resulting in secretion of inflammatory cytokines including tumour necrosis factor and interleukin-1. Membrane attacking complexes lysis red cells resulting in iron mediated toxicity and inflammation (Ducruet et al., 2009).

Two human studies have provided evidence for localised peri-haematomal blood-brain-barrier disruption. McCourt et al assessed for presence of blood-brain-barrier permeability using permeability-surface area product maps from CT perfusion images at 24 hours after ICH in 53 patients from the ICH-ADAPT study. The authors reported a significant increase in peri-haematomal blood-brain-barrier permeability when compared to the corresponding region in the contralateral hemisphere (permeability-surface area product 5.1 mL/100mL/minute vs 3.6 mL/100mL/minute, p<0.001) although the increased blood-brain-barrier permeability was not associated with relative oedema growth at 24 hours. (McCourt et al., 2015) In another study of 25 ICH patients using MRI dynamic contrast enhanced imaging performed at 1 week post symptom onset, Aksoy et al found a significant increase in peri-haematomal blood-brain-barrier permeability ($K_{trans}$ 0.055 vs 0.00 in the contralateral mirror region, p<0.0001) which was associated with increased oedema volume at day 1 ($p=0.62$, p=0.002) and day 7 ($p=0.35$, p=0.09) (Aksoy et al., 2013).
Figure 8. Stages of oedema formation after intracerebral haemorrhage

A. Normal resting state

Cerebral Interstitium
Na+ concentration ~140mMol/L

Vascular lumen
Na+ concentration ~140mMol/L

B. Cytotoxic oedema and progressive cell swelling

Cerebral Interstitium
Na+ concentration ~60mMol/L

Vascular lumen
Na+ concentration ~140mMol/L
Stages of oedema formation showing A) normal resting state, B) Early cytotoxic oedema resulting from adenosine triphosphate (ATP) depletion which inhibits Na-K-ATPase function and activates SUR1-TRPM4 channel. Chloride and water follow sodium into the intracellular space resulting in progressive cellular swelling. C) Swelling of endothelial cells result in distortion of tight junctions, allowing for plasma to move into the interstitial space resulting in vasogenic oedema. Subsequent cell death and membrane lysis occurs. Adopted from Urday (Urday et al., 2015b) and Simard (Simard et al., 2010a).
1.8.6e Non-localised blood-brain-barrier disruption

The blood-brain-barrier disruption after ICH may not be localised to the peri-haematomal region. In a small human MRI study of 46 subjects, a more widespread disruption of the blood-brain-barrier was suggested by post contrast hyperintense T2 signal in the cerebral spinal fluid in regions remote from the primary ICH. This imaging finding designated “hyperintense image marker” (figure 9) is present even in ICH patients imaged within 12 hours of symptoms onset (Kidwell et al., 2011) indicating that there may be a more widespread disruption of the blood brain barrier even early after ICH onset. However, it is possible that the blood-brain-barrier disruption reflects the severity of underlying angiopathy and may have predated the ICH as only 10 (22%) subjects had pre-ICH contrast enhanced MRI. It was not reported whether ‘hyperintense image marker’ was evident in the scans performed prior to index ICH, the results therefore need to be confirmed in larger cohorts.

Figure 9. Hyperintense image marker after intracerebral haemorrhage, from Kidwell et al 2011 (Kidwell et al., 2011).

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1.8.4 Natural history of oedema formation

Data on the natural history of oedema evolution is limited. In a study by Gebel et al (n=86) assessing oedema evolution within 24 hours of ICH onset, absolute and relative (oedema/haematoma volume ratio) oedema increased from a median of 6.9mL and 0.81 respectively, from baseline (< 3hours from ictus) to 14.4 mL and 0.47 on follow up scan at 20 hours (Gebel et al., 2002a). In the post-hoc analysis of the INTERACT studies (n=1119), the absolute oedema volumes also doubled at 24 hours from baseline imaging (Carcel et al., 2016). Several studies have explored the natural history of oedema evolution beyond the first 24 hours. Sansing et al modeled oedema growth using quadratic model for predicting oedema growth against time in 80 patients and suggested that peak of oedema is reached around day 5 after ictus (Sansing et al., 2003). However this study was limited by small sample size and the model for estimating growth was derived from 48 patients with at least two CT scans within 9 days of ICH onset. Venkatasubramanian reported in 22 patients with serial MRI scans that relative oedema volume (a unitless ratio calculated by oedema volume divided by haematoma volume) peaked in most patients in the second week following ICH onset (figure 10) (Venkatasubramanian et al., 2011). Staykov et al demonstrated in 90 patients with follow up CT scans that absolute oedema volume continues to increase significantly until the second week of ictus (figure 11) (Staykov et al., 2011). This group has published other studies demonstrating continual growth of oedema into the second week after ICH (Wagner et al., 2012; Volbers et al., 2016a; Volbers et al., 2016b). In a small study (n=25) by Fung et al that assessed the impact of decompressive hemicraniectomy on oedema evolution, in the 14 control patients the absolute oedema volume peaked at 35 days from ictus (Fung et al., 2016). Although 3 patients had ICH secondary to tumour (n=2) and infection (n=1), the oedema progression in this study and the oedema growth trajectory from other suggest that continual growth beyond week two may be possible.
Figure 10. Progression of relative oedema in 22 patients with serial MRI imaging, from Venkatasubramanian et al (Venkatasubramanian et al., 2011).

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Figure 11. Natural history of absolute oedema growth (n=90), from Staykov et al reproduced with permission (Staykov et al., 2011).

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1.8.5 Factors associated with oedema growth

1.8.5a Haematoma
In pre-clinical ICH models, treatment with iron chelator deferoxamine resulted in significantly reduced peri-haematomal iron deposition (Gu et al., 2009), and oedema (Okauchi et al., 2010) indicating potential association between haematoma related iron release and oedema growth. In INTERACT I (n=270), baseline haematoma volume was significantly associated with oedema growth at 72 hours (beta 0.184, SE 0.037, p<0.0001) (Arima et al., 2009). In the pooled analysis of the INTERACT studies (n=1138), baseline haematoma volume (beta 0.150 SE 0.017, p<0.0001) and 24 hour haematoma growth (beta 1.965 SE 0.241, p<0.0001) were independent predictors of oedema growth. Other reports have also consistently reported associations of ICH volume with oedema volumes (Levine et al., 2007; Sansing et al., 2011; Staykov et al., 2011; Appelboom et al., 2013; Li et al., 2013a; Volbers et al., 2016b). Further in the Minimally Invasive Surgery plus Recombinant Tissue-type Plasminogen Activator (MISTIE) II study the end of surgery oedema volumes were significantly lower in patients undergoing haematoma evacuation compared with controls (27.7 vs 41.7 mL, p<0.001) (Mould et al., 2013). The MISTIE II results suggest a role for ongoing inflammatory influence of the blood byproducts on oedema evolution additive to the initial rapid oedema growth associated with haematoma expansion.

1.8.5b Sex
Wagner et al assessed the sex differences in 387 patients with ICH and demonstrated no differences in the baseline oedema volume between different sexes (men 39.0 vs women 42.3 mL, p=0.32). However, female patients had significantly lower absolute oedema volumes between 2 to 4 (p=0.03) days and trended towards lower oedema volumes between days 5-7 (p=0.064) and 12-14 (p=0.1) after ICH. The MRI study by Venkatasubramanian demonstrated that men had significantly lower relative oedema at 48 hours with later attainment of peak oedema (Venkatasubramanian et al., 2011). The pooled INTERACT studies however did not find an association between sexes and 24 hour oedema growth (Yang et al., 2015).
1.8.5c Blood pressure
Hypertension may contribute to oedema formation by increasing hydrostatic pressure (Urday et al., 2015b). In INTERACT 1, pre-existing hypertension was associated with 72-hour oedema volume but, paradoxically, oedema volume was also associated lower systolic blood pressure (Arima et al., 2009). In the pooled INTERACT analysis, patients with intensive blood pressure control had less 24 hour oedema growth compared to control patients (4.77 vs 5.65 mL, p=0.04). These contrasting observations could potentially be accounted by blood pressure fluctuations following ICH due to impaired baroreflex sensitivity (Sykora et al., 2009). However other studies have not reported an association between blood pressure and oedema growth (Sykora et al., 2009; Qureshi et al., 2010; Sansing et al., 2011).

1.8.5d Glucose
In animal models, hyperglycaemia is associated with increased blood-brain-barrier disruption, neuronal death and brain oedema (Song et al., 2003; Liu et al., 2014). However, human data have not been able to associate glucose with oedema growth. A post hoc analysis of the ATACH I study (n=60) was unable to associate glucose level (analysed as glucose trend over 72 hours) with oedema growth at 24 hours (Qureshi et al., 2011). In single centre study of 135 patients, patients with mean glucose levels over 72 hours of ≥150mg/dL (8.33mmol/L) did not have more oedema growth (29.6% vs 31.3%, p=0.39) (Feng et al., 2012). A post-hoc analysis of the INTERACT 2 study also found no association between hyperglycaemia and oedema growth at 24 hours (glucose ≥6.5mMol/L vs <6.5mMol/L, 2.6 vs 3.0mL oedema growth respectively, p=0.293) (Saxena et al., 2016). Other studies using baseline glucose measurement have also reported no association with oedema (Levine et al., 2007; Mehdiratta et al., 2008; Naval et al., 2008; Sykora et al., 2009).

1.8.5e Body temperature
Fever, defined as a temperature of ≥37.5° C, is present in up to 25% of ICH patients and is associated with poor outcome (Schwarz et al., 2000; Rincon et al., 2013). The cause of fever after ICH is uncertain but likely an adaptive mechanism to the release of inflammatory mediators in response to brain injury (Rincon et al., 2013). In rat models of ICH, hypothermia was shown to reduce oedema development through reduced blood-brain-barrier disruption, and thrombin induced inflammatory response
There is limited human data on the impact of hypothermia (target temperature of 35°C) on oedema development with data published from one single centre (Kollmar et al., 2012; Staykov et al., 2013; Volbers et al., 2016a). The latest publication by Volbers et al consisted of 33 patients treated with hypothermia compared with 37 patients matched for ICH volume, age, ICH location and ventricular haemorrhage who were managed with standard care. The authors reported reduced oedema growth in patients with early initiation of hypothermia (Day 1-2) but not in those with delayed treatment (days 4-5) (figure 12). Therapeutic mild hypothermia after ICH appears safe (Volbers et al., 2016a) and is currently being assessed in randomised controlled trials (Kollmar et al., 2012; Rincon et al., 2014).

1.8.5f Anticoagulant use and thrombolytic use

Patients with ICH (n=74) due to systemic thrombolysis from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO 1) trial had less baseline oedema when compared to non-thrombolytic related ICH (n=97) patients (0 vs 6 mL, p<0.0001) (Gebel et al., 2000). In another study, ICH patients pre-treated with warfarin (n=49) trended towards less baseline relative oedema (0.38 vs 2.0, p=0.07) compared to non-anticoagulated patients (n=49), with warfarin being an independent predictor of oedema volume (beta -0.26, 95% CI [-0.51, -0.01], p<0.05) (Levine et al., 2007). In porcine models of ICH injection of ‘non-clotting’ blood with either heparin or tissue plasminogen activator resulted in significantly less oedema formation than pigs injected with non-treated blood (Xi et al., 1998; Wagner et al., 1999). In murine ICH models, formation of oedema required activation of the coagulation cascade by prothrombinase and conversely inhibition of thrombin resulted in significantly less oedema formation (Lee et al., 1996; Lee et al., 1997). These clinical and pre-clinical observations support the notion that thrombin and the coagulation cascade contribute to oedema growth.
Figure 12. Impact of mild hypothermia on oedema evolution, from Volbers 2016 (Volbers et al., 2016a).

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1.8.5f Other medications
Use of statins and anti-adrenergic medications prior to ICH has been associated in observational studies with less oedema formation (Naval et al., 2008; Sansing et al., 2011). Potential mechanisms for reduced oedema formation can be derived from animal models - statin use was shown to reduce the amount of blood-brain-barrier damage and oedema formation after ICH in rats (Yang et al., 2013a), while β-adrenergic blockade resulted in significant reduction in the expression of pro-inflammatory cytokines TNF-α and interleukin-6 (Wang et al., 2010).
1.9 Prognostic factors in intracerebral haemorrhage

1.9.1 Haematoma volume

It has been shown that initial haematoma volume is strongly predictive of mortality (Broderick et al., 1993; Hemphill et al., 2001). In the study by Broderick et al, patients with small baseline ICH volume (<30mL) had 22% mortality at 30-days compared to 65% in those with ICH volume of 30-60mL and 80% in those with large volume ICH of >60mL. Mortality increases further in patients with poor Glasgow Coma Score (GCS) (figure 13) (Broderick et al., 1993).

Figure 13. Volume dependent effect of baseline haematoma volume on outcome. Reproduced from Broderick et al (Broderick et al., 1993).

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1.9.2 Haematoma growth

Haematoma growth occurs in up ~70% of ICH patients on follow up imaging (Brott et al., 1997; Davis et al., 2006; Delcourt et al., 2012). The rate of growth is most rapid within the first two hours of ictus, after which it reduces exponentially (Rodriguez-Luna et al., 2016). Overall approximately one third of patients have significant haematoma expansion at 24 hours defined as 33% relative growth or 6mL.
absolute growth (Dowlatshahi et al., 2011). With each 10% increase in haematoma volume, there is an additional 5% increase in risk for 30-day mortality (Davis et al., 2006). For every 10 mL increase in ICH growth at 24 hours there is doubling of the odds of death or disability at 90 days (Delcourt et al., 2012).

A recently identified metric is ‘ultraearly haematoma growth’ (UHG), which is an estimation of the rate of haematoma growth from 0ml at onset to the volume measured on baseline imaging (Rodriguez-Luna et al., 2011). The UHG is calculated by the haematoma volume divided by time from onset to imaging in hours (ml/hour) in patients imaged under 6 hours from ictus. The speed of UHG has been correlated with poor outcome at 90 days in a single centre study (n=133) (Rodriguez-Luna et al., 2011), sub-analysis of the PREDICT registry (n=231) (Rodriguez-Luna et al., 2016) and the pooled INTERACT studies (n=2909) (Sato et al., 2014). The UHG rate in these studies has also been associated with an increased risk of early neurological deterioration, poor 90-day outcome, haematoma growth and presence of the CTA spot sign.

1.9.3 Ventricular haemorrhage

Intraventricular blood is observed in nearly 50% of patients with ICH (Hallevi et al., 2008; Meretoja et al., 2012; Yeh et al., 2014). Ventricular haemorrhage can be primary or isolated, which contributes to ~3% of all ICH presentation or, in the majority, secondary to parenchymal haemorrhage dissecting into the ventricular system (Gaberel et al., 2012). In contrast to early views that ventricular haemorrhage “decompressed” the ICH, it has been shown to be a significant adverse prognostic marker in ICH patients. In a meta-analysis of 13 studies, the odds of ICH mortality were increased 6-fold in patients with IVH compared to patients without IVH (Gaberel et al., 2012). Ventricular haemorrhage can result in obstructive hydrocephalus and elevated intracranial pressure, impeding cerebral blood flow (Gaberel et al., 2012). The presence of ventricular blood may also induce an iron-related local inflammatory response resulting in blood-blood-barrier breakdown, oedema formation and neuronal toxicity (Chen et al., 2011b).
1.9.4 Simultaneous intracerebral haemorrhages

In a relatively small proportion of ICH patients, simultaneous multiple intracerebral haemorrhages (SMICH) are present on initial imaging (figure 14). This observation has only been reported in a limited number of small single centre case series with reported prevalence between 1 to 6% of all ICH presentations (Weisberg 1981; Maurino et al., 2001; Yen et al., 2005; Sorimachi et al., 2007b; Stemer et al., 2010; Takeuchi et al., 2011; Laiwattana et al., 2014; Yeh et al., 2014; Chen et al., 2016). Presence of SMICH has been reported to be associated with higher mortality compared to patients with single ICH, with series by Chen and Yen reporting mortality rates of 78% and 60% respectively (Yen et al., 2005; Chen et al., 2016). However, other series have reported relatively low mortality rates with SMICH of 24% and 33% (Weisberg 1981; Stemer et al., 2010). The difference is likely accounted for by the larger total haematoma volume in series reporting higher mortality and predominance of deeply located ICH which is associated with poorer outcome (Samarasekera et al., 2015). The association of SMICH with outcome is therefore controversial and further understanding in the aetiology and outcome of SMICH would shed light on potential therapeutic approach to these patients.

Figure 14. Simultaneous multiple intracerebral haemorrhages from Wu et al with permission (Wu et al., 2017b).
1.9.5. Peri-haematomal oedema

Oedema growth can lead to neurological deterioration due to increased mass effect and transtentorial herniation. A number of studies have examined the association of oedema and patient outcome (table 2). Earlier studies have reported conflicting results. Gebel assessed the association between baseline relative oedema volume and 90-day outcome in 48 ICH patients. They found baseline relative oedema was associated with reduced odds of poor functional outcome (OR 0.09 per 1.0-unit [100%] increase; 95% CI, 0.01 to 0.64; \( P=0.016 \)) and suggested that early increase in oedema may reflect increased activation of haemostatic mechanisms which limits haematoma growth (Gebel et al., 2002b). Levine et al reported that baseline absolute oedema volume was associated with reduced odds (OR 0.41 95% CI 0.19-0.91, \( p=0.03 \)) of 90-day mortality in 98 patients (49 warfarin related ICH with 49 matched controls) (Levine et al., 2007).

Other studies have reported no significant association with outcome; Arima et al performed a post-hoc analysis of the INTERACT 1 study. They reported absolute oedema growth from baseline to 72 hours was associated with increased odds of 90-day death or disability on univariate analysis (OR for 1 SD increase in oedema volume, 1.68 95% CI 1.21-2.32, \( p=0.002 \)) (Arima et al., 2009). However this was no longer significant in the multivariable analysis when adjusted for age, sex, randomised treatment and baseline ICH volume (OR 1.05 95% CI 0.73-1.51, \( p=0.78 \)). In the study by Venkatasubramanian (n=22) higher relative peak oedema volume was not associated with 90-day functional outcome (\( p=0.80 \)) (Venkatasubramanian et al., 2011).

Other studies have reported an association between oedema outcome; three studies (n=315) have correlated absolute oedema volume on admission with in-hospital mortality (McCarron et al., 1999) and discharge outcome (Sansing et al., 2003; Appelboom et al., 2013). While three other studies (n=609) have associated absolute oedema volume at 72 hours with poor discharge (Volbers et al., 2016b) and 90-day outcome (Sansing et al., 2011; Li et al., 2013a). Further evidence associating oedema and outcome came from the pooled analysis of the INTERACT trials and data from VISTA-ICH. The pooled INTERACT studies (n= 1138) demonstrated that absolute oedema growth from baseline to 24 hours was independently associated with increased risk of 90-day death or disability (OR per 5 mL oedema growth, 1.17 95%
CI 1.17 (1.02-1.33) p=0.025 (Yang et al., 2015). The VISTA-ICH study (n=576) demonstrated that growth of oedema from baseline to 72 hours was independently associated with 90-day death or dependency (OR per mL oedema growth, 1.78 95% CI (1.12-2.64), p=0.011) (Murthy et al., 2015). Further a small study (n=110) by Urday et al suggested association with 90-day mortality with rate of oedema growth in the first 24 hours (OR 2.21 95% CI 1.05-4.64, p=0.04) (Urday et al., 2016). There is therefore emerging evidence that peri-haematomal oedema is independently associated with outcome after ICH, a summary of all the oedema studies is found on table 2.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Oedema metric</th>
<th>Outcome measure</th>
<th>Main findings</th>
<th>Factors adjusted in analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCarron 1999(McCarron et al., 1999)</td>
<td>102</td>
<td>Absolute volume</td>
<td>In-hospital mortality</td>
<td>Dead patients had higher mean baseline oedema 37.5 mL vs 17.2 mL, p&lt;0.01</td>
<td>Univariate analysis</td>
</tr>
<tr>
<td>Gebel 2002(Gebel et al., 2002b)</td>
<td>48</td>
<td>Relative index</td>
<td>90-day outcome (mRS 0-2 vs 3+)</td>
<td>Higher relative oedema was associated with less odds of poor outcome at 3 months. OR 0.09 per 1.0-unit [100%] increase; 95% CI 0.01 to 0.64; P=0.016</td>
<td>Relative oedema, GCS, IVH, ICH volume, age, MAP, time to CT, admission glucose, prothrombin time, platelet count, anti-platelet use, mass effect present</td>
</tr>
<tr>
<td>Sansing 2003(Sansing et al., 2003)</td>
<td>80</td>
<td>Baseline absolute oedema volume</td>
<td>Discharge and 90-day outcome based on mRS</td>
<td>Absolute oedema volume was associated with poor discharge (p=0.0002) and 90-day (p=0.0003) outcome on univariate analysis. On multivariable analysis, absolute oedema volume was associated with discharged outcome (OR 1.03 95% CI 1.00-1.07, p not report) but not with 90-day outcome (OR not reported).</td>
<td>Age, ICH volume, midline shift, ventricular haemorrhage, fever, elevated glucose and use of mannitol.</td>
</tr>
<tr>
<td>Levine 2007(Levine et al., 2007)</td>
<td>98</td>
<td>Baseline absolute oedema volume</td>
<td>90-day mortality</td>
<td>Higher baseline oedema volume was associated with reduced 90-day mortality OR 0.41 95% CI 0.19-0.91, p=0.03</td>
<td>ICH volume, warfarin use, age, IVH volume, GCS.</td>
</tr>
<tr>
<td>Arima 2009(Arima et al., 2009)</td>
<td>270</td>
<td>Absolute and relative oedema growth over 72 hours</td>
<td>90-day death or dependency</td>
<td>Neither absolute oedema growth (OR 1.05 95% CI 0.73-1.51, p=0.78) or relative oedema growth (OR 1.26 95% CI 0.94-1.70, p=0.13) were independently associated with 90-day outcome</td>
<td>Age, sex, randomised treatment and ICH volume.</td>
</tr>
<tr>
<td>Sansing 2011(Sansing et al., 2011)</td>
<td>287</td>
<td>Absolute oedema volume at 72 hours</td>
<td>90-day modified Rankin Scale</td>
<td>Absolute oedema was associated with higher 90-day mRS (OR 1.04 per mL oedema, 95% CI 1.02-1.05, p&lt;0.0001)</td>
<td>Age, ICH volume, infratentorial location, IVH, GCS.</td>
</tr>
<tr>
<td>Venkatasubramanian 2011(Venkatasubramanian)</td>
<td>27</td>
<td>Relative oedema index</td>
<td>90-day outcome</td>
<td>Relative oedema at 48 hours was not associated with either 90-day mortality (p=1.0) or median mRS score (p=0.85).</td>
<td>Univariate analysis only</td>
</tr>
<tr>
<td>Reference</td>
<td>N</td>
<td>Outcome Measure</td>
<td>Event Measure</td>
<td>Associated Factor</td>
<td>Univariate Analysis Only?</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----</td>
<td>------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Staykov 2011 Staykov et al., 2011</td>
<td>219</td>
<td>Absolute oedema volume</td>
<td>In-hospital mortality</td>
<td>Absolute oedema growth between day 1 and 3 was associated with in-hospital mortality (OR 1.04, p=0.014)</td>
<td>Age, ICH volume, IVH, mechanical ventilation</td>
</tr>
<tr>
<td>Li 2013 Li et al., 2013a</td>
<td>59</td>
<td>Absolute oedema volume</td>
<td>90-day death or dependency</td>
<td>Absolute oedema volume on day 3 was associated with poor outcome (p&lt;0.001) but not baseline oedema volume (p=0.062)</td>
<td>Age, GCS, infratentorial location, IVH, days from onset to scan.</td>
</tr>
<tr>
<td>Appelboom 2013 Appelboom et al., 2013</td>
<td>133</td>
<td>Baseline absolute oedema volume</td>
<td>Death or dependency on discharge</td>
<td>Absolute baseline oedema volume was associated with poor discharge outcome in patients with ICH volume &lt;30 mL. OR 1.123 95% CI 1.021-1.273, p=0.034</td>
<td>Age, ICH volume, GCS growth, ICH volume, IVH, ischaemic stroke, previous ICH, diabetes, treated hypertension, previous antiplatelet use, lipid lowering medication, time from ictus to CT, systolic BP, glucose, NIHSS &gt;13, lobar location, IVH, baseline ICH vol, ICH growth, mannitol treatment, randomised treatment and trial.</td>
</tr>
<tr>
<td>Yang 2015 Yang et al., 2015</td>
<td>1138</td>
<td>Absolute oedema volume</td>
<td>90-day death or dependency</td>
<td>Absolute oedema growth at 24 hours was associated with increased risk of death or dependency (OR 1.17 per 5mL growth 95% CI 1.02-1.33, p=0.025).</td>
<td>Age, sex, country, previous ICH, ischaemic stroke, previous ICH, diabetes, treated hypertension, previous antiplatelet use, lipid lowering medication, time from ictus to CT, systolic BP, glucose, NIHSS &gt;13, lobar location, IVH, baseline ICH vol, ICH growth, mannitol treatment, randomised treatment and trial.</td>
</tr>
<tr>
<td>Murthy 2015 Murthy et al., 2015</td>
<td>594</td>
<td>Absolute oedema volume</td>
<td>90-day death or dependency</td>
<td>Absolute oedema growth at 72 hours was associated with increased risk of 90-day death or dependency (OR 1.78 per mL 95% CI 1.12-2.64, p=0.011).</td>
<td>Age, ICH volume, GCS growth, ICH volume, IVH, warfarin use, time to baseline scan.</td>
</tr>
<tr>
<td>Urdy 2016 Urdy et al., 2016</td>
<td>110</td>
<td>Absolute oedema growth</td>
<td>90-day death, and mRS score</td>
<td>Absolute oedema growth at 24 hours was associated with 90-day mortality (OR 2.21 95% CI 1.05-4.64, p=0.04) and higher mRS score (2.07 95% CI 1.12-3.83, p=0.02)</td>
<td>Age, ICH volume, IVH and GCS.</td>
</tr>
<tr>
<td>Volbers 2016 Volbers et al., 2016b</td>
<td>220</td>
<td>Absolute oedema volume</td>
<td>Good outcome (mRS 0-3) on discharge</td>
<td>Peak absolute oedema volume was associated with reduced likelihood of good outcome (OR 0.977 95% CI 0.957-0.998, p not reported).</td>
<td>Peak ICH volume, lobar location, GCS, baseline mRS, frequency of elevated intracranial pressure, fever burden</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
1.9.6 ICH pathogenesis

The pathogenesis of ICH influences patient outcome. In the Helsinki ICH study, the authors systematically classified pathogenesis into 6 categories (structural vascular abnormality, systemic coagulopathy, medication related, cerebral amyloid angiopathy, hypertensive angiopathy and undetermined cause – the ‘SMASH-U’ classification system, discussed further in Chapter II) according to ICH location, patient risk factors, laboratory and imaging findings (Meretoja et al., 2012). Patients with systemic coagulopathy and medication related ICH had the worse long term mortality outcome whereas structural vascular causes had the best outcome. Patients with medication (anticoagulant/thrombolysis) related ICH had the highest ICH volume (Flaherty et al., 2008; Meretoja et al., 2012; Curtze et al., 2014) and are also more likely to experience haematoma expansion (Flibotte et al., 2004). In another study of over 4000 Taiwanese patients Yet et al also demonstrated similar long-term impact of pathogenesis on mortality with mortality being highest in patients with medication related and systemic coagulopathy related ICH (Yeh et al., 2014).

1.9.7 ICH location

Location of the haematoma impacts ICH outcome differently. Patients with infratentorial location, particularly in the brainstem, have poorer prognosis when compared to ICH located in lobar or deep regions (Anderson et al., 1994; Nilsson et al., 2002; Inagawa et al., 2003; Zia et al., 2009). In patients with pontine haemorrhage, even a small volume haemorrhage can result in mortality and poor functional recovery, likely resulting from the relatively densely packed critical structures of the posterior fossa (Jang et al., 2011). In patients with cerebellar haemorrhage the prognosis is variable, with reported mortality rates between 20 to 75% (Anderson et al., 1994; Hill and Silver 2001; Kirollos et al., 2001). Although supratentorial haemorrhages have better prognosis than infratentorial haemorrhages, deeply located haematomas portend a poorer outcome compared to lobar ICH (Zia et al., 2009; Samarasekera et al., 2015). Lobar haemorrhage may have better outcome compared to deep haemorrhage as a result of the location and more frequent association with cerebral atrophy in older patients thus offering protection against mass effect (Samarasekera et al., 2015). Furthermore deeply located haemorrhages
like more likely to result in ventricular haemorrhage which itself is a poor prognostic factor (Gaberel et al., 2012).

1.9.8 Age and sex

The overall case fatality of ICH at 1 month approaches ~50% but the mortality is different between young (<50 years of age) and older patients (van Asch et al., 2010). In hospital-based ICH cohorts of young adults, the case fatality at 1 month is in general less than 25% (Ruiz-Sandoval et al., 1999; Lai et al., 2005; Rutten-Jacobs et al., 2013; Koivunen et al., 2015). In INTERACT 2, adults less than 52 years of age had a 3-month mortality of 6.6% (Radholm et al., 2015). The INTERACT 2 study also demonstrated increasing risk of death with increasing age with patients >75 years of age having a 4-fold increase in the risk of 90-day mortality compared to younger adults (Radholm et al., 2015). The contribution of age to outcome may be, in part, related to different ICH pathogenesis: younger patients are more likely to have structural vascular lesions as the cause of ICH (Ruiz-Sandoval et al., 1999; Koivunen et al., 2014) compared to older patients in whom there is an increase in ICH related to anticoagulation (Bejot et al., 2013; Radholm et al., 2015).

Sex may also influence outcome after ICH. In the Helsinki ICH study, male sex was an independent risk factor for 90-day mortality (OR 1.74 95% CI 1.17-2.61, p=0.007) (Meretoja et al., 2012). In an earlier Finnish study of 411 ICH patients presenting to two central Finland County hospitals, male sex did not predict early death at 28 days, although it was a significant predictor of mortality in long-term follow-up (up to 16 years) in those who survived the initial 28 days (Fogelholm et al., 2005b). Other studies have reported mixed observations in the contribution of sex to outcome with majority of studies noted in two recent systematic reviews reporting no significant sex different in outcome (van Asch et al., 2010; Gokhale et al., 2015).

1.9.9 Stroke severity

The NIHSS and GCS provide objective clinical measures of stroke severity. Lower admission GCS has been consistently associated with poor outcome after ICH (Ariesen et al., 2005). Poor grade GCS worsens the short-term prognosis irrespective of the baseline ICH volume (Broderick et al., 1993) and is part of the widely used ICH score for outcome prognostication (Hemphill et al., 2001). However, the main problem with the GCS is that it is heavily biased against patients with aphasia who
score poorly on verbal responses but may not necessarily have truly depressed conscious state. The NIHSS was initially developed for assessment of ischaemic stroke (Brott et al., 1989) and has the advantage of being able to assess neurological dysfunction in addition to level of consciousness and, in general, is not biased against aphasic patients. The NIHSS has been shown in several hospital cohorts to be independently associated with ICH outcome (Cheung and Zou 2003; Weimar et al., 2006; Cheung et al., 2008; Meretoja et al., 2012). When the NIHSS was substituted for GCS into the original ICH score, the modified ICH score predicted mortality no better than the original ICH score (Table 3) (Cheung and Zou 2003).

However the major limitation of predictive scores is that perceived limited prognosis may influence institution of early do-not-resuscitate orders and early withdrawal of care for patients who may have benefited for ongoing early medical management (Zahuranec et al., 2010).

Table 3. The ICH score (from Hemphill et al 2001) and its association with mortality.

<table>
<thead>
<tr>
<th>Component</th>
<th>Score points</th>
<th>ICH score</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3-4</td>
<td>2</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>5-12</td>
<td>1</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>13-15</td>
<td>0</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>ICH volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30mL</td>
<td>1</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>&lt;30mL</td>
<td>0</td>
<td>6*</td>
<td>-</td>
</tr>
<tr>
<td>Ventricular haemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infratentorial origin of ICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No patients in the development cohort for ICH score scored 6 points, as all patients with 5 points died patients scoring 6 points would have very poor prognosis
1.9.10 Do-not-resuscitate orders and early withdrawal of care

The management for patients perceived to have poor prognosis is often limited by early institution of palliative care including do-not-resuscitate orders or withdrawal of care. Although do-not-resuscitate order does not technically equate to withdrawal of care (Holloway et al., 2014), in clinical practice the two are often instituted together resulting in limitation of active treatment (Hemphill et al., 2004; Silvennoinen et al., 2014). Early limitation or withdrawal of care is perhaps the most significant predictor of death after ICH (Becker et al., 2001; Hemphill et al., 2004) but it may result in the so-called ‘self-fulfilling prophecies’ (Becker et al., 2001) when instituted early in patients predicted to have poor prognosis based on the predictive models discussed earlier. Early limitation of treatment may deprive life saving treatment for individual patients with poor prognostic features who may otherwise make a reasonable functional recovery (Becker et al., 2001; Zahuranec et al., 2007; Morgenstern et al., 2015).

Becker et al demonstrated in a single centre study (87 supratentorial ICH patients) with a survey of treating physicians that both neurologists and neurosurgeons based their decision to withdrawal treatment on the initial clinical findings (Becker et al., 2001). In their study early limitation of treatment was associated with 100% mortality rate. However, of 27 patients with ICH volume >60mL and poor grade baseline GCS (≤8), 9 (33%) survived, of whom 6 (67%) were transferred to rehabilitation (Becker et al., 2001). In a prospective multi-centre study in ICH patients without pre-existing do-not-resuscitate orders, maintenance of medical support for first 5 days after ICH onset resulted in a 60% relative reduction in observed 30-day mortality compared to that predicted by ICH score, and of the survivors ~40% had good functional outcome at 90 days (modified Rankin Score <3) (Morgenstern et al., 2015).

In another report Zahuranec et al (n=487) analysed the influence of do-not-resuscitate orders on patient mortality when compared with 3 predictive models including the ICH score (Zahuranec et al., 2010). The authors demonstrated that compared with predictive models, patients with early do-not-resuscitate orders had between 30 to 44% higher 30-day mortality rate. Conversely in patients without early do-not-resuscitate order, the mortality rate was between 6 and 20% lower than predictive models (Zahuranec et al., 2010). Other studies have also consistently associated early
do-not-resuscitation order and limitation of care with increased ICH mortality (Hemphill et al., 2004; Zahuranec et al., 2007).

In clinical practice it is important not to underestimate the role of aggressive medical and surgical treatment in ICH patients, even those predicted to have poor outcome, as a significant minority of patients may derive benefit from aggressive treatment (Becker et al., 2001; Zahuranec et al., 2007; Morgenstern et al., 2015). If early limitation of treatment and do-not-resuscitate orders are considered, the decision should be consulted and an individualized approach should be formulated (Holloway et al., 2014; Hemphill et al., 2015) rather than utilising an ‘one size fits all’ approach. The current American Heart Association / American Stroke Association guidelines recommends considering early aggressive ICH therapy and considering delaying new do-not-resuscitate orders until second day following ICH ictus (Hemphill et al., 2015).

1.10 Medical complications of intracerebral haemorrhage

1.10.1 Hyperglycaemia

Hyperglycaemia is common among patients admitted with acute stroke, and in non-diabetic patients it is likely the result of so-called ‘stress’ hyperglycaemia resulting from release of stress hormones such as cortisol and noradrenaline (Capes et al., 2001). A number of studies have assessed the association between hyperglycaemia and ICH outcome. Most of the studies have attempted to associate single glucose measurements, usually taken at baseline, with outcome. One notable study was the post hoc analysis of the INTERACT studies (n=2653) (Saxena et al., 2016). The authors assessed the prognostic significance of admission glucose level on 90-day outcome. This study reported that admission glucose, both as a continuous variable and also the highest quartile (>7.9mMol/L), was independently associated with the combined outcome of death or disability (adjusted OR per mL glucose 1.35 95% CI 1.01-1.33, p=0.043; adjusted OR for 4th quartile of glucose level 1.34 95% CI 1.01-1.80, p for trend 0.015) (Saxena et al., 2016). However, the main limitation with using single glucose measurements is that it does not provide information on subsequent fluctuations in glucose metabolism. Only four studies (n=686) evaluated glucose trajectory on ICH outcome (Schwarz et al., 2000; Godoy et al., 2008; Qureshi et al.,
Schwarz et al reported in 196 ICH patients the independent association of persistent hyperglycaemia (defined as >11.0 mMol/L for more than 24-hour duration, n=32) on poor discharge outcome (OR 13.54 95% CI 2.24-81.78, p=0.005) adjusted for ventricular haemorrhage, GCS, ICH volume, ICH expansion, persistent hypertension and persistent hyperthermia (Schwarz et al., 2000).

1.10.2 Fever
Fever, defined by body temperature >37.5°C is relatively common (Schwarz et al., 2000; Commichau et al., 2003). In one study (n=196), 91% of patients had a fever at some stage during the first 72 hours of admission (Schwarz et al., 2000). In the same study, the presence of persistent hyperthermia at 72 hours was associated with poor outcome (OR for hyperthermia >48 hour duration 13.52 95% CI 2.22-82.23, p=0.005) (Schwarz et al., 2000). In a meta-analysis involving 14,431 patients (including both ischaemic stroke and ICH patients), the presence of fever was associated with increased mortality, poorer functional outcome and increased hospital length of stay irrespective of the stroke subtype (Greer et al., 2008). The cause of the fever is not always clear, and may have a non-infectious origin (Commichau et al., 2003). Non-infectious fever may result from direct damage to or compression of the thermoregulatory mechanisms in the hypothalamic region. However, irrespective of the underlying cause, fever is associated with poor outcome (Honig et al., 2015). Fever may contribute to poor outcome by exacerbating inflammation-associated secondary injury and peri-haematomaal oedema (Balami and Buchan 2012; Honig et al., 2015).

1.10.3 Seizures
Seizure after ICH is relatively common, occurring in up to 14% of patients with most of the seizures occurring within the first few weeks after ICH onset (Bladin et al., 2000; De Herdt et al., 2011). Cortical involvement is a major risk factor for seizure occurrence (Bladin et al., 2000; Haapaniemi et al., 2014). Late seizures can be predicted using the ‘CAVE’ score, a prediction score with a maximum of 4 points (1 point each for cortical involvement, age <65, ICH volume >10mL and early seizures within 7 days). Risk of seizures developing after 7 days increased exponentially with increasing CAVE score (late seizure risk with CAVE score: 0 = 0.6%, 1 = 3.6%, 2 = 9.8%, 3 = 34.8% and 4 = 46.2%) (Haapaniemi et al., 2014). The impact of seizures on
ICH outcome is controversial. In one retrospective study, early seizure after ICH was associated with worsening NIHSS and increasing midline shift but was not an independent predictor discharge outcome (Vespa et al., 2003). Other studies also did not find associations between early or late onset seizures and mortality (Woo et al., 2012; Haapaniemi et al., 2014).

1.10.4 Deep venous thrombosis

Patients with stroke are at risk of venous thromboembolism due to associated immobility. The risk of symptomatic deep venous thrombosis after ICH is between 3-7% (Goldstein et al., 2009; Kim and Brophy 2009) while asymptomatic deep venous thrombosis was detected in up to 40% of ICH patients scanned with ultrasound within 14 days of onset in two studies (Ogata et al., 2008; Kawase et al., 2009). Potential pre-disposing factors associated with venous thrombosis are increased stroke severity (increasing NIHSS, altered conscious state), paralysis, female sex and ethnicity (Christensen et al., 2008; Ogata et al., 2008; Kawase et al., 2009). Deep venous thrombosis may predispose a patient to pulmonary embolism which has a ~20% 3-month mortality rate in the general population (Goldhaber et al., 1999), and may be as high as 50% after ICH (Broderick et al., 2007).
1.11 Management of haematoma

1.11.1 Surgical management of supratentorial ICH

1.11.1a Haematoma evacuation

Haematoma is the most important prognostic factor after ICH due to its space occupying effects, and reducing haematoma may result in less ischaemic injury, oxidative and inflammatory damage and subsequent oedema development (Keep et al., 2012).

The International Surgical Trial in Intracerebral Haemorrhage (STICH) I randomised 1033 spontaneous supratentorial ICH patients to either early surgery (n=503) or initial conservative management (n=533) within 72 hours of symptom onset. The primary outcome of favourable outcome at 6 months using a prognosis based extended Glasgow outcome scale (available in 965 patients - surgery arm n=468, medical arm n=497) was not statistically significant with an absolute and relative benefit of surgery over conservative management of 2.3% (95% CI -3.2-7.7) and 10% (95% CI -13-33) respectively (Mendelow et al., 2005). In STICH II, 601 patients with lobar supratentorial ICH within 1 cm of the cortical surface were randomised to early surgical evacuation (n=307) or initial conservative management (n=294). Six-month outcome data was available for 583 patients (surgery n=297, conservative n=286) and demonstrated no difference between the two arms (OR for poor outcome in surgical patients 0.86 95% CI 0.62-1.20, p=0.367) (Mendelow et al., 2013). An updated meta-analysis accompanying the STICH II trial publication, which included 15 trials and 3366 patients, demonstrated that surgery was significantly associated with reduced risk of poor outcome (OR 0.74 95% CI 0.64-0.86, p<0.001). However there was significant heterogeneity between the included studies (p=0.0002). When the meta-analysis was limited to patients with lobar haematoma and no ventricular haemorrhage (7 studies, n=923, p=0.21 for heterogeneity), there was a strong trend towards improved outcome in the surgery group (OR 0.78 95% CI 0.59-1.02, p=0.07) (Mendelow et al., 2013).

A developing surgical technique is minimally invasive surgery which involves insertion of a large bore catheter stereotactically through a small craniotomy to drain
the haematoma, with or without aid of small doses of recombinant tissue plasminogen activator (tPA) (figure 15).

**Figure 15. Minimally invasive surgery for haematoma evacuation.**

A) Patient with right temporal haematoma (60mL) and (B, C) following insertion of draining catheter for haematoma drainage assisted with small boluses of tissue plasminogen activator.

A number of randomised controlled trials have assessed the impact of minimally invasive surgery on ICH outcome and were reviewed in a meta-analysis (Zhou *et al.*, 2012) The meta-analysis included 12 trials and 1955 patients and reported a significant reduction in death or dependency at the end of follow up (OR 0.54 95% CI 0.39-0.76, p=0.0004) (Zhou *et al.*, 2012). A large international multi-centre randomised controlled trial – MISTIE III (NCT01827046) study is actively recruiting patients after the initial dose finding and safety study (MISITE II, n=79) demonstrated safety of the procedure and indicated reduction in oedema in surgically treated patients (Mould *et al.*, 2013). MISTIE III is expected to complete recruitment soon. Although there is a theoretical concern that tPA may exacerbate blood-brain-barrier dysfunction and result in increased inflammation and oedema, the results of MISTIE II and other reports suggest intraclot thrombolysis does not exacerbate peri-haematomal oedema (Carhuapoma *et al.*, 2008; Mould *et al.*, 2013; Lian *et al.*, 2014).

1.11.1b External ventricular drain with thrombolysis for ventricular haemorrhage

The presence of ventricular haemorrhage is associated with increased mortality after ICH as it can cause obstructive hydrocephalus and lead to herniation (Tuhrim *et al.*, 2013).
Insertion of external ventricular drain can assist in relief of hydrocephalus and drainage of ventricular blood. Use of intraventricular tPA can increase the rate of ventricular blood drainage and help release cerebral spinal fluid obstruction faster (Findlay et al., 1993). A meta-analysis of 4 randomised controlled trials and 8 observational studies (n=316) demonstrated intraventricular thrombolysis significantly reduced the odds of mortality compared to external ventricular drain alone (OR 0.32 95% CI 0.19-0.52, p<0.00001) (Gaberel et al., 2011). The phase III study of the Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Haemorrhage randomised 500 patients to alteplase (n=249) and or saline (n=251) in patients with obstructive ventricular haemorrhage undergoing insertion of extraventricular drain. Six month outcome was available for 491 patients (alteplase, 246; saline 245) with similar proportions of patients achieving good outcomes (modified Rankin Scale 0-3) in both groups (alteplase 48% vs saline 45%; risk ratio 1.06 95% CI 0.88-1.28, p=0.554). The risk of mortality was lower in alteplase treated groups (18% vs 29%, hazard ratio 0.60 95% CI 0.41-0.86, p=0.006) (Hanley et al., 2017). There are plans for further trials of this approach but currently there has not been a change in guideline recommendations given the lack of reduction in disability.

1.11.1c Surgery decompressive craniectomy

Decompressive hemicraniectomy (DHC) is life saving in ischaemic stroke patients with significant space occupying effect from cerebral oedema (Vahedi et al., 2007; Juttler et al., 2014). Decompressive hemicraniectomy can also be performed in ICH with or without haematoma evacuation (figure 16).
Figure 16. Decompressive hemicraniectomy with partial clot evacuation after intracerebral haemorrhage.

A patient with large ICH with midline shift (A) proceeded to decompressive hemicraniectomy with partial clot evacuation (B). Significant delayed oedema 37 days post ICH onset but no evidence of midline shift (C).

Several retrospective case series and case-control studies have reported safety of the procedure after ICH and reasonable outcome (modified Rankin scale 0-3 achieved in ~50%) at follow up (Crudele et al., 2016). One caveat for decompressive hemicraniectomy is that it may worsen the peri-haematoma oedema (figure 16), although intracranial pressure is not increased due to the craniectomy. The Swiss Trial of Decompressive Craniectomy Versus Best Medical Treatment of Spontaneous Supratentorial Intracerebral Hemorrhage (SWITCH, NCT02258919) is currently recruiting patients with a final sample size of ~300. This study will shed light into the potential role of DHC in the surgical management of ICH patients.

1.11.1d Surgical management of cerebellar and brainstem haemorrhage

The management approach to cerebellar ICH is different to supratentorial ICH because of its proximity to other structures within the posterior cranial fossa. Mass effect can result in obstructive hydrocephalus and tonsilar herniation. Although no randomised controlled studies have been performed (and are unlikely to occur due to lack of equipoise), observational studies have suggested benefit of posterior fossa decompression and haematoma evacuation in patients with reduced GCS, pressure
effect on the fourth ventricle/basal cisterns or hydrocephalus (van Loon et al., 1993; Kirollos et al., 2001). The current American Heart Association and American Stroke Association guidelines endorse clot evacuation in patients with neurological deterioration or brainstem compression and/or obstructive hydrocephalus (Class I, level evidence B) (Hemphill et al., 2015). Treatment with EVD alone is also not recommended due to potential for upward herniation. Surgical evacuation of brainstem haematoma is not recommended due to potential for more harm from the procedure.

1.11.2 Medical management of intracerebral haemorrhage

1.11.2a Haemostatic agent – Factor VIIa
When a cerebral vessel ruptures there is local platelet aggregation and exposure of Factor VIIa to the subendothelium. Factor VIIa forms a complex with tissue factor which converts factor X to Xa with subsequent conversion of prothrombin into thrombin and formation of a haemostatic plug (Mayer 2003; Meretoja and Tatlisumak 2006). This process is amplified with administration of recombinant factor VIIa in pharmacological doses. In a phase II randomised controlled trial (n=399), recombinant factor VIIa administered within 4 hours of ICH onset versus placebo, treatment with recombinant factor VIIa (40, 80 and 160μg/kg) resulted in significantly less haematoma growth compared with placebo (16%, 14% and 11% vs 29%, p=0.01). Mortality was also reduced by 11% in the treatment group (18% vs 29%, p=0.02) (Mayer et al., 2005a). However, in the subsequent phase III trial (n=841, placebo n=268, 20μg/kg factor VIIa n=276, 80μg/kg factor VIIa n=297), despite a reduction in haematoma growth for the higher dose factor VIIa patients compared with placebo (11% vs 26%, p<0.001), there was no difference in the proportion of patients with poor clinical outcome with an increase in more arterial thrombotic events (Mayer et al., 2008).

The pooled results of the Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT, NCT00810888) and the Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT, NCT01359202) studies were presented at the International Stroke Conference in Houston, Texas, February 2017. Both these studies enrolled ICH patients presenting within 5 (STOP-IT) or 6 (SPOTLIGHT) hours of ictus who had also had CTA performed. In both studies, CTA spot sign
positive patients were randomised to treatment with either 80μg/kg of factor VIIa or placebo, while in STOP-IT, spot sign negative patients were enrolled into an observational study. Haematoma growth was assessed at 24 hours with repeat CT brain scan. Recruitment in both trials was stopped early due to completion of funding and slow recruitment. A total of 143 patients (73 patients were spot sign negative) were included in the pooled analysis. There was no difference in the median haematoma growth between the spot sign positive factor VIIa and spot sign positive placebo patients (factor VIIa 6mL vs placebo 9mL, p=0.9) and no difference in 90-day outcome was also noted (p=0.96) (Gladstone 2017). Although the median absolute haematoma growth in spot sign positive patients of 2.5mL was less than expected, spot sign predicted haematoma growth and poor outcome when compared to spot sign negative patients. The triallists concluded that the treatment may have been initiated too late with only about one third of factor VIIa patients treated within 3 hours of symptom onset, and future studies should consider utilising mobile stroke units to facilitate early ICH diagnosis and treatment (Gladstone 2017).

1.11.2b Tranexamic acid.
Tranexamic acid is an anti-fibrinolytic agent commonly used in menorrhagia and acute bleeding in the gastrointestinal and urinary tracts (Sprigg et al., 2014; Law et al., 2017). Its anti-fibrinolytic mechanism derives from binding of the lysine binding site on plasminogen, inhibiting its binding to fibrin and activation of plasmin (Mannucci 1998). A systematic review and meta-analysis identified two randomised controlled studies of tranexamic acid in patients with traumatic brain injury (n=510). Tranexamic acid when administered as a rapid infusion (1g) followed by 8-hour infusion (1g) was associated with reduced risk of haematoma expansion (≥25%, HR 0.76 95% CI 0.58-0.98) (Zehtabchi et al., 2015). The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2, n=20,211) study randomised patients with polytrauma within 8 hours of injury to either tranexamic acid or placebo and demonstrated a significant reduction in all cause mortality (RR 0.91, 95% CI 0.85-0.97, p=0.0035). The risk of death from bleeding was also significantly reduced (RR 0.85, 95% CI 0.76-0.96, p=0.0077) (Shakur et al., 2010). In a Japanese series of ICH patients (n=188), rapid administration of 2g of tranexamic acid resulted in only 8 (4.3%) patients developing haematoma growth (≥20%) on repeat CT scan at 24 hours (Sorimachi et al., 2007a). A Malaysian single-blinded randomised controlled study
randomised 30 patients within 8 hours of ICH onset to either tranexamic acid (1g bolus followed by 1g infusion over 8 hours) or placebo. Placebo patients had significant haematoma expansion (14.33 mL vs 17.99 mL, p=0.001) at 24 hours while the tranexamic acid treated patients did not (10.06 vs 10.08, p=0.313) (Arumugam et al., 2015).

A small pilot study (n=24, 16 with tranexamic acid, 8 placebo) demonstrated feasibility and safety of tranexamic acid (1g bolus followed by 1g infused over 8 hours) in acute ICH. Only one patient (6%) developed a thrombotic complication (deep vein thrombosis) in the tranexamic acid treated group (Sprigg et al., 2014). Ongoing randomised controlled trials using tranexamic acid in ICH are investigating the potential impact of tranexamic acid on haematoma growth and outcome (Meretoja et al., 2014; Sprigg et al., 2016).

1.11.2c Platelet transfusion

Antiplatelet agent use prior to onset of ICH has been shown to be associated with reduced platelet activity, haematoma growth and outcome (Naidech et al., 2009a). The only completed randomised controlled study - platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH) enrolled 190 patients within 6 hours of supratentorial ICH, prior antiplatelet use and GCS >8 to either platelet transfusion (n=97) or standard care (n=93). Patients treated with platelet transfusion had significantly increased risk of 3-month death or dependency (adjusted common OR 2.05 95% CI 1.18-3.56, p=0.0114) (Baharoglu et al., 2016). The increased risk of poor outcome observed in PATCH could potentially be accounted for by increased inflammatory response associated with platelet transfusion (Refaai et al., 2011) which could result in worsening blood-brain-barrier damage and increased oedema and mass effect. Although the increased thromboembolic adverse events in the platelet treated patients was not statistically significant, it could still have contributed to the study results.

1.11.2d Blood pressure lowering

Hypertension is associated with worse outcome after ICH, possibly through increased risk of haematoma expansion (Willmot et al., 2004). The INTERACT 1 pilot study randomized 404 ICH patients to intensive (target 140mmHg systolic) vs guideline-based target (target 180mmHg) within 6 hours of symptom onset. The study found no
safety concerns with treatment tolerated by patients and demonstrated a reduced proportion of patients with haematoma growth in the intensive blood pressure lowering group (13.7% vs 36.3%, p=0.04) (Anderson et al., 2008). The phase 3 INTERACT 2 study randomised 2839 patients to the same treatment protocol as INTERACT 1 with 2794 patients having available follow up information. The study demonstrated intensive blood pressure treatment was associated with a strong trend towards reduced odds of death and disability at 90-days (OR 0.87 95% CI 0.75-1.01, p=0.06) (Anderson et al., 2013). In the secondary outcome analysis, intensive blood pressure lowering was significantly associated with less disability in ordinal analysis of the modified Rankin scale (OR 0.87 95% CI 0.77-1.00, p=0.04). There was no significant difference in the proportion of patients with substantial (>33% or >12.5mL) ICH growth (26.1% vs 26.4%, p=0.899) or absolute ICH growth (adjusted mean growth 3.7 vs 2.3 mL, p=0.18) between the two groups of patients (Anderson et al., 2013).

The Antihypertensive Treatment of Acute Cerebral Haemorrhage 2 (ATACH-2) study included 1000 ICH patients within 4.5 hours from onset randomised to intravenous nicardipine with a blood pressure target of 110-139mmHg in the intensive treatment arm vs 140-179 in the standard treatment arm. In 961 patients with outcome data there was no difference in the risk of 90-day death or disability between the intensive treatment vs standard treatment groups (RR 1.04 95% CI 0.85-1.27 p=0.84) (Qureshi et al., 2016). The study was stopped early because of futility and there was an increased incidence of renal adverse events in the intensive BP lowering group. A further study, the Intracerebral haemorrhage Acute Decreasing Arterial Pressure Trial 2 (ICH-ADAPT 2, NCT 02281838) is currently recruiting to assess whether aggressive lowering of blood pressure would reduce haematoma growth and improve patient outcome.

1.11.2e Anticoagulant reversal
Anticoagulant effects of warfarin can be rapidly reversed using prothrombin complex or fresh frozen plasma with the aim of limiting further bleeding. A large retrospective multi-centre German observational study of 1176 warfarin-associated ICH patients demonstrated that reversal of INR to <1.3 within 4 hours resulted in significantly less patients with haematoma enlargement (>33% growth, 19.8% vs 41.5%, p<0.001) and reduced in-hospital mortality (13.5% vs 20.7%, OR 0.60 95% CI 0.37-0.95, p=0.03)
when compared with patients without rapid anticoagulant reversal (Kuramatsu et al., 2015). A pooled analysis of 1547 warfarin associated ICH patients from 16 stroke registries over 9 countries reported highest case fatality rate and hazard ratio for patients receiving no reversal treatment (61.7%, HR 2.540 95% CI 1.784-3.616, p<0.001), followed by fresh frozen plasma alone (45.6%, HR 1.344 95% CI 0.934-1.934, p=0.112), prothrombin complex alone (37.3% HR 1.445 95% CI 1.014-2.058, p=0.041) compared to combination of fresh frozen plasma and prothrombin complex (27.8%, used as reference) (Parry-Jones et al., 2015a). There was no difference in mortality between fresh frozen plasma or prothrombin complex (p=0.492). A limitation of this analysis is that early palliative care was instituted in half of the patients without reversal treatment. The decision for early palliative approach could have been influenced by local centre treatment guidelines. However in a post hoc shared frailty analysis the results remained consistent suggesting results were not attributable to centre-specific practices which may involve early palliation in patients with poor prognostic features.

The only randomised controlled trial in anticoagulant reversal in warfarin associated ICH (INCH) compared fresh frozen plasma to prothrombin complex in achieving INR normalisation and haematoma growth. The authors originally planned to enroll 74 patients but the study was stopped after enrolling 50 patients due to concerns over more haematoma expansion with fresh frozen plasma group (13/22 (59%) vs 12/27 (44%), p=0.048) (Steiner et al., 2016). Prothrombin complex treated patients were significantly more likely to achieve INR normalisation within three hours of treatment compared with fresh frozen plasma (67% vs 9%, adjusted OR 30.6 95% CI 4.7-197.9, p=0.003). There was also a trend towards less 90-day mortality in prothrombin complex treated patients (19% vs 35%, p=0.14) without a difference in 90-day functional independence (modified Rankin Score 0-3, 37% vs 39%, p=0.47) (Steiner et al., 2016).

The increasing use of DOAC for prevention of AF related thromboembolism will likely result in an increase in DOAC associated ICH but may also result in overall reduction in anticoagulant associated ICH given the reduced risk of haemorrhage compared with warfarin. A recently published multi-national study showed no difference in baseline ICH volume between NOAC and warfarin (14.4mL vs 10.6mL, ...
Despite the lack of specific reversal agents during the DOAC randomized trials, the outcome of ICH in the DOAC patients was no worse than warfarin patients who developed ICH, despite attempted reversal of warfarin (Hart et al., 2012; Hankey et al., 2014; Held et al., 2015). Of the commonly available NOACs (dabigatran, rivaroxaban, apixaban and edoxaban), only dabigatran has a commercially available reversal agent (idarucizumab) which was approved by the Food and Drug Administration and can completely reverse the anticoagulant effect of dabigatran within minutes of a 5g intravenous bolus injection (Pollack et al., 2015; Pollack et al., 2017). Andexanet alpha is a specific reversal agent that neutralizes the anticoagulant effects of both direct and indirect factor Xa inhibitors. In two randomised controlled trials with healthy volunteers, intravenous administration of andexanet alpha temporarily reversed the anticoagulant effect of full dose apixaban (5mg bd) and rivaroxaban (20mg daily) with restoration of thrombin activity (Siegal et al., 2015). A prospective multi-centre study of andexanet alpha infusion for treatment of major haemorrhage associated with factor Xa inhibitors is underway (ANNEXA-4, NCT02329327). The interim results of this study was published in 2016 (n=47, 26 on rivaroxaban, 20 on apixaban and 1 on enoxaparin) and demonstrated significant reduction of factor Xa activity (89% for rivaroxaban and 93% for apixaban) following an initial bolus injection and a subsequent 2-hour infusion of andexanet (Connolly et al., 2016).

1.12 Management of oedema

Several medical management options for oedema treatment can be considered and are discussed in the following paragraphs.

1.12.1 Osmotic agents

Mannitol and hypertonic saline are osmotic agents that can potentially reduce cerebral oedema through increasing intravascular osmolality (Kim et al., 2016). In a randomised controlled trial of 128 ICH patients, treatment with 4 hourly 20% 100mL of mannitol for 5 days, starting within 6 days of onset, did not result in mortality benefit at 1 month (Misra et al., 2005). Further, there was no difference in the number of patients who died from brain herniation. In a post-hoc analysis of the INTERACT 2 study (n=2839), treatment with mannitol did not reduce the odds of 90-day death or
disability (OR 0.87 95% CI 0.71-1.07, p=0.18) (Wang et al., 2015b). Another randomised controlled study (n=216) also did not find a mortality benefit at 6 months in ICH patients treated with intravenous glycerol (Yu et al., 1992). However, none of these studies reported whether there was an effect of osmotic agents on oedema reduction.

1.12.2 Celecoxib

The selective cyclooxygenase-2 inhibitor Celecoxib is a widely used anti-inflammatory agent. In a rat ICH model, intraperitoneal injection of Celecoxib was shown to significantly reduce brain oedema and peri-haematoma inflammatory infiltrate and reduced the degree of neuronal cell death (Chu et al., 2004). In a small randomised controlled trial of 44 Korean ICH patients, administration of 400mg Celecoxib twice a day for 14 days was safe and shown to result in significantly reduced oedema expansion (p=0.005) (Lee et al., 2013).

1.12.3 Fingolimod

Fingolimod is a sphingosine1-phosphate modulator approved for use of relapsing remitting multiple sclerosis. It inhibits lymphocyte egress from lymph nodes to prevent recirculation and trafficking of pathogenic cells into the central nervous system (Fu et al., 2014). In rodent ICH models, daily administration of fingolimod resulted in significant reduction in brain water content, peri-haematoma cell death and local inflammatory infiltrate (Rolland et al., 2013; Lu et al., 2014). In a small clinical trial of 23 ICH patients, treatment of 0.5mg of fingolimod for 3 days was associated with reduced absolute (47 vs 108 mL, p=0.04) and relative oedema at day 7 (relative oedema index 2.5 vs 6.4, p<0.001). A higher proportion (63% vs 0%, p=0.001) of fingolimod treated patients were independent (modified Rankin Score 0-1) at 3 months when compared to controls (Fu et al., 2014).

1.12.4 Deferoxamine

Iron is released as part of the haemoglobin degradation process following ICH. Iron related toxicity is thought to contribute to secondary injury through inflammation and breakdown of the blood-brain-barrier contributing to increased oedema. In murine and pig ICH models, treatment with the iron chelator deferoxamine resulted in a significant reduction in neuronal death and oedema and was associated with improved
neurological outcome (Gu et al., 2009; Okauchi et al., 2010). In a dose finding study, 20 patients with acute ICH were treated with intravenous deferoxamine at 5 different dose tiers for 3 consecutive days without drug related adverse events (Selim et al., 2011). A phase III study, High-Dose Deferoxamine in Intracerebral Haemorrhage (HI-DEF, NCT01662895) will assess the impact of deferoxamine on outcome after ICH and also assess impact of iron chelation treatment on oedema development (Yeatts et al., 2013).

1.12.5 Hypothermia

As discussed in earlier paragraphs, therapeutic hypothermia may alter oedema growth trajectory after ICH (Volbers et al., 2016b) based on retrospective analysis of patients from one centre. Two phase II randomised controlled trials of hypothermia in ICH will assess the feasibility, safety and potential impact on oedema development (Kollmar et al., 2012; Rincon et al., 2014).

1.13 Stroke unit care and management of medical complications

1.13.1 Stroke unit care

Organised stroke unit care involves treatment provided by a specialised multidisciplinary team consisting of stroke physicians / neurologists, nursing and allied health staff. Stroke unit care reduces mortality through prevention and management of complications of immobility including venous thromboembolic prophylaxis and pressure ulcer prevention, management of dysphagia and prevention and treatment of infection (Govan et al., 2007). In a large Swedish cohort study (n=105,043) comparing stroke unit care to non-stroke unit admissions, patients with ICH had significantly reduced odds of death or institutionalisation at 3 months (Terent et al., 2009). In a recent meta-analysis of 8 trials (n=2657), stroke unit care reduced death or dependency (risk ratio, 0.81 95% CI 0.47-0.92, p=0.0009) with no difference in benefit between ICH (risk ratio 0.79 95% CI 0.61-1.00) and ischaemic (risk ratio 0.82 95% CI 0.70-0.97, P_interacion=0.77) stroke patients (Langhorne et al., 2013). Stroke unit care benefitted the full spectrum of patients regardless of age and stroke severity.
1.13.2 Fever
The Quality in Acute Stroke Care (QASC) study randomised 1126 acute stroke patients in stroke units (51 (4.5%) had ICH) to a set of protocolised interventions for managing glucose, fever and swallowing dysfunction versus guideline management. The intervention group had reduced likelihood of 90-day death or disability (42% vs 58%, p=0.002) but interpreting these findings in ICH is difficult due to the small number of patients. It is also unclear which of the three interventions contributed to mortality reduction (Middleton et al., 2011).

1.13.3 Seizures
Treatment with anti-epileptic medication for patients with post ICH seizure is warranted. However, there is debate regarding the role of prophylactic anti-epileptic use. In one study of 98 ICH patients, prophylactic use of phenytoin was associated with increased death or dependency (mRS 4-6) at 3 months (OR 9.0 95% CI 1.2-68.5, p=0.03) (Naidech et al., 2009b). In a small double-blind randomised controlled study (n=72), treatment with sodium valproate for 1 month after ICH did not significantly reduce early (within 14 days of onset, 2.7% vs 11.1% p=0.4) or late seizure occurrence (after 14 days of onset, 16.6% vs 11.1%, p=0.5) (Gilad et al., 2011).

1.13.4 Venous thrombosis prophylaxis and treatment
A number of Clots in Legs Or sTockings after Stroke (CLOTS) studies examined the effectiveness of mechanical means in prevention of venous thrombosis after stroke. The CLOTS I trial randomised 2518 immobile acute stroke patients to routine care plus thigh length graduated compression stockings (n=1256) or to routine care and avoidance of graduated compressing stockings (n=1262). There was no significant reduction in the rates of proximal deep venous thrombosis within 30 days of enrolment (0.5% absolute reduction in stocking group, 95% CI -1.9-2.9) (CLOTS Trial Collaboration 2009). The CLOTS II trial randomised 3114 acute stroke patients to either thigh-length or below-knee stockings and demonstrated that below-knee stockings had higher rates of proximal venous thrombosis (8.8% vs 6.3%) (CLOTS Trial Collaboration 2010). In the multi-centre CLOTS III trial, 2876 stroke patients with randomised to receive treatment with intermittent pneumatic calf compression versus no treatment and included 322 patients with ICH (Dennis et al., 2013). The study found a reduction in the occurrence of proximal venous thrombosis in patients
treated with intermittent pneumatic compression (8.5% vs 12.1%), which was more prominent in ICH patients (6.7% vs 17.0%, OR 0.36 95% CI 0.17-0.75).

An alternative treatment for venous thrombosis is low dose anticoagulation with either unfractionated heparin or low molecular weight heparin. The main concern in ICH is that anticoagulation may worsen haematoma expansion. A meta-analysis of 4 studies including 2 randomised controlled trials (n=1000) assessed the difference in outcomes between anticoagulation and other treatments (elastic stockings, intermittent pneumatic compression). There was no difference in the risk of deep vein thrombosis (4.2% vs 3.3%, RR 0.77 95% CI 0.44-1.32, p=0.36) or mortality (16.1% vs 20.9%, RR 0.76 95% CI 0.57-1.03, p=0.07) but a significant reduction in risk of pulmonary embolism (1.7% vs 2.9%, RR 0.48 95% CI 0.17-0.80, p=0.01) in anticoagulated patients. There was also no significant difference in the rates of any haematoma enlargement (8.0% vs 4.0% RR 1.42 95% CI 0.57-3.53, p=0.45) (Paciaroni et al., 2011). In patients developing venous thrombosis or pulmonary embolism after ICH, it may be reasonable to consider full dose anticoagulation in patients with documented cessation of haematoma growth or alternatively consider insertion of an inferior vena cava filter (Hemphill et al., 2015).

1.13.5 Glycaemic control
The UK Glucose Insulin in Stroke Trial (GIST-UK) enrolled 933 stroke patients with admission glucose between 6.0 to 17.0mMol/L (134 (12.2%) had ICH) to targeted glycaemic control (4.0 to 7.0mMol/L) or no intervention (Gray et al., 2007). There was no reduction in 90-day mortality in the intervention group (OR 1.14 95% CI 0.86-1.51, p=0.37). Although 16% of intervention group developed required rescue intravenous glucose for hypoglycaemia (≤4.0mMol/L), there were no differences in the adverse effects or 90-day mortality (32.9% vs 29.4%, p=0.55). The current American Stroke Association guidelines support avoiding hyperglycaemia in ICH patients, while the European Stroke Organisation does not provide recommendations for glucose management (Steiner et al., 2014; Hemphill et al., 2015).
1.14 Summary

- Intracerebral haemorrhage is devastating with minimal opportunities for effective intervention.
- Haematoma volume is likely the strongest prognostic indicator for outcome. There is growing evidence that oedema is also independently associated with outcome in a volume-dependent manner.
- The evolution of oedema is dynamic and poorly understood and appears to be strongly associated with haematoma and inflammation.
- Interventions that target factors influencing oedema growth may also improve patient outcome.
1.15 Thesis aims

The current focus of ICH treatment is managing the primary injury caused by the haematoma. Ongoing trials are assessing the therapeutic efficacy of haemostatic agents on limiting haematoma growth and the impact of minimally invasive surgical haematoma evacuation on primary injury. There is emerging evidence that secondary injury ensues from development and progression of the peri-haematoma oedema, which appears also to influence ICH outcome in a volume dependent manner. An accurate estimation of haematoma and oedema volume is therefore vital for patient prognostication and in determining the impact of medical and surgical strategies. The association between haematoma volume and oedema growth has been consistently reported in literature however the impact of other modifiable factors such as glycaemic status is less clear. Furthermore there is increasing evidence that the sulphonylurea inhibited SUR1-TRPM4 channel influences oedema growth in ischaemic stroke and the molecular actions of this channel may also contribute to oedema development after ICH. Management of ICH in the future is likely to require a multi-pronged approach in minimising the impact of primary and secondary injury.

The general aims of this dissertation are to improve current understanding of the clinical and imaging factors influencing outcome after intracerebral haemorrhage.

Five studies have been designed to achieve this and the specific aims of the thesis are:

1. To assess the accuracy and reliability of automated software calculation of lesion volume from segmented regions of haemorrhage and oedema.
2. To analyse the association between pre-stroke use of oral anti-diabetic agents sulphonylurea and metformin and outcome after intracerebral haemorrhage
3. To describe the clinical and radiological features, pathogenesis, and outcome of patients with multiple simultaneous intracerebral haemorrhages
4. To report the natural history of peri-haematoma oedema, factors associated with oedema growth, and impact of oedema growth on outcome after intracerebral haemorrhage
5. To analyse the impact of early blood glucose trajectory on outcome and oedema evolution after intracerebral haemorrhage
Chapter II - General methods

This chapter introduces the general data sources used in the studies, software used to perform volumetric segmentation and general statistics used in the analyses. Detailed description of individual study methods will be explored in the respective chapters.

2.1 Data sources

2.1.1 Virtual International Stroke Trial Archive – Intracerebral Haemorrhage (VISTA-ICH)

The pooled repository of international stroke trials – VISTA is an international academic collaborative repository for stroke clinical trials and collects the data in an anonymised manner to allow for novel exploratory analyses (Ali et al., 2012). At the time of conducting PhD studies, VISTA-ICH had comprehensive data available from 8 trials with 3662 patients. Data collected from VISTA-ICH used in the analysis in Chapter IV were baseline medical history including drug use and ICH surgery, baseline stroke severity including NIHSS, GCS, baseline radiological variables including haematoma and oedema volumes, and 90-day mortality. Data from VISTA-ICH were used in the study Chapter V.

2.1.2 The Royal Melbourne Hospital intracerebral haemorrhage study

The Royal Melbourne Hospital (RMH) ICH study included consecutive ICH patients treated at RMH between 1 October 2007 and 31 January 2012. There were 539 ICH patients treated during the study period. In 58 patients (10.8%) baseline brain imaging data in the Digital Imaging and Communications in Medicine (DICOM) format was unavailable. One published analysis from the RMH ICH study assessed the effect of warfarin anticoagulation on haematoma volume and location (Ma et al., 2013). The patients from this study are part of the ongoing prospective RMH stroke registry. The
data and imaging for patients contained in this study were used for data pooling in Chapters IV and V.

2.1.3 Helsinki intracerebral haemorrhage study

The Helsinki ICH Study is a retrospective analysis of consecutive ICH patients admitted to Helsinki University Hospital between January 2005 and March 2010 (Meretoja et al., 2012). Patients with ICH secondary to tumour, trauma, haemorrhagic transformation of ischaemic infarction with or without thrombolysis, and primary subdural, extradural or subarachnoid haemorrhage were excluded. Patients were identified with the ICD-10 code of I61, which in Finland was coded by the treating physician and double checked by the senior physician. Patient information was collected retrospectively from medical records and ‘every patient had been seen by a neurologist with accordingly diligent chart notes’ (Meretoja et al., 2012).

A total of 1013 patients were included in this study which contains comprehensive clinical, laboratory and radiological data on individual patients as well as mortality outcome data. The clinical and imaging data for patients contained in this study were used for data pooling in Chapters III, IV and V. The imaging data was used to perform segmentation (discussed in detail later in this Chapter) and results used for analysis in Chapters VI and VII. The author of this thesis performed the segmentation on all available scans from the Helsinki database, which included over 2000 CT images, blinded to all clinical data.

2.1.4 Salford Royal Hospital intracerebral haemorrhage registry

Salford Royal Hospital is a large tertiary hospital based in the Greater Manchester region in the United Kingdom. The Salford Royal Hospital ICH registry includes patients admitted with between 2008 and 2015. During the performance of the study in Chapter IV, imaging and basic clinical data were available for 316 patients treated at Royal Salford Hospital between January 2013 and May 2015. The imaging data for these patients were pooled with patients from Helsinki ICH study for the study performed in Chapter IV.
2.2 Stroke severity and outcome measures

2.2.1 The National Institutes of Health Stroke Scale (NIHSS)

The NIHSS is an 11 item neurological scale with a maximum score of 42 designed in the late 1980s to coincide with studies of intravenous thrombolysis. (Brott et al., 1989) The NIHSS is scored based on absence or presence of neurological features from different domains including conscious state, language, motor, sensation and inattention/neglect. It has high inter-rater agreement (Brott et al., 1989) and can also be assessed through retrospective chart review (Kasner et al., 1999). The limitation of the NIHSS is that posterior circulation symptoms are under represented (Linfante et al., 2001) while also weighted heavily towards motor, sensory and language domains over vision or cranial nerves. The NIHSS is an objective assessment of stroke severity and is a prognostic indicator of outcome after ICH (Meretoja et al., 2012).

2.2.2 Mortality

Functional scales such as the Barthel Index and modified Rankin Score have been used to assess outcome of stroke patients in both ischaemic stroke (Sulter et al., 1999) and ICH (Anderson et al., 2013; Qureshi et al., 2016). We did not have uniform availability of these scores in the databases used in this thesis, therefore mortality was used as an outcome measure in the studies. Although we may have potentially underestimated the effect of an association with clinical outcome in ICH, mortality is a robust measure of outcome in ICH patients.

2.2.3 ICH Classification system

In Chapter IV the SMASH-U ICH classification system for ICH aetiology (Meretoja et al., 2012) was used. The flow chart illustrates the steps in classifying ICH into 6 different categories (figure 17):
Figure 17. Flow chart for ICH classification using the SMASH-U system, reproduced from Meretoja 2012 (Meretoja et al., 2012).

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Patient Selection and Etiologic Classification</td>
</tr>
<tr>
<td>2.</td>
<td>We used the World Health Organization definition of stroke to differentiate between stroke ICH and nonstroke ICH: “rapidly developing clinical signs of focal or global disturbance of cerebral function leading to death or lasting more than 24 hours with no apparent cause other than a vascular one.”</td>
</tr>
<tr>
<td>3.</td>
<td>None of our patients were free of clinical signs and symptoms at 24 hours. We excluded as nonstrokes the patients with primary subdural/epidural hematoma or traumatic ICH or hemorrhage due to a tumor (nonvascular origin, n1100518). Stroke due to primary subarachnoid hemorrhage with or without ICH and hemorrhagic transformation of a cerebral infarction with or without thrombolytic therapy (n11005179) are not initially ICH and were excluded.</td>
</tr>
<tr>
<td>4.</td>
<td>We included all other ICHs treated at any department of our hospital, whether primary, like with hypertensive or amyloid angiopathy, or secondary, either due to an underlying structural vascular pathology such as arteriovenous malformation or cavernoma, coagulopathy, anticoagulation, or other medication such as systemic thrombolysis of noncerebral thrombosis or any other vascular cause.</td>
</tr>
<tr>
<td>5.</td>
<td>Patients with previous ICH before the study period were included only if they had a new ICH during the study period. Patients with</td>
</tr>
<tr>
<td>6.</td>
<td>imaging or pathology confirmed structural vascular malformation diagnosed at ICH site</td>
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<td>7.</td>
<td>History, imaging or pathology of:</td>
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<tr>
<td>8.</td>
<td>• Traumatic ICH,</td>
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<tr>
<td>9.</td>
<td>• Sub-/ epidural hemorrhage or</td>
</tr>
<tr>
<td>10.</td>
<td>• Hemorrhage from co-localized tumor</td>
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<tr>
<td>11.</td>
<td>Non-stroke</td>
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<tr>
<td>12.</td>
<td>Yes</td>
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<tr>
<td>13.</td>
<td>No</td>
</tr>
<tr>
<td>14.</td>
<td>Imaging or pathology of primary:</td>
</tr>
<tr>
<td>15.</td>
<td>• Subarachnoid hemorrhage or</td>
</tr>
<tr>
<td>16.</td>
<td>• Ischemic stroke (IS) with hemorrhagic transformation, also after thrombolytic therapy</td>
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<tr>
<td>17.</td>
<td>Stroke, non-ICH</td>
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<tr>
<td>18.</td>
<td>Yes</td>
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<tr>
<td>19.</td>
<td>No</td>
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<tr>
<td>20.</td>
<td>Systemic or other determined cause for ICH a, except for anticoagulation, hypertension or amyloid angiopathy</td>
</tr>
<tr>
<td>21.</td>
<td>Systemic/other disease</td>
</tr>
<tr>
<td>22.</td>
<td>Yes</td>
</tr>
<tr>
<td>23.</td>
<td>No</td>
</tr>
<tr>
<td>24.</td>
<td>Warfarin with INR ≥ 2.0, novel oral anticoagulants within 3 days, full-dose heparin, or non-IS systemic thrombolysis</td>
</tr>
<tr>
<td>25.</td>
<td>Medication</td>
</tr>
<tr>
<td>26.</td>
<td>Yes</td>
</tr>
<tr>
<td>27.</td>
<td>No</td>
</tr>
<tr>
<td>28.</td>
<td>Amyloid angiopathy</td>
</tr>
<tr>
<td>29.</td>
<td>Yes</td>
</tr>
<tr>
<td>30.</td>
<td>Lobar, cortical, or corticosubcortical hemorrhage and age ≥ 55</td>
</tr>
<tr>
<td>31.</td>
<td>Hypertension</td>
</tr>
<tr>
<td>32.</td>
<td>Yes</td>
</tr>
<tr>
<td>33.</td>
<td>No</td>
</tr>
<tr>
<td>34.</td>
<td>Undetermined</td>
</tr>
<tr>
<td>35.</td>
<td>Deep or infratentorial hemorrhage with pre-ICH hypertension b</td>
</tr>
<tr>
<td>36.</td>
<td>No</td>
</tr>
<tr>
<td>37.</td>
<td>No</td>
</tr>
</tbody>
</table>

a Liver cirrhosis implicated when known liver disease combined with spontaneously elevated INR or liver enzymes >3 x upper limit of the reference range, and thrombocytopenia when thrombocyte count <50 E9/L.

b Hypertension defined as: a) most recent pre-ICH blood pressure ≥ 160/100 mmHg, either on or off antihypertensive therapy or, when pre-ICH blood pressure was not known, either b) mention of pre-ICH elevated blood pressure by patient, relative, or medical records together with a left ventricular hypertrophy as a biomarker of hypertension, or c) any pre-ICH use of blood pressure medication.

This image/material has been removed by the author of this thesis for copyright reasons.
2.3 Computer assisted planimetry

Semi-automated segmentation of haematoma and peri-haematomal oedema was performed to derive volume output for these regions of interest (ROI). Below outlines the technique used and the steps used in deriving volume output.

2.3.1 Semi-automated planimetry

A Hounsfield Unit (HU) based threshold approach was used to segment ROIs using the method developed by Volbers et al (Volbers et al., 2011). In this thesis, segmentation was performed using Analyze 12.0 software (Biomedical Imaging Resource; Mayo Clinic) and Osirix 6.5 (Pixmeo; Geneva; Switzerland). A limiting boundary was placed around the ICH and oedema complex to exclude ventricles and other structures and to limit the segmentation to contents contained within this boundary. Following this a seed point was placed within the ROI to enable segmentation. For oedema segmentation, the lower HU limit is fixed at 5 with the upper boundary manually adjusted to a maximum of 33 HU range using visual inspection and comparison to the contralateral hemisphere for background leukoaraiosis. For ICH segmentation the HU range was kept within 44-100 HU and manual editing of ROI was allowed at the rater’s discretion.

2.3.2 Analyze 12.0

Analyze is a software that contains tools for imaging processing, visualisation and analysis. It allows for 3-dimensional visualisation of ROIs and adjustments. Volume output for ROIs can be automatically derived from the software by the sum of voxels contained in the ROIs. Semi-automated segmentation on Analyze is demonstrated on figure 18. Analyze is available commercially either for purchase outright for a one off fee or for renewal annually with a license fee. Information and software support for Analyze is at http://analyzedirect.com/analyze-12-0/
2.3.3 Osirix 6.5

Osirix is an open source imaging processing software utilising images stored in the DICOM format. Osirix enables imaging processing and visualisation in 3-dimensional view and is able to produce ROI volumes automatically using by multiplying the slice thickness with ROI area. Semi-automated segmentation is similar to Analyze and is represented on Figure 19. One major difference is that Osirix does not have a boundary tool similar to Analyze (Figure 19, step 2) therefore masking the background non-affected brain regions is required to perform segmentation (Figure 19, steps 3,4). A basic version of Osirix is available as freeware and can be downloaded from [http://www.osirix-viewer.com/AboutOsiriX.html](http://www.osirix-viewer.com/AboutOsiriX.html)

Figure 19. Steps to semi-automated segmentation of oedema on Osirix
2.4 General statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS 22 - 23, IBM, Armonk, New York) in all the chapters. Additionally R 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and the ‘MatchIt’ package were used for additional analyses in Chapters IV, V and VII. Specific statistical analyses are elaborated in each Chapter. A p value of <0.05 was considered statistically significant.
Chapter III: Reliability of semi-automated planimetry and impact of voxel depth processing on volume output

3.1 Introduction and summary

Baseline haematoma volume and haematoma growth are two important determinants of ICH outcome (Davis et al., 2006; Delcourt et al., 2012). Haematoma growth has been the focus of previous and ongoing randomised controlled medical management trials (Mayer et al., 2008; Anderson et al., 2013; Meretoja et al., 2014; Sprigg et al., 2016; Gladstone 2017). Oedema growth is also emerging as an important prognostic factor after ICH (Murthy et al., 2015; Yang et al., 2015). Oedema evolution is strongly associated with baseline haematoma volume (Arima et al., 2009). It is therefore important to have a reliable, accurate and accessible method for calculating ICH and oedema volumes for the purposes of assessing the impact of an intervention or investigating factors influencing haematoma or oedema growth.

In this study we assessed the performance and reliability of semi-automated planimetric segmentation of haematoma and oedema using two commonly used planimetric softwares Osirix and Analyze. One hundred patients were randomly selected from the Helsinki ICH study (50 patients) and Salford ICH registry (50 patients) and 3 raters segmented haematoma and oedema using both softwares. In performing the study we discovered an intrinsic fault in both softwares in scans with variable slice thickness as the software assumed uniform thickness and extrapolated thickness from the lowest (infratentorial) slice to the entire series. This resulted in a consistent deviation of software reported volumes by up to 41% when compared to true volume derived from an in-house method that adjusts for varying slice thickness and also for gantry tilt. Semi-automated planimetric segmentation otherwise was found to be reliable, provided that the best practice method for volume calculation is used. As part of the publication we have made available a plugin that provides this output automatically for Osirix and also the technical code for Analyze.
Software output from semi-automated planimetry can underestimate intracerebral haemorrhage and peri-haematomal oedema volumes by up to 41 %

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Abstract

Haematoma and oedema size determines outcome after intracerebral haemorrhage (ICH), with each added 10 % volume increasing mortality by 5 %. We assessed the reliability of semi-automated computed tomography planimetry using Analyze and Osirix softwares.

Methods

We randomly selected 100 scans from 1329 ICH patients from two centres. We used Hounsfield Unit thresholds of 5–33 for oedema and 44–100 for ICH. Three raters segmented all scans using both softwares and 20 scans repeated for intra-rater reliability and segmentation timing. Volumes reported by Analyze and Osirix were compared to volume estimates calculated using the best practice method, taking effective individual slice thickness, i.e. voxel depth, into account.

Results

There was excellent overall inter-rater, intra-rater and inter-software reliability, all intraclass correlation coefficients >0.918. Analyze and Osirix produced similar haematoma (mean difference: Analyze − Osirix = 1.5 ± 5.2 mL, 6 %, p ≤ 0.001) and oedema volumes (−0.6 ± 12.6 mL, −3 %, p = 0.377). Compared to a best practice approach to volume calculation, the automated haematoma volume output was 2.6 mL (−11 %) too small with Analyze and 4.0 mL (−18 %) too small with Osirix, whilst the oedema volumes were 2.5 mL (−12 %) and 5.5 mL (−25 %) too small, correspondingly. In scans with variable slice thickness, the volume underestimations were larger, −29%/−36 % for ICH and −29%/−41 % for oedema. Mean segmentation times were 6:53 ± 4:02 min with Analyze and 9:06 ± 5:24 min with Osirix (p < 0.001).

Conclusion

Our results demonstrate that the method used to determine voxel depth can influence the final volume output markedly. Results of clinical and collaborative studies need to be considered in the context of these methodological differences.

Keywords

Intracerebral haemorrhage · Oedema · Planimetry · Validation · Reliability

Introduction

Intracerebral haemorrhage (ICH) is a highly fatal stroke subtype, and the only proven treatments are blood pressure control and stroke unit care [1, 2]. Primary injury results from direct mechanical pressure of the haematoma in a volume-dependent manner [3]. Secondary injury ensues from peri-haematomal oedema [4], with emerging evidence of oedema’s...
association with poor clinical outcome [5]. Effective oedema management may improve outcome and is the target of several early phase clinical trials [6–9]. Accurate volumetric assessment of both ICH and oedema is therefore vital to the analysis of clinical and collaborative studies.

The volume of tissue with oedema and ICH can be quantified on computed tomography (CT) using Hounsfield unit (HU) threshold semi-automated segmentation [10–14]. From a technical perspective, the most accurate measure of volume of a segmented region is the cumulative total volume of the voxels contained within this region. In turn, the individual voxel volume is determined by the product of voxel area and voxel depth. The voxel width and height, which determine the voxel area, are easily accessible in the Digital Imaging and Communications in Medicine (DICOM) header. The voxel depth that should be used for volume calculation is the distance between slice centres. This information is generally not directly available in the DICOM header, but must be calculated based on other spatial information in the header. The method with which voxel depth is calculated by imaging analysis software has not been explored in detail in published studies. Several softwares are available for segmentation, but no reports have directly assessed the reliability of planimetric measurements between softwares.

The aims of this study were two fold. First, we assessed the reliability and time taken for segmentation using semi-automated planimetry between Analyze 12.0 (Biomedical Imaging Resource, Mayo Clinic) and Osirix 6.5 (Pixmeo, Geneva, Switzerland). Secondly, we analysed the impact of different methods for voxel depth estimation on the final estimated volumes. We hypothesised that the segmented volumes and times taken for segmentation are different between Analyze and Osirix and that the volumes are influenced by the method of voxel depth determination.

Methods

Image selection

A convenient sample of 100 cases was chosen for this study. The baseline scans of randomly selected patients from the combined database of 1329 consecutive ICH patients from Helsinki University Hospital, Finland, and Salford Royal Hospital, UK, were used after institutional approval. Fifty scans were randomly chosen from each centre. The Helsinki ICH study is a retrospective analysis of consecutive ICH patients admitted to Helsinki University Central Hospital between January 2005 and March 2010 [15]. Patients from Salford Royal Hospital were ICH patients treated at the centre between January 2013 and May 2015.

Image processing and segmentation

The de-identified images were transferred in the DICOM format to a central workstation. The DICOMs were then converted into Neuroimaging Informatics Technology Initiative (NIfTI) format using a DCM-to-NIfTI conversion tool before loading on Analyze. The NIfTI allows the individual DICOM images to be saved and loaded from one single file. For Osirix, the DICOMs were loaded directly.

Segmentation steps

The semi-automated method reported by Volbers et al. was used [10]. A limit boundary was placed around the ICH and oedema complex, following which a seed point was placed within the region of interest (ROI). For oedema segmentation, the lower HU limit is fixed at 5, with the upper boundary manually adjusted to a maximum of 33-HU range using visual inspection and comparison to the contralateral hemisphere for background leucoaraisois. For ICH segmentation, the HU range was kept within 44–100 and manual editing of ROI was allowed at the rater’s discretion.

Video demonstrations of the segmentation process on each of the softwares are available in the Electronic supplementary material.

Rater workflow

All 100 scans were segmented using Analyze and Osirix by each rater (T.Y.W., O.S., and R.H.) independently and blinded to patient’s clinical details. T.Y.W. is a neurologist with 6 years of experience in stroke imaging. Twenty scans (ten from Helsinki and ten from Salford) were chosen randomly and repeat segmentation was performed in these for intra-rater assessment. Intra-rater assessment was performed after a minimal interval of 7 days. The time taken to perform segmentation for each software was measured for the intra-rater scans.

ROI volume calculation

The volume estimates were determined by automated software output (‘Sampling Options’ in Analyze and ‘ROI manager’ in Osirix) and then by subjecting the software outputs to the “best practice” volume estimation. The best practice volume was calculated using an in-house script developed using Matlab (The MathWorks, Inc., MA, USA; Supplementary Table). To this end, the ROI object files from Analyze were used whilst the ROI segmented on Osirix was exported in DICOM format using an in-house plug-in (Supplementary File). The Matlab script
determined the number of voxels within the ROI, which was then multiplied by the voxel volume. The voxel volume was derived from the product of voxel width and voxel height (DICOM header 0028, 0030) and voxel depth. The voxel depth may or may not be equivalent to the slice thickness presented in the DICOM header (0018, 0050), which is not well defined in the DICOM standard and used differently between scanner manufacturers. Therefore, the in-house script uses the best practice method for determining inter-slice distance, which is to determine the normal vector to the image slice orientation (identical for all slices) using ‘Image Orientation Patient’ (DICOM header 0020, 0037).

The location of each slice ‘Image Position Patient’ (IPP; DICOM header 0020, 0032) is then projected onto the slice normal vector, producing one value per slice expressing the location of the slice on the slice normal as a scalar value (Zpos). This calculation is not influenced by gantry tilt, which can overestimate the voxel depth by approximately 5% (Supplementary Fig. 1).

The Zpos was then used to calculate the voxel depth using the equation,

\[
\text{Voxel depth} = \frac{|Zpos(n + 1) - Zpos(n)|}{2} + \frac{|Zpos(n) - Zpos(n - 1)|}{2}
\]

where \( n \) is the image slice, \((n - 1)\) the image slice below and \((n + 1)\) the slice above. For the first and last slices of the scan, we considered the thickness to be the same as the second slice and the penultimate slice, respectively. This calculation approximates the slice distance not just between slices with identical distance between them but also in the interface where slice thickness changes from, for example, 7.5 to 5 mm, where an overlap (Fig. 1a) can be present. Our in-house method adjusts for any slice overlap and is direction-insensitive (Fig. 1b). We will demonstrate using a case illustration the impact of varying voxel depth on volume output. We developed this approach because the Z position within IPP is direction- and gantry tilt-sensitive and can overestimate the volume when slice overlap is present.

### Statistical analysis

Intraclass correlation coefficients (ICCs) were calculated using two-way random effects model and used to measure inter-rater and intra-rater reliability for ICH and oedema. An ICC was considered moderate agreement if 0.41–0.60, substantial agreement if 0.61–0.80 and excellent if 0.81–1.00 [16]. Bland-Altman plots were used to assess for systematic bias. Paired t test or one-way analysis of variance (ANOVA) was used to compare means, where appropriate. A \( p \) value \(<0.05\) was considered significant. All statistics were performed using SPSS 22 (IBM, Armonk, NY).

### Reporting standards

This study was reported in accordance with the Guidelines for Reporting Reliability and Agreement Studies [17].

### Results

#### Patient characteristics

Of the 100 scans included in this study, 87 were performed within 24 h of ictus. The median age was 69 years, 48% were men, baseline median National Institutes of Health Stroke Scale score was 10, median time to scan was 2.8 h, and ICH location was lobar in 36%, deep in 43% and infratentorial in 10%.

#### Volumetric output and agreement statistics

The mean ± standard deviation haematoma volumes segmented on Analyze were 23.4 ± 29.6 and 20.9 ± 25.6 mL for oedema. The overall inter-rater ICCs were 0.994 for ICH and 0.952 for oedema; the intra-rater ICCs were 0.998 for ICH and 0.983 for oedema. The mean volumes for haematoma and oedema performed on Osirix were 21.9 ± 27.0 and 21.5 ± 24.4 mL, respectively. The inter-rater ICCs were 0.997 for ICH and 0.944 for oedema, and the intra-rater ICCs were 0.996 for ICH and 0.918 for oedema. The inter-software ICCs were 0.991 for ICH and 0.932 for oedema (Table 1). ICH volume was 1.5 mL (±5.2 mL, 6%, \( p \leq 0.001 \)) larger in Analyze and oedema was 0.6 mL (±12.5 mL, 3%, \( p = 0.377 \)) larger in Osirix.

The difference in the ICH or oedema volumes obtained between raters was not statistically significant (Table 2). The Bland-Altman plots for inter-rater agreement (Fig. 2 and Supplementary Fig. 2), presented as volume difference between raters 1 and 2, raters 2 and 3, and raters 1 and 3, demonstrated bias values of 0.6, −1.1 and −0.5 mL, respectively, for ICH and 0.5, −0.4 and 0.1 mL, respectively, for oedema segmented on Analyze. The inter-rater bias values for Osirix were 1.4, −1.4 and 0 mL for ICH and 6.7, −1.8 and 4.9 mL for oedema.

The mean segmentation times were 6:53 ± 4:02 min with Analyze and 9:06 ± 5:24 min with Osirix, with a difference of 2:13 ± 3:10 min (\( p < 0.001 \)) in favour of Analyze.

#### Comparing in-house method with Analyze automated output

The ICCs between our in-house method and Analyze’s automated output were 0.986 and 0.980 respectively for ICH and oedema. The automated output underestimated ICH by 2.6 mL (−11%, \( p < 0.001 \)) and oedema by 2.5 mL (−12%, \( p < 0.001 \); Table 3 and Figs. 3 and 4). When analysis was
restricted to scans with variable slice thickness (n = 50), the underestimation increased to 6.4 mL (−29%, p < 0.001) for ICH and 6.0 mL (−29%, p < 0.001) for oedema. The automated output from Analyze overestimated ICH by 1.3 mL.
Comparing in-house method with Osirix automated output

The analysis was performed on 98 patients as automated output failed in two patients with ROIs limited to a single CT image slice. The ICCs between the in-house method and Osirix automated output were 0.983 for ICH and 0.921 for oedema (Table 3). The automated output underestimated ICH by 4.0 mL (−18 %, \( p < 0.001 \)) and oedema by 5.5 mL (−25 %, \( p < 0.001 \)). The underestimations in scans with uniform slice thickness were 7.5 mL (−36 %, \( p < 0.001 \)) for ICH and 9.4 mL (−41 %, \( p < 0.001 \)) for oedema. The differences for scans with variable slice thickness were −0.3 mL (−1 %, \( p = 0.045 \)) for ICH and −1.7 mL (−8 %, \( p < 0.001 \)) for oedema. The Bland–Altman plots for these comparisons are in Figs. 3 and 4.

Influence of calculated voxel depth/slice thickness on volume output

The detailed workflow for ROI volume calculation for a case with variable slice thickness and a case with uniform thickness is represented in the supplementary online spreadsheet. The non-gantry-adjusted voxel depth from the infratentorial region was used as the effective voxel depth in both softwares to calculate volume in the automated output when scans were loaded as a single series (Fig. 1c). When compared to our in-house method, there were underestimations of 12 and 24 % using automated outputs from Analyze and Osirix, respectively, in the case with variable thickness. For the case with uniform thickness, Analyze overestimated by 1 % whilst Osirix underestimated volume by 7 %.

Discussion

The main findings of our study are twofold. Firstly, there is excellent inter-rater, intra-rater and inter-software reliability in semi-automated segmentation of ICH and oedema. Secondly, our results demonstrate that the automated outputs from the two softwares consistently underestimate volumes in scans with variable slice thickness by up to 41 %.

Reliability of semi-automated planimetry

We demonstrated excellent inter-rater and intra-rater reliability in both Analyze and Osirix using a validated semi-automated planimetry approach [10]. The reliability of the ICC measurement in our study is consistent with that reported in the literature (inter-rater and intra-rater ICCs >0.900) [12, 14, 18]. Divani et al. demonstrated in a simulated cadaveric ICH model that Analyze software and Medical Imaging Processing, Analysis and Visualization (Center for Information Technology, National Institutes of Health, Bethesda, MD) software produced less error than the ABC/2 method when compared to the actual volume of simulated blood injected, but the authors did not directly compare the volumes produced by the different softwares [19]. To our knowledge, our report is the first to directly compare ICH and oedema volume outputs from different softwares.

Table 1 Inter-rater, intra-rater and inter-software intraclass correlation coefficients

<table>
<thead>
<tr>
<th></th>
<th>Analyze (n = 100)</th>
<th>Osirix (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inter-rater ICC</td>
<td>Intra-rater ICC</td>
</tr>
<tr>
<td></td>
<td>(95 % CI)</td>
<td>(95 % CI)</td>
</tr>
<tr>
<td>All ICH</td>
<td>0.994 (0.992–0.996)</td>
<td>0.997 (0.996–0.998)</td>
</tr>
<tr>
<td>All oedema</td>
<td>0.952 (0.933–0.966)</td>
<td>0.944 (0.922–0.961)</td>
</tr>
</tbody>
</table>

Table 2 Mean volume output of intracerebral haemorrhage and oedema

<table>
<thead>
<tr>
<th></th>
<th>Analyze (n = 100)</th>
<th>Osirix (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICH, mean ± SD (mL)</td>
<td>Oedema, mean ± SD (mL)</td>
</tr>
<tr>
<td></td>
<td>ICH, mean ± SD (mL)</td>
<td>Oedema, mean ± SD (mL)</td>
</tr>
<tr>
<td>Rater 1</td>
<td>23.4 ± 28.7</td>
<td>21.1 ± 27.3</td>
</tr>
<tr>
<td>Rater 2</td>
<td>22.8 ± 28.5</td>
<td>20.6 ± 21.4</td>
</tr>
<tr>
<td>Rater 3</td>
<td>23.9 ± 31.8</td>
<td>21.0 ± 27.9</td>
</tr>
<tr>
<td>( p ) value*</td>
<td>0.97</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*One-way ANOVA
The oedema inter-rater ICCs are also in agreement with the largest oedema study to date—the pooled analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT) using the same semi-

intrarater ICC 0.999

Interrater ICC 0.988

Rater 2 intrarater ICC 0.999

Interrater ICC 0.992

Rater 3 intrarater ICC 0.992

Interrater ICC 0.996

Rater 1 intrarater ICC 0.992

Interrater ICC 0.995

Rater 2 intrarater ICC 0.999

Interrater ICC 0.989

Rater 3 intrarater ICC 0.992

The oedema inter-rater ICCs are also in agreement with the largest oedema study to date—the pooled analysis of the both had large right frontotemporal hematomas with heterogeneous density. The other outlier had moderate movement artefact together with moderate ventricular hemorrhage. Osirix outliers: The outliers with <50 mL ICH had large volume ventricular hemorrhage and the other outliers had heterogeneous ICH density.

Table 3  Reliability statistics and volume difference between in-house technique and automated outputs from Analyze and Osirix

<table>
<thead>
<tr>
<th></th>
<th>Automated output, mean ± SD (mL)</th>
<th>In-house output, mean ± SD (mL)</th>
<th>Difference (mL)</th>
<th>p value*</th>
<th>ICC (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analyze</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full sample (n = 100)</td>
<td>ICH 20.8 ± 28.5</td>
<td>23.4 ± 29.6</td>
<td>−2.6 (−11 %)</td>
<td>&lt;0.001</td>
<td>0.986 (0.983–0.989)</td>
</tr>
<tr>
<td></td>
<td>Oedema 18.4 ± 23.7</td>
<td>20.9 ± 25.6</td>
<td>−2.5 (−12 %)</td>
<td>&lt;0.001</td>
<td>0.980 (0.975–0.984)</td>
</tr>
<tr>
<td>Variable thickness (n = 50)</td>
<td>ICH 15.4 ± 17.3</td>
<td>21.8 ± 25.1</td>
<td>−6.4 (−29 %)</td>
<td>&lt;0.001</td>
<td>0.968 (0.956–0.977)</td>
</tr>
<tr>
<td></td>
<td>Oedema 14.6 ± 17.3</td>
<td>20.6 ± 24.5</td>
<td>−6.0 (−29 %)</td>
<td>&lt;0.001</td>
<td>0.961 (0.947–0.972)</td>
</tr>
<tr>
<td>Uniform thickness (n = 50)</td>
<td>ICH 26.3 ± 35.5</td>
<td>25.0 ± 33.5</td>
<td>1.3 (±5 %)</td>
<td>&lt;0.001</td>
<td>0.999 (0.999–0.999)</td>
</tr>
<tr>
<td></td>
<td>Oedema 22.2 ± 27.3</td>
<td>21.2 ± 26.9</td>
<td>1.0 (±5 %)</td>
<td>&lt;0.001</td>
<td>0.999 (0.998–0.999)</td>
</tr>
<tr>
<td><strong>Osirix</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full sample (n = 98)</td>
<td>ICH 18.4 ± 22.3</td>
<td>22.4 ± 27.1</td>
<td>−4.0 (−18 %)</td>
<td>&lt;0.001</td>
<td>0.983 (0.979–0.987)</td>
</tr>
<tr>
<td></td>
<td>Oedema 16.5 ± 20.8</td>
<td>22.0 ± 24.5</td>
<td>−5.5 (−25 %)</td>
<td>&lt;0.001</td>
<td>0.921 (0.901–0.937)</td>
</tr>
<tr>
<td>Variable thickness (n = 49)</td>
<td>ICH 13.6 ± 16.2</td>
<td>21.1 ± 23.6</td>
<td>−7.5 (−36 %)</td>
<td>&lt;0.001</td>
<td>0.961 (0.946–0.972)</td>
</tr>
<tr>
<td></td>
<td>Oedema 13.5 ± 17.0</td>
<td>22.9 ± 25.1</td>
<td>−9.4 (−41 %)</td>
<td>&lt;0.001</td>
<td>0.957 (0.940–0.969)</td>
</tr>
<tr>
<td>Uniform thickness (n = 49)</td>
<td>ICH 23.3 ± 31.2</td>
<td>23.6 ± 30.2</td>
<td>0.3 (−1 %)</td>
<td>0.045</td>
<td>0.999 (0.999–0.999)</td>
</tr>
<tr>
<td></td>
<td>Oedema 19.4 ± 23.8</td>
<td>21.1 ± 23.9</td>
<td>−1.7 (−8 %)</td>
<td>&lt;0.001</td>
<td>0.949 (0.930–0.963)</td>
</tr>
</tbody>
</table>

*Paired t test

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Fig. 2 Bland–Altman plots for haematoma segmentation. Bland–Altman plots with intraclass correlation coefficients (ICC) for semi-automated planimetry of hematoma segmentation on Analyze and Osirix. Solid line represents the mean difference and dotted lines the limits of 95 % agreement. Analyze outliers: the two outliers with approximately 120 mL ICH both had large right frontotemporal hematomas with heterogeneous density. The other outlier had moderate movement artefact together with moderate ventricular hemorrhage. Osirix outliers: The outliers with <50 mL ICH had large volume ventricular hemorrhage and the other outliers had heterogeneous ICH density.
automated approach ($n = 1138, \text{MIS}^\text{3.2} \text{ software})\); oedema inter-rater ICCs of 0.91 for INTERACT 1 and 0.93 for INTERACT 2; ICH ICCs not reported) [5]. Other threshold-based planimetry segmentation, including the methods proposed by McCourt et al. (inter-rater ICC for oedema at 24 h of 0.99) [13] using an upper HU limit for oedema of 23 and the edge detection technique by Urday et al. (inter-rater and intra-rater ICCs both 0.99) [11], have also used Analyze and demonstrated excellent reliability. Osirix was also used in the Minimally Invasive Surgery and rt-PTA in ICH Evacuation (MISTIE) phase II study for the assessment of ICH and oedema volumes, but rater reliability assessment was not reported [20].

Although excellent ICCs and similar volumes were demonstrated between Analyze and Osirix, there is more inter-rater oedema variability with Osirix. The variability in oedema volume in Osirix could have resulted from the need to ‘black out’ brain regions (Online Supplementary Video) outside of the peri-haematomal region, which may interfere the rater’s ability to distinguish oedema from leucoaraiosis without visibility of the contralateral hemisphere.

Implications for clinical studies

We observed 3–4 mL or 11–18 % underestimation of ICH volume and 3–6 mL or 12–25 % underestimation of oedema volume using the automated software outputs. These are substantial errors in measurement, as a 1 mL increase in ICH volume has been associated with a 5 %
An increase in death and dependency \cite{21} and a 10\% increase in ICH volume with a 5\% increase in overall mortality \cite{22}. The $>6$ mL difference in ICH between our in-house output and the automated output in scans with variable slice thickness may influence the outcome of clinical studies. The 6 mL difference is defined in some ongoing ICH clinical trials as the marker of significant haematoma expansion \cite{23}. Furthermore, there is emerging evidence of the volume-dependent effect of peri-haematoma oedema on outcome \cite{5, 24, 25}. The largest analysis of oedema on outcome comes from the pooled analysis of the INTERACT studies, demonstrating that absolute oedema growth at 24 h was independently associated with increased odds of death or dependency at 90 days ($OR = 1.17$ (1.02–1.33), $p = 0.025$) \cite{5}. In this analysis, per millilitre of oedema growth is associated with a 3\% increase of poor outcome, and a 10 mL growth increased the risk of poor outcome by 40\%. We have identified significant volume underestimation in patients with variable slice thickness, and given the volume-dependent effect of ICH and oedema on outcome, the results of future studies will need to be considered in the context of these findings.

We have also demonstrated a 2-min (24\%) difference in segmentation time per scan in favour of Analyze over Osirix. Analyze is available commercially for an annual licence renewal fee or outright purchase, whilst the basic version of Osirix is a downloadable freeware. The cost of software and time taken for segmentation may influence the choice of software by researchers.

**Fig. 4** Bland–Altman plots for oedema volume difference between software output and in-house method. Bland–Altman plots comparing oedema volume produced by software output from Analyze (top panels) by uniform ($n = 50$) or variable ($n = 50$) image slice thickness. Oedema volume comparisons with Osirix (bottom panels) were available for 49 patients with uniform slice thickness and 49 patients with variable slice thickness as automated output failed in two patients with the region of interest limited to one single image slice. Solid line represents the mean difference and dotted lines the limits of 95\% agreement.
Failure of automated output in variable slice thickness

Our results indicate that software-generated volume output is unreliable in scans with variable slice thickness. Analyze underestimates volume on average by nearly 30 % whilst Osirix by approximately 40 %. Our analysis indicates that the software uses the voxel depth of the infratentorial slices for volume calculation when the scans are loaded as one single series (Fig. 1c and Supplementary Excel File). A solution to this issue is loading the supratentorial and infratentorial regions separately, which can be performed using the ‘DICOM tool’ function in Analyze and manually in Osirix. This approach still requires the software to adjust for effect of gantry tilt on voxel depth, which can additionally overestimate by including the overlap region at the interchange between supratentorial and infratentorial regions. This approach would also increase segmentation and processing time and impact on research output productivity. The automated output from Osirix uses the average area between adjacent image slices multiplied by voxel depth to calculate volume (Supplementary Excel File), and consequently, ROIs present on a single image slice could not be derived from the automated output and is an additional source of underestimation. Previous studies have also included patients with variable slice thickness [10, 14, 25]. In the Efficacy of Nitric Oxide in Stroke Study, the investigators were unable to obtain automated output from Osirix in scans with variable slice thickness and had to multiply the surface area by scan thickness to derive volume [14], whilst other studies did not specifically address how voxel depth was calculated [10, 25]. Our in-house method remains an estimate of the factual volume, but minimises potential for error.

Limitations

This study is limited by the inclusion of mainly early scans, with the majority of the scans performed within 24 h. Oedema increases in volume and evolves over a period of 2 weeks, whilst haematoma resorption takes place over the same time. Our study could not address whether semi-automated segmentation is also reliable for late oedema. We also did not have magnetic resonance imaging (MRI) scans to correlate with CT-based segmentation as MRI is not routinely performed for stroke diagnosis at the study centres. The reliability of the threshold-based approach against MRI has already been demonstrated previously [10, 11]. Thirdly, our in-house calculation requires additional technical expertise and manipulation beyond the planimetric segmentation, which may not be available to all research centres. A new version of Osirix (7.5) was made available after completion of the study, but the approach to segmentation is unchanged. Since completion of this work, we have modified the in-house Osirix plug-in (developed by S.C.) to enable automated volumetric output using the best practice method, which is available for download with this manuscript. Our work will help others in the future by providing codes and plug-in to achieve the corrections needed to take true slice thickness into account.

Conclusion

Our results demonstrate that semi-automated volumetric segmentation of haematoma and oedema provides consistent inter-rater, intra-rater and inter-software results and can be performed in a timely manner. The method used to determine voxel depth can substantially influence volumetric measurement, and this is of critical importance to the accuracy of multicentre studies.

Acknowledgments

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Compliance with ethical standards

We declare that all human and animal studies have been approved by the Helsinki University Hospital and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that given no identifiable patient data is presented, Helsinki University Hospital waived informed consent for this observational registry study.

Conflict of interest

We declare that we have no conflict of interest.

References

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3.2.1 Additional electronic materials

Effect of gantry tilt on voxel depth calculation. Two representative image slices of 7.5 mm thickness with a gantry tilt of 16.5°. Slice thickness is derived from midpoint to midpoint distance. 

a) Gantry tilt was not adjusted when image position patient (DICOM header, 0020, 0032) coordinates were used resulting in an inter-slice distance of 7.82 mm, solid line. 

b) Gantry tilt was adjusted using our in-house method and the inter-slice distance was 7.5 mm, dotted line.
**Supplementary figure 2**

Bland–Altman plots for oedema segmentation. Inter-rater Bland–Altman plots with intraclass correlation coefficients (ICC) for semi-automated planimetry of oedema segmentation on Analyze and Osirix. The solid line represents mean volume difference between raters and the dotted lines are the limits of 95% agreement. The outliers all had significant white matter changes.
Supplementary Table. Technical code of the workflow for volume calculation

Zpos is the representation of voxel depth for each slice

**Calculation of Zpos using**
- DICOM tag ImageOrientation which contains six values represented as Image_Ori
- DICOM tag ImagePositionPatient which contains three values represented as Image_Pos

**Function Calculate_Zpos (Image_Ori, Image_Pos)**

\[
\begin{align*}
\text{distance_normal_direction_cosine}_x &= \text{Image_Ori}[1] \times \text{Image_Ori}[5] - \text{Image_Ori}[2] \times \text{Image_Ori}[4] \\
\text{distance_normal_direction_cosine}_y &= \text{Image_Ori}[2] \times \text{Image_Ori}[3] - \text{Image_Ori}[0] \times \text{Image_Ori}[5] \\
\text{distance_normal_direction_cosine}_z &= \text{Image_Ori}[0] \times \text{Image_Ori}[4] - \text{Image_Ori}[1] \times \text{Image_Ori}[3]; \\
\end{align*}
\]

\[Zpos = \text{distance_normal_direction_cosine}_x \times \text{Image_Pos}[0] + \text{distance_normal_direction_cosine}_y \times \text{Image_Pos}[1] + \text{distance_normal_direction_cosine}_z \times \text{Image_Pos}[2]; \]

return Zpos

**We calculated interslice distance as**

**Function Calculate_inter_slice_distance (Zpos)**

\{For slice n = 2: last - 1\}

\[\text{inter_slice_distance}[\text{slice}] = \frac{[Zpos(\text{slice } n) - Zpos(\text{slice } n-1)]}{2} + \frac{[Zpos(\text{slice } n+1) - Zpos(\text{slice } n)]}{2}\]

\[\text{inter_slice_distance}[1] = \text{inter_slice_distance}[2]\]

\[\text{inter_slice_distance}[\text{last}] = \text{inter_slice_distance}[\text{last - 1}]\]

return \text{inter_slice_distance}

Region of interest files were converted into MINC format (3D format) containing
- Region one representing haemorrhage
- Region two representing oedema
- Region three representing ventricular haemorrhage

for the complete volume

**Volume Calculation**

\{Read MINC volume comprising region of interest from segmented from software\}

Read Zpos from the MINC header

Create a variable volume_region_one
Create a variable volume_region_two
Create a variable volume_region_three

inter_slice_distance = Calculate_inter_slice_distance (Zpos)

For each slice[first-last] of MINC volume

(Region_One_nonzero_voxels = Nonzero voxel of region one in slice (each))

Region_two_nonzero_voxels = Nonzero voxel of region two in slice (each)

Region_three_nonzero_voxels = Nonzero voxel of region three in slice (each)

Slice Volume of Region one = Region_One_nonzero_voxel \times \text{Voxel width from header} \times \text{Voxel height from header} \times \text{inter_slice_distance(each)}

Slice Volume of Region two = Region_Two_nonzero_voxel \times \text{Voxel width from header} \times \text{Voxel height from header} \times \text{inter_slice_distance(each)}

Slice Volume of Region three = Region_Three_nonzero_voxel \times \text{Voxel width from header} \times \text{Voxel height from header} \times \text{inter_slice_distance(each)}

Volume Region One =+ Slice Volume of Region one
Volume Region Two =+ Slice Volume of Region two
Volume Region Three =+ Slice Volume of Region three
3.3 Additional unpublished analyses

The published results were presented as mean differences. When absolute differences were examined, large absolute differences were observed between different raters in some cases. The maximum differences between the raters for ICH and oedema volumes are noted on Table 4.

**Table 4. Maximum absolute volume (mL) differences between raters**

<table>
<thead>
<tr>
<th>Rater 1 - Rater 2</th>
<th>Mean volume</th>
<th>Rater 1 - Rater 3</th>
<th>Mean volume</th>
<th>Rater 2 - Rater 3</th>
<th>Mean volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyze ICH</td>
<td>15.41</td>
<td>66.71</td>
<td>-49.88</td>
<td>130.58</td>
<td>-43.24</td>
</tr>
<tr>
<td>Osirix ICH</td>
<td>19.78</td>
<td>95.00</td>
<td>-10.66</td>
<td>45.02</td>
<td>-21.54</td>
</tr>
<tr>
<td>Analyze oedema</td>
<td>59.95</td>
<td>94.42</td>
<td>59.83</td>
<td>124.41</td>
<td>-79.23</td>
</tr>
<tr>
<td>Osirix oedema</td>
<td>53.64</td>
<td>111.66</td>
<td>61.09</td>
<td>75.83</td>
<td>-49.42</td>
</tr>
</tbody>
</table>

In the majority of scans with large absolute between-rater difference, the mean volumes were large. We found that regions of hyperacute blood which appear less hyperdense on CT scan were frequently responsible for interrater disagreement (figure 20).

**Figure 20. Regions of less hyperdense hyperacute blood confounding ICH measurement**
In scans with large oedema discrepancy, the background white matter disease is likely to have contributed to the differences (figure 21).

**Figure 21.** CT scans with significant background white matter disease confounding oedema measurement.
Chapter IV: Simultaneous multiple intracerebral haemorrhages

4.1 Introduction and summary

Simultaneous multiple ICHs (SMICH) are observed in a small subset of ICH patients on baseline imaging. With only 9 reported studies documenting SMICH in 323 patients (Weisberg 1981; Maurino et al., 2001; Yen et al., 2005; Sorimachi et al., 2007b; Stemer et al., 2010; Takeuchi et al., 2011; Laiwattana et al., 2014; Yeh et al., 2014; Chen et al., 2016), this type of ICH presentation is not well understood. Previous single centre studies have reported potential association of cerebral microhaemorrhages with presence of SMICH (Sorimachi et al., 2007b; Stemer et al., 2010). This observation supports Fisher’s ‘avalanche’ theory of a progressive recruitment and rupture of vessels at risk surrounding the primary bleeding point (Fisher 1971). It is known that cerebral amyloid angiopathy can present with SMICH (Knudsen et al., 2001) but the association with other ICH aetiologies with SMICH is uncertain. The clinical significance of SMICH is also uncertain with suggestion that SMICH may portend poorer clinical outcome with increased risk of cognitive dysfunction and future epilepsy risk (Chen et al., 2016).

The aims of this study were to report the prevalence of SMICH, to determine the aetiological association and assess for potential impact on mortality after ICH. Patient imaging data from the Helsinki ICH study and the Royal Melbourne ICH study were reviewed for SMICH and association with outcome was assessed using logistic regression analysis. We found SMICH was not rare, presenting in approximately 1 in 20 ICH presentations. Cerebral amyloid angiopathy and hypertensive aetiology accounted for over 50% of SMICH pathogenesis. However, there was no association of SMICH with 3-month mortality in logistic regression analyses, after adjusting for known predictors of outcome. This remained the case using propensity score matching. Management of SMICH should therefore target the underlying pathology.
Simultaneous Multiple Intracerebral Hemorrhages (SMICH)

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Background and Purpose—Simultaneous multiple intracerebral hemorrhages (SMICHs) are uncommon. Few single-center studies have analyzed characteristics and outcome of SMICH. We analyzed clinical characteristics and outcome of SMICH patients from 2 comprehensive stroke centers.

Methods—Baseline imaging from consecutive intracerebral hemorrhage (ICH) patients (n=1552) from Helsinki ICH study and Royal Melbourne Hospital ICH study was screened for SMICH. ICH pathogenesis was classified according to the structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, undetermined classification system (SMASH-U). ICH caused by trauma, tumor, and aneurysmal rupture was excluded. Baseline clinical and radiological characteristics and 90-day mortality were compared between SMICH and single ICH patients. Association of SMICH with 90-day mortality was assessed in multivariable logistic regression models adjusted for predictors of ICH outcome.

Results—Of 1452 patients, 85 (5.9%) were classified as SMICH. SMICH were more often female (58% versus 42%; P=0.004), had lower baseline Glasgow Coma Scale (12 versus 14; P=0.008), and more frequent lobar location (59% versus 34%; P<0.001) compared with single ICH. The SMASH-U pathogenesis of SMICH patients was less often hypertensive (20% versus 37%; P=0.001), more often systemic coagulopathy (12% versus 3%; P<0.001), and trended toward more cerebral amyloid angiopathy (32% versus 23%; P=0.071). SMICH was not associated with 90-day mortality on univariate (37% versus 35%; P=0.610), multivariable (odds ratio, 0.783; 95% confidence interval, 0.401–1.529; P=0.518), or propensity score–matched analyses (odds ratio, 0.760; 95% confidence interval, 0.352–1.638; P=0.610).

Conclusions—SMICH occurs in ≈1 in 20 ICH, more commonly with lobar located hematomas and systemic coagulopathy with less hypertensive angiopathy. The associated mortality is similar to single ICH. Given varied etiologies, SMICH management should target the underlying pathology. (Stroke. 2017;48:581-586. DOI: 10.1161/STROKEAHA.116.015186.)

Key Words: cerebral hemorrhage ■ mortality ■ multiple ■ pathogenesis

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DOI: 10.1161/STROKEAHA.116.015186
Table 1. Summary of Reported Studies in Patients With Simultaneous Intracerebral Hemorrhages (SMICHS)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>SMICH/Single ICH (n/total, %)</th>
<th>Country</th>
<th>SMICH Pathogenesis</th>
<th>Age</th>
<th>Total ICH Volume, mL</th>
<th>SMICH Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weisberg, 6 1981</td>
<td>12/600 (2%)</td>
<td>United States</td>
<td>Undetermined: 12 (100%)</td>
<td>NR</td>
<td>NR</td>
<td>3/12 (33%), follow-up time not defined</td>
</tr>
<tr>
<td>Mauriño et al. 6 2001</td>
<td>4/142 (2.8%)</td>
<td>Argentina</td>
<td>Hypertension: 4 (100%)</td>
<td>55</td>
<td>NR</td>
<td>0/4 (0%) at 3 mo</td>
</tr>
<tr>
<td>Yen et al. 4 2005</td>
<td>10/1304 (0.9%)</td>
<td>Taiwan</td>
<td>Hypertension: 10 (100%)</td>
<td>61</td>
<td>NR</td>
<td>6/10 (60%) at 6 mo</td>
</tr>
<tr>
<td>Sorimachi et al. 7 2007</td>
<td>9/190 (4.7%)</td>
<td>Japan</td>
<td>Hypertension: 9 (100%)</td>
<td>69</td>
<td>11 NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Stermer et al. 8 2010</td>
<td>29/522 (5.6%)</td>
<td>United States</td>
<td>CAA: 3 (10.3%); hypertension: 11 (37.9%); secondary ICH: 15 (51.7%)</td>
<td>59</td>
<td>7</td>
<td>7/29 (24%)</td>
</tr>
<tr>
<td>Takeuchi et al. 5 2011</td>
<td>20/2198 (0.9%)</td>
<td>Japan</td>
<td>Hypertension (100%)</td>
<td>61</td>
<td>28</td>
<td>9/20 (45%) at discharge</td>
</tr>
<tr>
<td>Lawawatana et al. 6,9 2014</td>
<td>105/NR†</td>
<td>Mixed</td>
<td>NR</td>
<td>61</td>
<td>NR</td>
<td>46/105 (44%), follow-up time not defined</td>
</tr>
<tr>
<td>Yeh et al. 10 2014</td>
<td>136/3785 (3.6%)</td>
<td>Taiwan</td>
<td>CAA: 14 (10.3%); hypertension: 14 (10.3%); structural vascular: 3 (2.2%); medication: 16 (11.8%); systemic: 70 (51.5%); undefined: 19 (13.9%)</td>
<td>NR</td>
<td>NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Chen et al. 11 2016</td>
<td>32/562 (5.7%)</td>
<td>France</td>
<td>CAA: 8 (25.0%); deep vessel vasculopathy: 5 (15.6%); undefined: 19 (59.4%)</td>
<td>69</td>
<td>31</td>
<td>25/32 (78%) at 6 mo</td>
</tr>
<tr>
<td>Current study</td>
<td>85/1452 (5.9%)</td>
<td>Australia, Finland</td>
<td>CAA: 27 (31.7%); hypertension: 17 (20.0%); structural vascular: 5 (5.9%); medication: 14 (16.5%); systemic: 10 (11.8%); undefined: 12 (14.1%)</td>
<td>74</td>
<td>22</td>
<td>31/83 (37%) at 3 mo</td>
</tr>
</tbody>
</table>

CAA indicates cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; and NR, not reported.

*Stermer et al classified ICH as secondary in patients with coagulopathy, treatment with anticoagulant, history of illicit drug abuse, with cerebral vasculitis, or infective endocarditis at the time of ICH.

†This systematic review consists of publications in both English and non-English journals and contains both case reports and case series including 34 patients from series by Mauriño et al., Yen et al., and Takeuchi et al.

of consecutive ICH patients admitted to Helsinki University Hospital between January 2005 and March 2010. The RMH ICH study included consecutive ICH patients admitted between October 2007 and January 2012, with one report published on impact of warfarin on hematoma location and volume. The diagnosis of ICH in both studies was based on the World Health Organization definition of stroke requiring rapidly developing clinical signs of focal or global disturbance of cerebral function leading to death or lasting >24 hours with no apparent cause other than a vascular one, always combining with the imaging finding of ICH. In both studies, cerebral hemorrhage caused by trauma, tumor, hemorrhagic transformation of cerebral infarction with or without thrombolysis, or primary subarachnoid hemorrhage were excluded. Traumatic ICH was diagnosed as per routine clinical practice based on all available history, clinical findings, and imaging findings. Coexisting acute subdural or epidural hematomas or coup-countercoup contusions would result in a diagnosis of traumatic ICH.

We defined SMICH as 2 or more discrete, noncontiguous acute intraparenchymal hematomas on initial diagnostic computed tomography. For the present analysis, we additionally excluded patients without available baseline planimetric data because of unavailable baseline computed tomographic images or films unsuitable for computerized imaging analysis performed at another institution, pure ventricular hemorrhage, and where patients presented on >1 occasion only the first episode was included. T.Y.W. screened all patients for SMICH. N.Y. then reviewed the images of potential patients. Ineligible patients were excluded by mutual agreement. In the case of disagreement, A.M. was consulted for a final decision regarding inclusion.

Images at both centers were acquired using multislice computed tomographic scanners (Helsinki, Siemens Somatom Plus 4, Siemens Definition AS+, Siemens Medical, Germany, and GE Medical Systems LightSpeed Ultra/LightSpeed VCT, GE Healthcare, United States; RMH, Siemens Somatom Sensation, Siemens Medical, Germany). Hematoma volume was calculated using semiautomated planimetry using Analyze 12.0 (Biomedical Imaging Resource; Mayo Clinic). Hemorrhage was classified lobar if the ICH involved cortical surface or the juxta-cortical region of the frontal, parietal, temporal, or occipital lobes; deep when located within the deep structures (caudate, lentiform, thalamus, internal, or external capsule). In SMICH, the hematoma with the largest volume was used for location and etiologic determination. The total volume of all the hematomas in SMICH was used for other analyses. Etiologic classification for the cause of ICH was graded according to the SMASH-U classification into 6 categories, namely, hypertensive angiopathy, cerebral amyloid angiopathy, structural vascular abnormalities, medication related, other systemic causes, and undefined causes. Vascular lesion at the site of the ICH was classified as the responsible pathogenesis. Other systemic causes include hepatic cirrhosis, systemic coagulopathy (platelet count ≤50×10^9/L), cerebral venous sinus thrombosis, and drug-induced coagulopathy. Cerebral venous sinus thrombosis was considered a cause if the thrombosis caused a primary bleed, not if there was first an ischemic stroke and then a hemorrhagic transformation of the same. Cerebral venography was performed in younger patients, cases with predisposing factors, and those with suspicious imaging, such as ragged cortical ICH. Medication-related ICH was classified in a patient on warfarin with international normalized ratio ≥2.0, novel oral anticoagulants within 3 days, full-dose heparin, or systemic thrombolysis for nonstroke indication. Sole antiplatelet use was not considered medication-related pathogenesis. Cerebral amyloid angiopathy was classified in patients ≥55 years of age with a lobar, cortical, or subcortical hematoma. Hypertensive angiopathy was considered in patients with pre-ICH hypertension with deep or infratentorial hematoma. Finally, undetermined pathogenesis was considered when ICH could not be classified into other categories.

Systematic follow-up of all patients was not routine during the study period for either of the ICH cohorts. For patients who survived their acute hospitalization, we checked whether they had further visits...
or investigations >90 days from ICH. If not, we contacted the unit they were transferred to. If no data on vital status were available, the patients were considered lost to follow-up. In Helsinki, we additionally had comprehensive vital status data from the national death registry kept by Statistics Finland.

Institutional approval for the observational registry study was granted from relevant authorities in Helsinki and Melbourne with no requirement for patient consent, allowing for all consecutive patients to be included.

Statistical Analysis
Data are reported as median with interquartile range or n (%) and analyzed with Mann-Whitney U test, Pearson χ², or Fisher exact tests as appropriate. Association with 90-day mortality was assessed in a multivariable logistic regression model adjusted for baseline Glasgow Coma Scale (GCS), baseline ICH volume, age, male sex, previous warfarin use, ventricular extension, and infratentorial location.7 There were no missing data for the covariates included in the logistic regression model; therefore, only patients with missing outcome data were excluded from this analysis. Testing for collinearity demonstrated no collinearity between the variables with all variance inflation factors <1.5. To validate the findings from the logistic regression model, the primary analysis was repeated using matched controls. We used propensity score matching with the nearest neighbor method to match SMICH patients and single ICH patients 1:2 on baseline demographics (age and male sex), medication use (warfarin, antplatelet agent, antihypertensive medications, statins), medical history (atrial fibrillation, ischemic heart disease, dyslipidemia, diabetes mellitus, previous ICH, or ischemic stroke), radiological characteristics (ICH volume and ICH location), and pathogenesis. Patients with missing baseline and outcome information were included in the univariate comparison between SMICH and single ICH patients but excluded from the propensity score matching analysis. We used R 3.1.0 and the MatchIt package46 for propensity score matching and SPSS 23 (IBM, Armonk, NY) for other statistical analyses. A 2-sided P value <0.05 was considered statistically significant.

Results
From the pool of 1552 patients (Helsinki n=1013, RMH n=539), 100 (6.4%) were excluded because of lack of appropriate baseline planimetric data (70), recurrent admissions (19), and pure intraventricular hemorrhage (11; Figure). Of the remaining 1452 patients, 85 (overall 5.9%; Helsinki 47/978 [4.8%], RMH 38/474 [8.0%]) patients were classified with SMICH according to the predefined criteria.

SMICH Location and Laterality
There were 197 discrete hematomas in the SMICH patients, and 36 (42%) patients had hematomas located bilaterally. Most patients had 2 hematomas with 14 (16%) patients having 3 or more hematomas on baseline imaging (Table 2). Most of the hematomas were lobar (124, 63%) in location, whereas 54 (27%) hematomas were deep, with 6 (3%) hematomas in the brain stem and 13 (7%) in the cerebellum. None of the 6 patients with simultaneous brain stem and supratentorial deep or lobar hemorrhage had duret brain stem hemorrhage caused by uncal herniation. Fourteen (16%; 6/47 [13%] Helsinki, 8/38 [21%] RMH) SMICH patients had a secondary hemorrhage <5 mm in diameter. Representative images of SMICH are presented in the Figure in the online-only Data Supplement.

Baseline Clinical Characteristics and Pathogenesis
Patients with SMICH were more often female (58% versus 42%; P=0.004) and had lower baseline GCS (12 versus 14; P=0.008) when compared with patients with single ICH. Other baseline clinical risk factors did not differ (Table 3). In terms of pathogenesis, SMICH patients had more cerebral amyloid angiopathy (32% versus 23%; P=0.071), medication-related ICH (16% versus 14%; P=0.433), systemic defined pathogenesis (12% versus 3%; P<0.001), and structural vascular lesions (6% versus 4%; P=0.418), with less hypertensive angiopathy (20% versus 37%; P=0.001) and undetermined causes (14% versus 18%; P=0.324; Table 3). Of the 10 (12%) patients with systemic defined pathogenesis, 4 were attributed to liver cirrhosis, 3 from thrombocytopenia, and 3 had cerebral venous sinus thrombosis. Cerebral venous sinus thrombosis was diagnosed in 2 (0.1%) single ICH patients. Of the medication-related ICH group, warfarin was the cause in 9 of 14 (64%) SMICH and 169 of 184 (92%) single ICH patients, and one of the other medications in 5 of 14 (36%) SMICH and 15 of 184 (8%) single ICH patients. All patients (n=5; 6%) with structural vascular abnormality had multiple cavernous venous malformations. Table in the online-only Data Supplement presents the univariate comparison between SMICH and single ICH patients according to pathogenesis. SMICH patients with cerebral amyloid angiopathy were older (79 versus 74; P=0.034) with lower admission GCS (11 versus 14; P=0.003), medication-related SMICH patients were more often female (63% versus 29%; P=0.021), with less warfarin use (64% versus 92%; P=0.007), and more exposure to antplatelet agents (50% versus 17%; P=0.007). No other differences were found within these subgroups (Table in the online-only Data Supplement).

![Figure. Study flow chart. ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; RMH, Royal Melbourne Hospital; and SMICH, simultaneous intracerebral hemorrhage.](image-url)
Table 2. Location of the Larger Hematomas* in Patients With Simultaneous Multiple Intracerebral Hematomas

<table>
<thead>
<tr>
<th>Location</th>
<th>All (n=1452)</th>
<th>SMICH (n=85)</th>
<th>Single ICH (n=1367)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar</td>
<td>38</td>
<td>18</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Deep</td>
<td>...</td>
<td>12</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Brain stem</td>
<td>...</td>
<td>...</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*In 14 (16%) patients with >2 hematomas, the largest 2 hematomas were used to determine location.

Radiological Variables

The dominant hematoma location (Table 3) differed between SMICH and single ICH patients with higher proportion of lobar hematomas (59% versus 34%; P<0.001) and less deeply located (34% versus 52%; P=0.001) or infratentorial ICH (7% versus 14%; P=0.073). The groups did not differ in baseline ICH volume (22 versus 15 mL; P=0.225) or ventricular extension (35% versus 42%; P=0.205). When analyzed by pathogenesis, medication-related SMICH had more lobar (79% versus 28%; P<0.001) and less deep (14% versus 56%; P=0.004) hematomas when compared with single ICH patients, but the groups did not otherwise differ (Table in the online-only Data Supplement).

Mortality

Mortality data were available in 1421 (98%) patients. Of the 31 (2.85 [2%] SMICH and 29/1367 [2%] single ICH) patients with missing mortality data, 9 were from Helsinki and 22 from RMH. There was no difference in mortality at 90 days between patients with SMICH and single ICH (37% versus 35%; P=0.610; Table 3). In medication-related ICH, SMICH patients had lower mortality (21% versus 55%; P=0.023), but there were no other differences in mortality by etiologic subgroups (Table in the online-only Data Supplement).

Factors associated with 90-day mortality in SMICH patients on univariate analysis were lower baseline GCS (7 versus 14; P<0.001), larger baseline ICH volume (59 versus 12 mL; P<0.001), and presence of ventricular extension (55% versus 25%; P<0.001). After excluding 31 patients (2 with SMICH) with missing mortality data, 1421 patients were included in the multivariable model with unmatched controls (Table 4). The presence of SMICH was associated with less 90-day mortality (odds ratio, 0.783; 95% confidence interval, 0.401–1.529; P=0.473) although this was not statistically significant. After excluding 52 (3.6%; 4 with SMICH) patients with missing baseline and outcome variables, propensity score matching resulted in 243 patients with balanced baseline characteristics. In the postmatching logistic regression analysis, SMICH was also not associated with 90-day mortality (odds ratio, 0.760; 95% confidence interval, 0.352–1.638; P=0.484; Table 4). In the post hoc analysis, the presence of SMICH was also not associated with 90-day mortality after excluding 14 SMICH patients with small secondary hemorrhage (<5 mm in diameter) in both the unmatched (n=1407; odds ratio, 0.733; 95% confidence interval, 0.351–1.531; P=0.408) and the propensity matched (n=201; odds ratio, 1.330; 95% confidence interval, 0.572–3.090; P=0.507) logistic regression analyses.

Table 3. Baseline Clinical and Radiological Factors and Mortality in Patients With and Without SMICHs

<table>
<thead>
<tr>
<th>Factor</th>
<th>All (n=1452)</th>
<th>SMICH (n=85)</th>
<th>Single ICH (n=1367)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 (60–79)</td>
<td>74 (61–81)</td>
<td>70 (60–79)</td>
<td>0.258</td>
</tr>
<tr>
<td>Male sex</td>
<td>831 (57%)</td>
<td>36 (42%)</td>
<td>795 (58%)</td>
<td>0.004</td>
</tr>
<tr>
<td>GCS</td>
<td>14 (10–15)</td>
<td>12 (8–15)</td>
<td>14 (10–15)</td>
<td>0.006</td>
</tr>
<tr>
<td>Warfarin</td>
<td>203 (14%)</td>
<td>9 (11%)</td>
<td>194 (14%)</td>
<td>0.422</td>
</tr>
<tr>
<td>Antplatelet</td>
<td>432 (30%)</td>
<td>29 (34%)</td>
<td>403 (30%)</td>
<td>0.364</td>
</tr>
<tr>
<td>Statin</td>
<td>312 (22%)</td>
<td>20 (24%)</td>
<td>292 (21%)</td>
<td>0.637</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>223 (15%)</td>
<td>17 (20%)</td>
<td>206 (15%)</td>
<td>0.221</td>
</tr>
<tr>
<td>Hypertension</td>
<td>951 (66%)</td>
<td>55 (65%)</td>
<td>901 (66%)</td>
<td>0.820</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>321 (22%)</td>
<td>17 (20%)</td>
<td>304 (22%)</td>
<td>0.629</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>243 (17%)</td>
<td>12 (14%)</td>
<td>231 (17%)</td>
<td>0.505</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>136 (9%)</td>
<td>8 (9%)</td>
<td>128 (9%)</td>
<td>1.000*</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>128 (9%)</td>
<td>9 (11%)</td>
<td>119 (9%)</td>
<td>0.553</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>67 (5%)</td>
<td>7 (8%)</td>
<td>60 (4%)</td>
<td>0.107</td>
</tr>
<tr>
<td>90-day mortality$</td>
<td>494 (35%)</td>
<td>31 (37%)</td>
<td>463 (34%)</td>
<td>0.610</td>
</tr>
<tr>
<td>Baseline ICH volume, mL</td>
<td>15 (6–43)</td>
<td>22 (6–58)</td>
<td>15 (6–42)</td>
<td>0.225</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>608 (42%)</td>
<td>30 (35%)</td>
<td>578 (42%)</td>
<td>0.205</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Lobar</td>
<td>512 (35%)</td>
<td>50 (59%)</td>
<td>462 (34%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep</td>
<td>752 (52%)</td>
<td>29 (34%)</td>
<td>723 (52%)</td>
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<tr>
<td>Infratentorial</td>
<td>199 (14%)</td>
<td>6 (7%)</td>
<td>193 (14%)</td>
<td>0.073*</td>
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<tr>
<td>SMASH-U classification</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Amyloid</td>
<td>344 (24%)</td>
<td>27 (32%)</td>
<td>317 (23%)</td>
<td>0.071</td>
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<tr>
<td>Hypertension</td>
<td>528 (36%)</td>
<td>17 (20%)</td>
<td>511 (37%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Medication</td>
<td>198 (14%)</td>
<td>14 (16%)</td>
<td>184 (14%)</td>
<td>0.433</td>
</tr>
<tr>
<td>Structural</td>
<td>64 (4%)</td>
<td>5 (6%)</td>
<td>59 (4%)</td>
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</tr>
<tr>
<td>Systemic defined</td>
<td>55 (4%)</td>
<td>10 (12%)</td>
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<td>263 (18%)</td>
<td>12 (14%)</td>
<td>251 (18%)</td>
<td>0.324</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) or n (%). GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; SMASH-U, structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, undetermined classification; and SMICH, simultaneous intracerebral hemorrhages.

*Fisher exact test.
+Thirteen patients had missing baseline statin use data.
§Sixteen patients had missing preexisting dyslipidemia data.
║Thirty-one patients had missing 90-day mortality data.

Discussion

In this dual-center study of SMICH patients, we derived several points of interest. First, in our large series of consecutive patients, we found a relatively high proportion of SMICH patients (5.9%) compared with previous literature.
Second, mortality did not differ between SMICH patients and those with single ICH, which contrasts with previous reports that did not adjust for baseline variables.\textsuperscript{4,5,10} Finally, we have detailed the etiologic associations of patients with SMICH.

SMICH has been considered uncommon in ICH (Table 1), but 4 of 6 hospital-based studies in the past decade have reported SMICH presenting in between 4.7% and 5.9% or \textasciitilde 1 in every 20 of all ICH patients. In 14 (16%) SMICH patients in this study, the secondary hematoma was \textasciitilde 5 mm in diameter; therefore, thicker computed tomographic image slices such as 13 mm slices in the study by Weisberg\textsuperscript{7} may potentially have missed patients with smaller simultaneous hemorrhages.

Mortality in SMICH has been reported to range from 0% to 78% (Table 1) and is likely to be influenced by the pathogenesis and location of the SMICH. Laiwattana et al\textsuperscript{4} systematically reviewed 105 patients with primary SMICH by combining published case reports and case series and examined the association of location of SMICH and outcome. The authors found that deep SMICH had the highest mortality rate (27/54; 50\%) compared with SMICH located in bilateral lobar or cerebellar regions (0/2; 0\%) or nonbilateral SMICH (19/49; 37\%).

The SMICH mortality rate of 37\% in our study is similar to reports by Weisberg\textsuperscript{8} (33\%) and Stermer et al\textsuperscript{8} (24\%) but lower than that reported by Chen et al\textsuperscript{10} (78\%), Yen et al\textsuperscript{11} (60\%), and Takeuchi et al\textsuperscript{12} (45\%). The higher mortality rate in other studies\textsuperscript{4,5,10} is likely accounted for by hematoma location and hematoma volume, which are both important mediators of ICH outcome.\textsuperscript{11,12} Yen et al\textsuperscript{11} and Takeuchi et al\textsuperscript{12} included only hypertensive SMICH with almost all hematomas located in the deep brain region, whereas 44\% of the subjects in the study by Chen et al\textsuperscript{10} had deep hematomas compared with 27\% in our study. The total hematoma volume in studies by Takeuchi et al (28 mL) and Chen et al (31 mL) was higher than our study (22 mL), whereas hematoma volume was not reported in the study by Yen et al (Table 1).

Etiologic consideration after ICH is important because it mediates outcome in ICH patients in both European and Asian patients.\textsuperscript{2,3,11} We demonstrated using the SMASH-U classification system\textsuperscript{2} that the pathogenesis in SMICH is also widely distributed similar to that in patients with single ICH (Table 3), with hypertensive angiopathy and cerebral amyloid angiopathy accounting for 52\% of all SMICH. This finding is consistent with a recent report by Chen et al,\textsuperscript{10} where cerebral amyloid angiopathy and deep vessel vasculopathy accounted for 41\% of their SMICH patients. This is in contrast to the study by Yeh et al,\textsuperscript{12} who also classified Taiwanese SMICH patients using the SMASH-U system. The authors reported 51\% of SMICH were because of systemic causes, whereas hypertension accounted only for 10\% of their cohort likely reflecting ethnic differences for ICH pathogenesis. Future SMICH studies need to standardize ICH classification and include all nontraumatic, nontumor-related ICH patients.

The strengths of our study are the relatively large sample with well-characterized baseline data and 90-day mortality, allowing us to assess the effect of SMICH on mortality after adjustment for known predictors of ICH outcome.

This study has several limitations. First, it is retrospective in nature and is subject to selection bias. We minimized bias by prespecifying objective criteria to define SMICH, and potential cases were screened by neurologists experienced in stroke imaging. Furthermore, only 6.4\% of consecutive ICH patients were excluded. Second, as we included centers with patients of predominantly European descent, our results may not be generalizable to patients from other ethnic backgrounds. Third, magnetic resonance imaging was not routinely performed at the study centers during the study period, and only 14 (16\%) SMICH patients had follow-up magnetic resonance imaging performed. Consequently, the presence and location of microhemorrhages could not be assessed to assist in etiologic determination. Finally, we did not have functional outcome assessment for our study patients and therefore could not assess the effect of SMICH on functional recovery. However, mortality is a robust outcome measure in ICH.

**Conclusions**

SMICH occurs in \textasciitilde 1 in 20 ICH patients with higher proportion of lobar hematomas and systemic coagulopathy and less
often related to hypertensive angiopathy. The presence of SMICH was not associated with excess mortality. Given the varied etiologies, the management of SMICH should therefore target the underlying pathology.

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**Disclosures**

None.

**References**


**Supplementary table.** Baseline differences between SMICH and single ICH patients grouped according to etiology.

<table>
<thead>
<tr>
<th></th>
<th>Cerebral amyloid angiopathy</th>
<th>Hypertensive angiopathy</th>
<th>Medication related</th>
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<td>SMICH n=27</td>
<td>Single ICH n=317</td>
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</tr>
<tr>
<td>Age, years</td>
<td>79 (73-84)</td>
<td>74 (74-81)</td>
<td>0.034</td>
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<tr>
<td>Male sex</td>
<td>9 (33%)</td>
<td>158 (50%)</td>
<td>0.112*</td>
</tr>
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<td>GCS</td>
<td>11 (10-14)</td>
<td>14 (11-15)</td>
<td>0.003</td>
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<td>Warfarin</td>
<td>0</td>
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<td>1.000*</td>
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<td>Antiplatlet</td>
<td>11 (41%)</td>
<td>114 (36%)</td>
<td>0.620</td>
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<td>Statin</td>
<td>7 (26%)</td>
<td>78 (25%)</td>
<td>0.820*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (15%)</td>
<td>21 (7%)</td>
<td>0.121*</td>
</tr>
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<td>Hypertension</td>
<td>18 (67%)</td>
<td>188 (60%)</td>
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<td>Diabetes</td>
<td>4 (15%)</td>
<td>71 (22%)</td>
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<td>Ischemic heart disease</td>
<td>0</td>
<td>37 (12%)</td>
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<td>Previous ischemic stroke</td>
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<td>Previous ICH</td>
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<td>24 (8%)</td>
<td>0.457*</td>
</tr>
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<td>90-day mortality</td>
<td>9 (36%)</td>
<td>92 (30%)</td>
<td>0.652</td>
</tr>
<tr>
<td>Baseline ICH volume, mL</td>
<td>41 (22-81)</td>
<td>31 (10-62)</td>
<td>0.131</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>9 (33%)</td>
<td>81 (26%)</td>
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<tr>
<td>Location</td>
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<tr>
<td>Lobar</td>
<td>27 (100%)</td>
<td>316 (100%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Deep</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>0</td>
<td>1 (0%)</td>
<td>1.000*</td>
</tr>
</tbody>
</table>

*Fisher exact test.*

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; SMICH, simultaneous multiple intracerebral hemorrhages.
Supplementary table (continued). Baseline differences between SMICH and single ICH patients grouped according to etiology

<table>
<thead>
<tr>
<th>Systemic defined etiologies</th>
<th>Structural vascular abnormality</th>
<th>Undefined</th>
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<tbody>
<tr>
<td>SMICH n=5</td>
<td>Single ICH n=59</td>
<td>SMICH n=12</td>
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<tr>
<td><strong>Age, years</strong></td>
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<tr>
<td>SMICH n=10</td>
<td>Single ICH n=45</td>
<td>p</td>
</tr>
<tr>
<td>Age, years</td>
<td>62 (42-74)</td>
<td>57 (46-64)</td>
</tr>
<tr>
<td>Male sex</td>
<td>6 (60%)</td>
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</tr>
<tr>
<td>GCS</td>
<td>14 (3-15)</td>
<td>15 (10-15)</td>
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<tr>
<td>Warfarin</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>1 (10%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Statin</td>
<td>1 (10%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (10%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (40%)</td>
<td>20 (44%)</td>
</tr>
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<td>Dyslipidemia</td>
<td>1 (10%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (10%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>1 (10%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>5 (50%)</td>
<td>16 (36%)</td>
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<tr>
<td>Baseline ICH volume, mL</td>
<td>9 (3-55)</td>
<td>19 (4-44)</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>3 (30%)</td>
<td>16 (36%)</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
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<tr>
<td>Lobar</td>
<td>7 (70%)</td>
<td>21 (47%)</td>
</tr>
<tr>
<td>Deep</td>
<td>2 (20%)</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>1 (10%)</td>
<td>8 (18%)</td>
</tr>
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</table>

*Fisher exact test.
GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; SMICH, simultaneous multiple intracerebral hemorrhages
**Supplementary figure.** Representative images of simultaneous intracerebral hemorrhages (SMICH).

Representative samples of SMICH with arrows indicating very small hematomas, demonstrating A) lobar, B-C) lobar and deep, D) lobar and brainstem, E-F) lobar and cerebellar, G) lobar, deep and brainstem, H) deep and cerebellar, I-J) lobar, K) cerebellar, L) deep, M-N) deep and cerebellar patterns of SMICH.
Chapter V: Impact of pre-stroke sulphonylurea and metformin use on mortality of intracerebral haemorrhage

5.1 Introduction and summary

Post stroke oedema influences patient outcome in ischaemic stroke patients with large territory infarction (Simard et al., 2007) and peri-haematomaal oedema is also emerging as a potential prognostic marker after ICH (Urday et al., 2015b). Glyburide a sulphonylurea used to treat diabetes mellitus, inhibits the SUR-1 TRPM4 channel and resulted in reduced post stroke oedema in preclinical models of ischaemic stroke and ICH (Simard et al., 2010b; Jiang et al., 2017). A phase 2 (n=86) randomised controlled trial in ischaemic stroke patients with large volume infarction demonstrated intravenous glyburide resulted in significantly reduced midline shift when compared to placebo (4.6mm vs 8.5mm, p=0.0006) (Sheth et al., 2016). Metformin, another commonly used diabetic agent, has been associated with improved ischaemic stroke outcome (Favilla et al., 2011; Horsdal et al., 2012), possibly due to reduced metabolic stress and lactate generation (Li et al., 2010).

The aim of this study was to assess for a potential association between pre-stroke use of sulphonylurea or metformin on outcome of diabetic ICH (n=374) patients. Diabetic ICH patients from VISTA-ICH (n=151), Helsinki ICH study (n=138) and RMH ICH study (n=85) were pooled and logistic regression analysis performed to assess the association between pre-stroke use of metformin and sulphonylurea on 90-day mortality adjusted for other known predictors of outcome (ICH volume, NIHSS, GCS, male sex, previous warfarin use, ventricular extension, infratentorial location).

The results showed that pre-stroke sulphonylurea use was not associated with 90-day mortality (OR 0.96 95% CI 0.49-1.88, p=0.906) while pre-stroke metformin use was associated with reduced risk of death (OR 0.51 95% CI 0.26-0.97, p=0.041). Despite a high discontinuation rate on admission (sulphonylurea 71%, metformin 59%) there was no interaction between drug discontinuation and outcome.
The results of this study need to be considered in light of the following limitations. Although there was also no difference in the baseline oedema between users and non-users of either diabetic medication, information on subsequent oedema growth was unavailable and the potential impact of these medications on oedema evolution could not be assessed in this study. Secondly, information on early institution of do-not-resuscitate order or limitation of care was unavailable in the RMH ICH dataset and not requested from the VISTA-ICH dataset. As a consequence, the influence of early palliation on the association between metformin or sulphonylurea and ICH mortality was not considered. Finally, as the results presented are considered hypothesis generating, therefore Bonferroni correction for multiple hypothesis testing was not applied. Further validation in independent cohorts is required before consideration can be given for a clinical trial.
Impact of pre-stroke sulphonylurea and metformin use on mortality of intracerebral haemorrhage

Teddy Y Wu, Bruce CV Campbell, Daniel Strbian, Nawaf Yassi, Jukka Pataala, Turgut Tatlisumak, Stephen M Davis and Atte Meretoja; on behalf of the VISTA-ICH Collaboration*

Abstract

Introduction: Few proven therapies for intracerebral haemorrhage exist. Preliminary observational evidence suggests that sulphonylurea and metformin may be protective in ischaemic stroke. We assessed the association of pre-intracerebral haemorrhage sulphonylurea and metformin use on outcome in diabetic patients.

Methods: We merged datasets from the consecutive single-centre Helsinki ICH Study, the intracerebral haemorrhage arm of the Virtual International Stroke Trials Archive (VISTA-ICH) and the Royal Melbourne Hospital ICH Study. Logistic regression adjusting for known predictors of intracerebral haemorrhage outcome (age, sex, baseline Glasgow Coma Scale, National Institutes of Health Stroke Scale, intracerebral haemorrhage volume, infratentorial location, intraventricular extension, and pre-intracerebral haemorrhage warfarin use) estimated the association of metformin and sulphonylurea with all-cause 90-day mortality.

Results: From a dataset of 2404 consecutive intracerebral haemorrhage patients, we included 374 (16%) patients with diabetes. Of these, 113 (30%) died by 90 days. Metformin was used in 148 (40%) patients and sulphonylurea in 115 (31%) patients at intracerebral haemorrhage onset. After adjusting for baseline characteristics, metformin use was associated with lower 90-day mortality (OR 0.51; 95% CI 0.26–0.97; p = 0.041) irrespective of whether the drug was continued or not during the admission, while sulphonylurea use was not associated with mortality (OR 0.96; 95% CI 0.49–1.88; p = 0.906). Haematoma location or evacuation did not modify the association between metformin and mortality; neither did adding insulin use, baseline glucose and serum creatinine into the model (OR 0.50; 95% CI 0.25–0.99; p = 0.047).

Conclusion: Pre-intracerebral haemorrhage metformin use was associated with improved outcome in diabetic intracerebral haemorrhage patients. Our results generate hypotheses which after further validation could be tested in clinical trials.

Keywords
Intracerebral haemorrhage, sulphonylurea, metformin, diabetes

Date received: 14 May 2016; accepted: 8 August 2016

Introduction

The only currently proven interventions for intracerebral haemorrhage (ICH) are organised stroke unit care and blood pressure control. In ischaemic stroke, observational studies have reported both neutral and beneficial results of pre-stroke sulphonylurea and metformin use. A recently completed phase II randomised controlled trial demonstrated less midline shift in patients with large territory ischaemic stroke treated with intravenous glyburide when compared to placebo.
Sulphonylurea inhibits the SUR-1-TRPM4 ion channel, which is up-regulated within several hours of ischaemic stroke and also within the peri-haematomal region after ICH. Up-regulated SUR-1-TRPM4 can lead to an unchecked intracellular influx of sodium ion accompanied by chloride and water, resulting in cell swelling and cytotoxic oedema. In a rat subarachnoid haemorrhage model, sulphonylurea reduced inflammation and improved cognitive recovery. In a mouse ischaemic stroke model, chronic pre-stroke metformin administration reduced lactate production and infarct volume.

There are no published reports assessing the association of sulphonylurea or metformin with ICH outcome. We hypothesised that pre-stroke sulphonylurea or metformin use is associated with better 90-day outcome independent of known predictors.

Methods

Study design

We combined datasets from the single-centre Helsinki ICH study, the Royal Melbourne Hospital (RMH) ICH study, and the ICH arm of the pooled repository of trials Virtual International Stroke Trials Archive (VISTA). The Helsinki ICH study is a retrospective analysis of consecutive ICH patients admitted to Helsinki University Central Hospital between January 2005 and March 2010. The RMH ICH study retrospectively analysed the impact of warfarin on location and haematoma volume in ICH patients admitted between October 2007 and January 2012. VISTA is an international academic collaborative repository for stroke clinical trials and collects the data in an anonymised manner to allow for novel exploratory analyses. All included patients had non-traumatic spontaneous ICH. Approval for this analysis was granted by the Melbourne Health Human Research Ethics Committee.

We obtained anonymised patient data for baseline demographics, National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), imaging, medications, and 90-day outcome. In the VISTA-ICH database extensive demographic, clinical and outcome information was collected prospectively as part of the individual trials. Anatomical therapeutic chemical (ATC) classification system was used to determine use of metformin (A10BA) and sulphonylurea (A10BB) in the VISTA-ICH dataset. In the Helsinki ICH study, data collection was performed retrospectively by chart review with reconstruction of NIHSS where it was not recorded at time of stroke assessment. In the RMH ICH study baseline patient information was recorded as part of the prospective stroke database. Chart review was performed by TYW to reconstruct baseline NIHSS where not pre-recorded, obtain medication information, baseline glucose and creatinine and to assess for 90-day outcome. In both the Helsinki ICH and RMH ICH cohorts, anti-diabetic medication use was determined by documented use of generic or trade drug names in medication charts. Medication discontinuation was defined as a pause of >24h during the first two days of ICH.

We included all consecutive diabetic patients irrespective of treatment. Non-diabetic patients were excluded from analysis due to confounding by indication for anti-diabetic use. Initial pooling was performed between Helsinki and VISTA-ICH datasets and RMH patients were subsequently added to increase the number of unselected real-life patients and the generalisability of the findings. Diabetes was defined as a pre-existing diagnosis prior to the ICH and not on basis of diabetic medication use. The primary outcome was 90-day mortality, adjusted for pre-defined covariates known to influence ICH outcome: age, gender, NIHSS, GCS, pre-stroke warfarin use, baseline ICH volume, infratentorial location of haemorrhage, and ventricular extension. Patients with missing data on any of these variables were excluded.

Statistical analysis

Data are reported as median with interquartile range or n (%) and analysed with Mann–Whitney U Test, Pearson χ² or Fisher’s exact tests as appropriate. Crude unadjusted survival is presented as Kaplan–Meier curves. The primary outcome of 90-day mortality was analysed with a logistic regression model with all the pre-defined covariates entered into the model. Test for multi-collinearity for the variables included in the logistic regression model demonstrated variance inflation factor of <3 indicating no significant multicollinearity. Receiver operator characteristic area under the curve (AUC) analysis was performed to assess the regression model fit. Several post-hoc analyses assessing potential confounding factors impacting the regression model were performed including propensity score matching 1:1 to the nearest neighbour with caliper set at 0.2 standard deviations of the logit of the propensity scores. The primary analysis was duplicated in the propensity matched population. We used SPSS 22 (IBM, Armonk, NY, USA). A two-sided p < 0.05 was considered statistically significant. As the analysis is hypothesis generating, we did not adjust for multiple testing.

Results

From a dataset of 2404 consecutive ICH patients, the proportion of diabetic patients was 148/1013 (15%)
in Helsinki, 87/404 (22%) in RMH, and 173/987 (18%) in VISTA-ICH. After excluding 34 cases with missing pre-defined covariates (Helsinki \( n = 10 \), RMH \( n = 2 \), VISTA-ICH \( n = 22 \)), we included 374 diabetic patients (Helsinki \( n = 138 \), RMH \( n = 85 \), VISTA-ICH \( n = 151 \)) in the analysis. Excluded patients had similar 90-day mortality (33% vs. 30%, \( p = 0.721 \)) and baseline characteristics with less metformin (28% vs. 40%, \( p = 0.202 \)) and sulphonylurea (24% vs 31%, \( p = 0.455 \)) use. Most (90%) patients presented within 24 h of symptom onset.

Metformin use was recorded in 148 (40%) patients while 115 (31%) patients used sulphonylurea at ICH onset. Metformin users compared to non-users had smaller ICH, milder symptoms, and lower mortality (24% vs. 34%, \( p = 0.045 \)) in univariate analysis (Table 1 and Figure 1). There was no difference in the baseline oedema volume between users and non-users of metformin (7.8 vs. 8.7 mL, \( p = 0.206 \)) or sulphonylurea (8.8 vs 7.9 mL, \( p = 0.617 \)) (Table 1). Metformin users had lower mortality rates across all strata of NIHSS and baseline ICH volumes (Figure 2 and Supplementary Table). Sulphonylurea users were older with more concurrent insulin use than non-users, but the other characteristics and mortality (30% vs. 31%; \( p = 0.860 \)) were similar. Metformin was paused or stopped in 105 (71%) and sulphonylurea in 68 (59%) of patients in the first two days.

In the multivariable model, there was no association with sulphonylurea (OR 0.96; 95% CI 0.49–1.88; \( p = 0.906 \)) on outcome. Metformin use prior to ICH was associated with lower 90-day mortality (OR 0.51; 95% CI 0.26–0.97; \( p = 0.041 \)) (Table 2). The association of metformin and 90-day mortality remained significant when analysis was limited to real life consecutive Helsinki and RMH ICH patients. There was no treatment interaction by any of the three datasets (\( p = 0.334 \) for interaction). Discontinuation of metformin on admission did not influence the association (\( p = 0.471 \) for interaction). The regression model fit was good (AUC 0.88; 95% CI 0.85–0.92).

**Post-hoc analyses**

The association of metformin and outcome remained significant after including pre-ICH insulin use, baseline glucose and creatinine into the model (OR 0.50; 95% CI 0.25–0.99; \( p = 0.047 \)). Prior insulin use, (OR 0.82; 95% CI 0.35–1.89; \( p = 0.635 \)), baseline glucose (OR 0.97; 95% CI 0.90–1.05; \( p = 0.486 \)) or serum creatinine (OR 1.00; 95% CI 0.99–1.01; \( p = 0.781 \)) were not independently associated with 90-day mortality.

After excluding 24 (6.4%) patients who underwent surgical haematoma evacuation, the association with metformin and 90-day mortality remained (OR 0.44; 95% CI 0.20–0.88, \( p = 0.020 \)).

There were 159 (43%) lobar and 215 non-lobar (57%) haemorrhages by location. The location did not influence the association of metformin and 90-day mortality (\( p = 0.502 \) for interaction).

**Table 1.** Baseline characteristics and 90-day mortality.

<table>
<thead>
<tr>
<th></th>
<th>Diabetic ((n = 374))</th>
<th>Metformin ((n = 148))</th>
<th>Non-metformin ((n = 226))</th>
<th>Sulphonylurea ((n = 115))</th>
<th>Non-SU ((n = 259))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>68 (60–76)</td>
<td>68 (62–75)</td>
<td>70 (59–76)</td>
<td>0.984</td>
<td>71 (62–78)</td>
<td>67 (59–75)</td>
</tr>
<tr>
<td>Male</td>
<td>258 (69.0%)</td>
<td>101 (68.2%)</td>
<td>157 (69.5%)</td>
<td>0.802</td>
<td>82 (71.3%)</td>
<td>176 (68.0%)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>12 (6–19)</td>
<td>11 (4–19)</td>
<td>13 (8–19)</td>
<td>0.024</td>
<td>11 (4–18)</td>
<td>13 (7–19)</td>
</tr>
<tr>
<td>GCS</td>
<td>14 (12–15)</td>
<td>14 (12–15)</td>
<td>14 (12–15)</td>
<td>0.584</td>
<td>15 (13–15)</td>
<td>14 (11–15)</td>
</tr>
<tr>
<td>ICH volume (mL)</td>
<td>12.6 (4.9–29.5)</td>
<td>10.6 (3.4–26.8)</td>
<td>14.3 (5.8–30.8)</td>
<td>0.024</td>
<td>11.1 (4.3–30.0)</td>
<td>13.2 (4.9–28.7)</td>
</tr>
<tr>
<td>Oedema volume (mL)</td>
<td>8.2 (4.0–20.4)</td>
<td>7.8 (3.1–21.3)</td>
<td>8.7 (4.4–19.6)</td>
<td>0.206</td>
<td>8.8 (3.9–19.6)</td>
<td>7.9 (4.2–20.8)</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>48 (12.8%)</td>
<td>23 (15.5%)</td>
<td>25 (11.1%)</td>
<td>0.205</td>
<td>14 (12.2%)</td>
<td>34 (13.1%)</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>141 (37.7%)</td>
<td>64 (43.2%)</td>
<td>77 (34.1%)</td>
<td>0.073</td>
<td>51 (44.3%)</td>
<td>90 (34.7%)</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>65 (17.4%)</td>
<td>32 (21.6%)</td>
<td>33 (14.6%)</td>
<td>0.080</td>
<td>26 (22.6%)</td>
<td>39 (15.1%)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>113 (30.2%)</td>
<td>36 (24.3%)</td>
<td>77 (34.1%)</td>
<td>0.045</td>
<td>34 (29.6%)</td>
<td>79 (30.5%)</td>
</tr>
<tr>
<td>Admission glucose (mmol/L)</td>
<td>87 (23.3%)</td>
<td>29 (19.6%)</td>
<td>58 (25.8%)</td>
<td>0.167</td>
<td>14 (12.2%)</td>
<td>73 (28.3%)</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>9.9 (7.8–13.1)</td>
<td>10.1 (7.9–12.4)</td>
<td>9.9 (7.7–13.5)</td>
<td>0.972</td>
<td>10.4 (8.4–13.7)</td>
<td>9.6 (7.8–12.6)</td>
</tr>
<tr>
<td></td>
<td>80 (62–97)</td>
<td>72 (60–93)</td>
<td>81 (63–102)</td>
<td>0.003</td>
<td>80 (64–93)</td>
<td>80 (62–100)</td>
</tr>
</tbody>
</table>

Note: All values are median (interquartile range) or n (%). NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; SU, sulphonylurea.
Propensity score matching reduced the sample size to 254 patients. The logistic regression analysis performed following matching demonstrated a trend towards reduced 90-day mortality in patients with pre-ICH metformin use (OR 0.55; 95% CI 0.24–1.24; p = 0.15).

**Discussion**

To our knowledge, this is the first study to investigate the association of pre-ICH metformin or sulphonylurea use on outcome. We demonstrated that pre-ICH metformin use was associated with halved odds of death by 90 days in diabetic ICH patients. In contrast to observational studies in ischaemic stroke, pre-ICH metformin administration did not attenuate infarct growth at 72 h from stroke onset. In contrast, chronic pre-stroke metformin administration reduced lactate production and infarct volume while chronic post-stroke use starting at 24 h and continued for three weeks improved neurological recovery with enhanced angiogenesis and reduced glial scarring in an AMPK dependent mechanism. The effect of metformin preconditioning may persist for at least 96 h after drug cessation. The survival benefit observed in the present study may be mediated by a similar mechanism of reduced metabolic stress and improved glycaemic control.

Hyperglycaemia has been associated with mortality after ICH, likely mediated through increased risk of infection and cardiac complications. In the present study, baseline glucose was not associated with metformin or sulphonylurea use, nor with outcome. In a rat model of ICH, hyperglycaemia significantly increased oedema volume and peri-haematomal cell death.

![Kaplan Meier curve for all-cause mortality at 90 days for users (n = 148) and non-users (n = 226) of metformin.](image-url)
Although limited human data suggest no significant effect of glucose on oedema growth\textsuperscript{19–21} and we observed no difference in baseline oedema volume between drug groups, it is plausible that metformin pre-conditioning resulted in benefits through other pathways, such as decreased lactate production via AMPK and fewer medical complications through improved glycaemic control. Despite a high drug discontinuation rate and the negative statistical interaction of drug cessation on outcome, it is likely that continuation of metformin will influence ICH outcome through these mechanisms.

The results of our analysis were derived from multiple datasets and the different management approaches to ICH may potentially influence the results. There was, however, no difference in the association of metformin with outcome by dataset ($p = 0.334$ for interaction), which adds to the external validity of our findings.

We acknowledge that our results are based on a relatively small sample and the association is at risk from type I error. However, our analysis was defined a priori and the association remained significant in a number of post-hoc analyses including adjustment for baseline glucose, creatinine and removing the potential impact
be safe in non-diabetic subjects. Metformin for Insulin Resistance (CAMERA) trial to been demonstrated in the Carotid Atherosclerosis:

nylurea is inherently not random. It is possible that our patients with diabetes, the use of metformin or sulphonylurea use are based on a relatively small sample size and thus only rule out a major mortality benefit, still allowing for the possibility of a modest effect.

Table 2. Multivariable logistic regression on factors associated with 90-day mortality in diabetic ICH patients (n = 374).

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.06</td>
<td>(1.03–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>2.87</td>
<td>(1.39–5.93)</td>
<td>0.004</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.11</td>
<td>(1.05–1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GCS (per point)</td>
<td>0.91</td>
<td>(0.79–1.05)</td>
<td>0.199</td>
</tr>
<tr>
<td>ICH volume (per mL)</td>
<td>1.03</td>
<td>(1.01–1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intratentorial location</td>
<td>3.10</td>
<td>(1.11–8.68)</td>
<td>0.031</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>3.02</td>
<td>(1.63–5.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>1.06</td>
<td>(0.48–2.34)</td>
<td>0.890</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>0.96</td>
<td>(0.49–1.88)</td>
<td>0.906</td>
</tr>
<tr>
<td>Metformin</td>
<td>0.51</td>
<td>(0.26–0.97)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage.

Conclusion
In conclusion, we have observed an association between metformin use and improved outcome in ICH. Metformin has a known safety profile and may provide an economical and accessible therapeutic option in ICH. Our results generate hypotheses which after further validation could be tested in clinical trials.

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None

Declaration of Conflicting Interests
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Ethical approval
This study was approved by the Melbourne Health Human Research Ethics Committee, reference number QA2015049.

Informed consent
This observational registry study was approved with no formal patient consent required.

Guarantor
AM.

Contributorship
TYW and AM conceived and designed the study and performed statistical analysis. TYW drafted the manuscript. TYW, DS, JP, and AM collected data. All authors interpreted the data and revised the manuscript for intellectual content.

References


**Supplementary Table. Three-month mortality rates stratified by metformin treatment status, baseline ICH volume and NIHSS**

<table>
<thead>
<tr>
<th>ICH volume, mL</th>
<th>All (n=374)</th>
<th>Metformin (n=148)</th>
<th>Non-metformin (n=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>10/98 (10.2%)</td>
<td>4/52 (7.7%)</td>
<td>6/46 (13.0%)</td>
</tr>
<tr>
<td>5-10</td>
<td>15/70 (21.4%)</td>
<td>3/21 (14.3%)</td>
<td>12/49 (24.5%)</td>
</tr>
<tr>
<td>10-15</td>
<td>9/44 (20.5%)</td>
<td>2/19 (10.5%)</td>
<td>7/25 (28.0%)</td>
</tr>
<tr>
<td>15-30</td>
<td>22/71 (31.0%)</td>
<td>6/22 (27.3%)</td>
<td>16/49 (32.7%)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>57/91 (62.6%)</td>
<td>21/34 (61.8%)</td>
<td>36/57 (63.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NIHSS</th>
<th>All (n=374)</th>
<th>Metformin (n=148)</th>
<th>Non-metformin (n=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>7/84 (8.3%)</td>
<td>4/50 (8.0%)</td>
<td>3/34 (8.8%)</td>
</tr>
<tr>
<td>6-10</td>
<td>13/73 (17.8%)</td>
<td>3/24 (12.5%)</td>
<td>10/49 (20.4%)</td>
</tr>
<tr>
<td>11-15</td>
<td>14/87 (16.1%)</td>
<td>2/25 (8.0%)</td>
<td>12/62 (19.4%)</td>
</tr>
<tr>
<td>16-20</td>
<td>28/60 (46.7%)</td>
<td>8/20 (40%)</td>
<td>20/40 (50.0%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>51/70 (72.9%)</td>
<td>19/20 (65.5%)</td>
<td>32/41 (78%)</td>
</tr>
</tbody>
</table>

All values are x/y (%).

ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale
5.3 Additional unpublished analyses

The paper was not designed to assess the association between oedema growth and antidiabetic medications. One factor limiting the ability to address this is the lack of routine follow up imaging. In Chapter VI, an oedema growth trajectory equation was created using the average growth trajectory of approximately 1500 scans. Equations for both absolute oedema (expected absolute oedema volume = 72.144*days^{0.09628} - 42.49 mL) and the oedema extension distance – EED (expected EED = 2.210*days^{0.07331}−1.478 cm), were formulated based on the Helsinki data (Wu et al., 2017a). Using this equation, expected oedema volume or EED was interpolated from observed time of the scan closest to 72 hours in the Helsinki ICH dataset with the assumption that oedema continued to evolve at the same proportional growth. This method was also used to derive absolute oedema volumes and EED for the VISTA-ICH and RMH datasets using the volumes from the baseline imaging and the association between pre-stroke use of either metformin and sulphonylurea was associated using generalized linear models, with adjustment for baseline ICH volume in the multivariable analysis.

5.3.1 Association between oral antidiabetic medications and interpolated 72-hour oedema

There was no association on univariate analysis between pre-stroke use of metformin (p=0.316) or sulphonylurea (p=0.672) and interpolated 72-hour absolute oedema volume (table 5). In multivariable analysis adjusted for oral diabetic medication status and baseline ICH volume, the association remained statistically insignificant.

<table>
<thead>
<tr>
<th></th>
<th>beta</th>
<th>standard error</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ICH volume</td>
<td>0.016</td>
<td>0.001</td>
<td>0.014-0.019</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sulphonylurea use</td>
<td>-0.001</td>
<td>0.084</td>
<td>-0.165-0.163</td>
<td>0.986</td>
</tr>
<tr>
<td>Metformin use</td>
<td>-0.126</td>
<td>0.079</td>
<td>0.030-2.520</td>
<td>0.112</td>
</tr>
</tbody>
</table>

Table 5. Association between oral antidiabetic medication, ICH volume and interpolated 72-hour absolute oedema volume
Although there was a trend towards less 72-hour EED (table 6) in users of metformin (p=0.142) or sulphonylurea (p=0.106) on univariate analysis, this association was not significant in the multivariable analysis.

Table 6. Association between oral antidiabetic medication, ICH volume and interpolated 72-hour EED

<table>
<thead>
<tr>
<th></th>
<th>beta</th>
<th>standard error</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ICH volume</td>
<td>0.008</td>
<td>0.001</td>
<td>0.006-0.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sulphonylurea use</td>
<td>-0.075</td>
<td>0.070</td>
<td>-0.212-0.062</td>
<td>0.281</td>
</tr>
<tr>
<td>Metformin use</td>
<td>-0.101</td>
<td>0.066</td>
<td>-0.230-0.029</td>
<td>0.128</td>
</tr>
</tbody>
</table>
Chapter VI – Natural history of peri-haematomatomal oedema and impact on outcome after intracerebral haemorrhage

6.1 Introduction and summary:
A rim of peri-haematomatomal oedema develops in most ICH patients and oedema development appears to evolve over a number of weeks (Urday et al., 2015b). The natural history of oedema evolution in human ICH comes from limited number of studies. In a post-hoc analysis of the INTERACT 2 trial (n=1100), absolute oedema volume roughly doubled in volume over the first 24 hours in patients with small to medium size ICH (Carcel et al., 2016). In 3 publications (Staykov et al., 2011; Wagner et al., 2012; Volbers et al., 2016b) from University of Erlangen, Germany (largest study n=383) oedema growth continued into the second week after ICH. The oedema growth trajectory in these studies suggests growth beyond the second week is possible.
Earlier studies associating oedema and ICH outcome have reported conflicting results (table 2). One study even associated increased oedema with improved outcome. (Gebel et al., 2002b) More recent analyses from the pooled analysis of INTERACT trials (Yang et al., 2015) and the VISTA-ICH collaboration (Murthy et al., 2015) have associated oedema growth at 24 and 72 hours with outcome, independent of other prognostic indicators (table 2).
Factors influencing oedema progression are not well understood but ICH volume has been the most consistently associated with oedema volume (Arima et al., 2009; Staykov et al., 2011; Yang et al., 2015). Hematoma volume is postulated to influence oedema growth in the acute stage through hydrostatic pressure and clot retraction while haemoglobin degradation products contribute to inflammation and blood-brain-barrier breakdown (Keep et al., 2012). Other factors associated with oedema growth are less certain.
The aims of this study were to describe the natural history of oedema up to 3 weeks from ICH onset using available imaging data from the Helsinki ICH Study and to investigate factors associated with outcome. A recently proposed oedema metric, the Edema Extension Distance (EED) was used in this study (Parry-Jones et al., 2015b). The relationship between EED rate and time from onset was assessed and used to create a mathematical equation enabling calculation of expected EED at any time point up to 3 weeks from ictus. The resulting oedema growth trajectory demonstrated that oedema evolves most rapidly in the acute stage with ~60% of expected oedema growth reached after 24 hours followed by slower subacute stage of growth. We also interpolated the expected EED at 72 hours and found an independent association with 6-month mortality. The potentially modifiable factors associated with EED growth were baseline ICH volume and glucose level. There were also higher rates of do-not-resuscitate orders in patients with more rapid oedema growth (45% vs 30%). This observation suggests decision to institute limitation of care may in some patients have been based on presence of poor prognostic indicators such as increased early oedema and ICH volume. The negative impact of oedema on outcome reported in this study and previous published studies could be used in conjunction with other variables to provide a general prognostication but the decision of initiating early limitation of care should be considered individually.

In conclusion the results of this study support the notion that early oedema growth influences ICH outcome and is potentially an important translational target for ICH research.
Natural History of Perihematomal Edema and Impact on Outcome After Intracerebral Hemorrhage

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Background and Purpose—Edema may worsen outcome after intracerebral hemorrhage (ICH). We assessed its natural history, factors influencing growth, and association with outcome.

Methods—We estimated edema volumes in ICH patients from the Helsinki ICH study using semiautomated planimetry. We assessed the correlation between edema extension distance (EED) and time from ICH onset, creating an edema growth trajectory model up to 3 weeks. We interpolated expected EED at 72 hours and identified clinical and imaging characteristics associated with faster edema growth. Association of EED and mortality was assessed using logistic regression adjusting for predictors of ICH outcome.

Results—From 1013 consecutive patients, 861 were included. There was a strong inverse correlation between EED growth rate (cm/d) and time from onset (days): EED growth=0.162×days exp(−0.927), R²=0.82. Baseline factors associated with larger than expected EED were older age (71 versus 68; P=0.002), higher National Institutes of Health Stroke Scale score (14 versus 8; P<0.001), and lower Glasgow Coma scale score (13 versus 15; P<0.001), larger ICH volume (19.7 versus 12.7 mL; P<0.001), larger initial EED (0.42 versus 0.30; P<0.001), irregularly shaped hematoma (55% versus 42%; P<0.001), and higher glucose (7.6 versus 6.9 mmol/L; P=0.001). Patients with faster edema growth had more midline shift (50% versus 31%; P<0.001), herniation (12% versus 4%; P<0.001), and higher 6-month (46% versus 26%; P<0.001) mortality. In the logistic regression model, higher-than-expected EED was associated with 6-month mortality (odds ratio, 1.60; 95% confidence interval, 1.04–2.46; P=0.032).

Conclusions—Edema growth can be readily monitored and is an independent determinant of mortality after ICH, providing an important treatment target for strategies to improve patient outcome. (Stroke. 2017;48:873-879. DOI: 10.1161/STROKEAHA.116.014416.)

Key Words: cerebral hemorrhage ■ edema ■ mortality ■ natural history ■ stroke

Edema evolution after intracerebral hemorrhage (ICH) is complex and incompletely understood. Results of early studies of edema have reported conflicting associations of edema on ICH outcome. More recent studies have associated early edema volume and early edema growth to patient outcome.

It is generally accepted that edema evolves over several stages from initial acute stage of ionic edema resulting from combination of hydrostatic pressure and clot retraction with potential contribution of energy-dependent ion channels to a subacute stage of vasogenic edema secondary to inflammation-mediated disruption of the blood–brain barrier. Limited human natural history data suggest that edema growth is rapid in the 24 hours after ictus followed by a stage of slow progressive edema growth peaking around the second week after ICH. Hematoma volume has been shown in edema studies to be highly correlated with subsequent edema volume, but the association with other clinical and laboratory factors is less clear. An improved understanding of edema evolution is vital in ICH management because edema increases intracranial pressure and can lead to neurological deterioration and death. Strategies targeting edema growth are likely to result in improved patient outcome. The aims of the present study are to provide a descriptive narrative of edema evolution, factors associated with increased edema volume and impact of edema on mortality using data from the HICHS (Helsinki ICH Study).
Methods

Patient Selection

HICHS methodology has been previously described. Briefly, HICHS is a retrospective analysis of consecutive ICH patients admitted to the Helsinki University Hospital between January 2005 and March 2010 and included 1013 patients. Data collection was performed retrospectively by chart review and etiologic classification performed by the SMASH-U classification system. For the present analysis, patients were excluded if there was no imaging available, if they had pure intraventricular hemorrhage, according to their brain stem location, if they underwent surgical evacuation, or if the baseline imaging was performed >7 days after ictus. There were no systematic follow-up visits of the HICHS patients, and for this reason, we do not have long-term functional outcome data. All-cause mortality was available for 1003 patients (99%) using national vital records up to November 2014. Institutional approval for the study was granted by the Helsinki University Hospital.

Hematoma and Edema Volume Ascertainment

The planimetric methods and volume processing have been described in detail elsewhere. Briefly, computed tomographic (CT) scans were transferred in a deidentified manner in the Digital Imaging and Communications in Medicine format to a central workstation. The Digital Imaging and Communications in Medicine formats were then converted into Neuroimaging Informatics Technology Initiative format before loading on Analyze 12.0 (Biomedical Imaging Resource; Mayo Clinic). Semi-automated planimetry as reported by Volbers et al was used. Edematous regions were segmented using a fixed lower Hounsfield unit (HU) of 5 and a flexible upper limit with a ceiling of 33 HU, comparing to the unaffected hemisphere for visual estimate of edema versus leukoaraiosis. For segmentation of ICH, the HU range was kept within 44 to 100 HU. A single rater (T.Y.W.) segmented ICH and edema on all scans. Volume was calculated by estimating the gantry tilt adjusted voxel depth for each slice, and an in-house script determined number of voxels within the region of interest of each slice using Matlab (The MathWorks, Inc, MA). The region of interest volume was then determined by multiplying voxel count by individual voxel volume. The reliability of this method was assessed in a separate publication consisting of 100 patients. The interrater and intrarater intraclass coefficients were 0.952 and 0.983 for edema and 0.994 and 0.999 for ICH, respectively.

Hematoma Shape Determination

Hematoma shape was rated using the 5-point visual rating scale reported by Barras et al. The hematoma shape was then dichotomized into regular (category 1) or irregular shaped (categories 2–5) hematomas for analysis.

Perihematoma Edema Metric

Edema extension distance (EED), a recently proposed novel edema metric is used in the primary analysis. The EED represents the average thickness in centimeter of the edema around the ICH and is calculated using the following equation:

$$\sqrt{\frac{\text{Edema volume} + \text{ICH volume}}{4/3\pi}} - \sqrt{\frac{\text{ICH volume}}{4/3\pi}}$$

EED was used as the edema metric in this study over absolute edema volume or relative edema index because EED has been shown to be relatively independent of ICH volume in contrast to absolute edema volume, and it does not provide disproportionately large value in smaller hematomas as in the case of edema index.

Edema Growth-to-Time Relationship Calculation

The EED growth rate (cm/d) for each scan was estimated by change in EED since previous scan divided by time since previous scan. The EED was assumed to be zero at onset. On the basis of this assumption, the growth rate between onset and baseline imaging was calculated. Scans performed within 3 weeks of ictus were included in the growth rate estimation. The EED growth rate-to-time relationship was plotted on a scatter graph. A negative exponential formula with a ceiling growth of 10 cm/d had a best fit. The ceiling growth rate of 10 cm/d was chosen as there are no real-life observations in the first seconds or minutes from ICH onset and the observed exponential fit equates to an average growth rate of 10 cm/d at 16 minutes. This equates to an unrealistic rate of EED growth or cumulative average EED of 0.5 cm at 3 minutes. The average EED was 0.35 cm from an average of 3.5 hours from onset and maximum median growth rate of 10 cm/d equates to a plausible cumulative EED of 0.12 cm at 16 minutes from onset. We, therefore, used this to calculate the expected EED at any given time point. In a secondary analysis, we derived a separate equation for calculating expected absolute edema volume at any given time point with the absolute edema volume growth rate ceiling (387mL/d) derived from the same time point used in the EED analysis.

Edema Dichotomization

To overcome the lack of routine follow-up CT scans at fixed time points, we used the derived equation to interpolate expected EED at 72 hours. As patients were scanned at different time points in routine clinical practice, we interpolated EED from observed time of the available scan closest to 72 hours from ictus, assuming the same proportional growth to 72 hours. We used the 72-hour EED for each patient to dichotomize into groups with higher-than-expected EED or lower-than-expected EED using the modeled EED growth rate-to-time data. Baseline clinical and radiological characteristics were compared between groups to assess for potential factors associated with higher EED. We also performed the same dichotomization after interpolating absolute edema volume to 72 hours. Additionally, we calculated absolute edema growth rate in patients with available baseline (<12 hours from ictus) and day-1 (12–36 hour from ictus) CT scans using method reported by Urday et al.

Statistical Analysis

Standard descriptive statistics were used, χ² or Fisher exact test was used for categorical variables and Mann–Whitney test used for continuous variables. We used mortality at 6 months, which is the norm for ICH trials as our time point of interest. Association of higher-than-expected EED with 6-month mortality was assessed with logistic regression adjusted for factors known to influence outcome: age, baseline National Institutes of Health Stroke Scale score, baseline Glasgow coma scale score, prestroke warfarin use, baseline hematoma volume, and ventricular extension. Patients with missing mortality data were included in the EED progression analysis but excluded from the logistic regression model. Testing for multicollinearity demonstrated variance inflation factor of <3.7 (range: 1.07–3.61) between variables in the logistic regression model indicating no significant multicollinearity. Receiver–operator characteristic area under the curve analysis was performed to assess the regression model fit. In the secondary analyses, we repeated the primary analysis by replacing the 72-hour EED dichotomization with different edema metrics in the multivariable model. The edema metrics were 72-hour dichotomization using interpolated absolute edema volume, interpolated 72-hour EED, interpolated 72-hour absolute edema volume and absolute edema growth rate in patients with available baseline, and day 1 CT scan. An a priori sample size calculation was not performed. Instead we used a convenience sample of all the patients in the registry. A P value of <0.05 was considered significant. All statistics were performed using SPSS 23 (IBM, Armonk, NY).

Results

Patient Characteristics

From a pool of 1013 patients, we excluded 152, leaving 861 patients for the analysis (Figure 1). A total of 1463 scans were
used for EED growth calculation, and 362 patients (42%) had at least 2 scans. The median time to baseline imaging was 8.3 hours. Patients included in this analysis had a median age of 69 years, and 503 patients (58%) were men. Baseline information was missing for heart failure in 14 patients (2%), statin use in 14 patients (2%), dyslipidemia in 10 patients (1%), and glucose in 14 patients (2%), whereas 9 patients (1%) had missing mortality data. International normalized ratio was performed in 740 patients (86%). The median baseline National Institutes of Health Stroke Scale score was 11, median baseline hematoma volume was 14.0 mL, baseline absolute edema volume was 11.9 mL, and baseline EED was 0.35 cm. Osmotic agent was used in 54 patients (6%). Hematoma shape was considered irregular in 403 patients (47%). All-cause mortality occurred in 293 patients (34%) by 6 months. Table 1 summarizes the clinical and radiological features of included patients.

Modeled Edema Progression

There was a strong inverse relationship between EED growth rate (cm/d) and time, EED growth rate=0.162*days−0.545, R²=0.820 (Figure 2). The most rapid growth occurred within the first few hours after ictus followed by an exponential slowing of the EED growth rate. On average, the EED thickness was already 60% of peak by 24 hours. The fitted model for edema volume expressed as EED up to 3 weeks is shown on Figure 3. The EED growth rate formula yields a mathematical formula of EED=2.210×days0.820−1.478, which was used to calculate the expected EED at 72 hours from onset for the patients included in the analysis. The derived growth model for absolute edema volume is represented in the Figure in the online-only Data Supplement.

Factors Associated With Higher Peak EED

Three hundred and fifty-eight patients (42%) in the study had EED that was above expected at 72 hours compared with 503 patients (58%) who had lower-than-expected EED (Table 1). On univariate analysis of clinical and radiological variables, larger-than-expected EED was associated with older age (71 versus 68; P=0.002); higher baseline National Institutes of Health Stroke Scale score (14 versus 8; P<0.001); lower baseline Glasgow Coma scale score (13 versus 15; P<0.001); higher baseline glucose (7.6 versus 6.9 mmol/L; P<0.001); larger baseline hematoma volume (19.7 versus 12.7 mL; P<0.001); irregularly shaped hematoma (55% versus 42%; P<0.001); larger baseline EED (0.42 versus 0.30 cm; P<0.001); larger baseline absolute edema volume (18.1 versus 9.3 mL; P<0.001); larger baseline relative edema, a unit-less ratio calculated by edema volume/ICH volume (0.90 versus 0.72; P<0.001); shorter onset to baseline CT time (2.1 versus 7.9 hours; P<0.001), with more patients with midline shift (n=177 [50%] versus n=157 [31%]; P<0.001); and herniation (n=43 [12%] versus n=20 [4%]; P<0.001). Previous warfarin use was associated with increased edema growth (P=0.037), whereas osmotic agent use was not (P=0.153). There was more do-not-resuscitate order (n=161 [45%] versus n=149 [30%]; P<0.001) and higher 6-month mortality (n=162 [46%] versus n=131 [26%]; P<0.001) for patients with larger than expected EED.

Association of Higher EED With Mortality

After excluding 9 patients with missing mortality data (7/503 patients [1%] with below-expected EED and 2/358 patients [1%] with above-expected EED), 852 patients were included in the logistic regression analysis. In the multivariable model, higher-than-expected EED was independently associated with mortality at 6 months (odds ratio [OR], 1.60 [95% confidence interval [CI], 1.04–2.46; P=0.032) after adjusting for age, male sex, previous warfarin use, baseline National Institutes of Health Stroke Scale score, Glasgow Coma scale score, ventricular extension, and baseline ICH volume (Table 2). There was no interaction by anticoagulant (P=0.545) or osmotic agent use (P=0.755) or hematoma shape (P=0.112) on the association of EED and mortality. Neither osmotic agent use (OR, 0.77; 95% CI, 0.37–1.63; P=0.502) nor hematoma shape (OR, 1.06; 95% CI, 0.66–1.71; P=0.797) was associated with 6-month mortality when added to the logistic regression model. The logistic regression model was of good fit (area under the curve 0.91; 95% CI, 0.89–0.93).

Association Between Other Edema Metrics and Mortality

When dichotomization was performed using interpolated 72-hour absolute edema, the association was not significant (OR, 1.45; 95% CI, 0.91–2.33; P=0.122). When edema metrics were used as a continuous variable, the 72-hour absolute edema volume was associated with mortality (OR, 1.02 per mL; 95% CI, 1.01–1.02; P<0.001), whereas 72-hour EED demonstrated a trend toward increased mortality (OR, 1.58 per cm; 95% CI, 0.92–2.71; P=0.101). In 96 patients with baseline and day-1 CT scans available, the absolute edema growth rate (mL/h) was associated with mortality (OR, 2.95 per mL/h; 95% CI, 1.41–6.14; P=0.004).
Discussion

There are 2 main findings from this study. First, there is a strong inverse relationship between edema growth and time from ICH onset; second patients with larger-than-expected edema are associated with increased mortality.

We present a model of edema growth ≤21 days derived from a large real-life data set of ICH patients. We demonstrate that edema growth was most rapid within the first 24 hours after ICH with significantly slower growth rate in the subacute period in agreement with previous natural history studies in humans.

Results from the pooled INTERACT studies (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; n=1110) and a single-center study (n=86) demonstrated doubling of absolute edema volume from baseline (under 6 hours from onset) to 24 hours.

Natural history studies with edema data ≤28 days (n=1102) indicate that peak edema volume is usually reached between week 2 and 3 after ICH onset.3,5,7,9,22–24

Our model of edema growth is also consistent with the putative 2-stage edema progression. The first stage is characterized by an initial rapid growth largely driven by clot retraction and

Table 1. Patient Clinical and Radiological Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=861)</th>
<th>Above-Expected EED (n=358)</th>
<th>Below-Expected EED (n=503)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69 (50–78)</td>
<td>71 (60–80)</td>
<td>68 (58–76)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male sex</td>
<td>503 (58)</td>
<td>197 (55)</td>
<td>306 (61)</td>
<td>0.093</td>
</tr>
<tr>
<td>Hypertension</td>
<td>549 (64)</td>
<td>226 (63)</td>
<td>323 (64)</td>
<td>0.774</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>127 (15)</td>
<td>49 (14)</td>
<td>78 (16)</td>
<td>0.496</td>
</tr>
<tr>
<td>Baseline glucose*</td>
<td>7.2 (6.1–8.9)</td>
<td>7.6 (6.4–9.2)</td>
<td>6.9 (5.9–8.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>117 (14)</td>
<td>51 (14)</td>
<td>66 (13)</td>
<td>0.687</td>
</tr>
<tr>
<td>Heart failure*</td>
<td>41 (5)</td>
<td>23 (7)</td>
<td>18 (4)</td>
<td>0.073</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>131 (15)</td>
<td>62 (17)</td>
<td>69 (14)</td>
<td>0.150</td>
</tr>
<tr>
<td>Baseline INR*</td>
<td>1.0 (1.0–1.2)</td>
<td>1.0 (1.0–1.2)</td>
<td>1.0 (1.0–1.1)</td>
<td>0.867</td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>170 (149–192)</td>
<td>173 (150–195)</td>
<td>169 (147–191)</td>
<td>0.126</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>176 (21)</td>
<td>73 (21)</td>
<td>103 (21)</td>
<td>1.000</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>49 (6)</td>
<td>30 (6)</td>
<td>39 (6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Any antiplatelet</td>
<td>239 (28)</td>
<td>207 (30)</td>
<td>132 (26)</td>
<td>0.247</td>
</tr>
<tr>
<td>Warfarin</td>
<td>121 (14)</td>
<td>61 (17)</td>
<td>60 (12)</td>
<td>0.037</td>
</tr>
<tr>
<td>Statin use*</td>
<td>169 (20)</td>
<td>75 (22)</td>
<td>94 (19)</td>
<td>0.383</td>
</tr>
<tr>
<td>Antihypertensive use</td>
<td>428 (50)</td>
<td>176 (50)</td>
<td>252 (50)</td>
<td>0.836</td>
</tr>
<tr>
<td>Osmotic agent use†</td>
<td>54 (6)</td>
<td>17 (5)</td>
<td>37 (7)</td>
<td>0.153</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>11 (4–19)</td>
<td>14 (6–22)</td>
<td>8 (3–17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline GCS</td>
<td>14 (11–15)</td>
<td>13 (9–15)</td>
<td>15 (12–15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular ICH</td>
<td>351 (41)</td>
<td>135 (38)</td>
<td>216 (43)</td>
<td>0.139</td>
</tr>
<tr>
<td>Baseline edema volume</td>
<td>11.9 (5.0–27.3)</td>
<td>18.1 (7.9–43.0)</td>
<td>9.3 (3.5–19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline EED</td>
<td>0.35 (0.22–0.48)</td>
<td>0.42 (0.30–0.54)</td>
<td>0.30 (0.16–0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline relative edema</td>
<td>0.80 (0.49–1.22)</td>
<td>0.90 (0.64–1.39)</td>
<td>0.72 (0.39–1.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline hematoma volume</td>
<td>14.0 (6.1–40.1)</td>
<td>19.7 (7.5–63.2)</td>
<td>12.7 (5.4–27.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Irregular shaped hematoma</td>
<td>403 (47)</td>
<td>196 (55)</td>
<td>207 (42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset to baseline scan, hours</td>
<td>3.5 (1.6–15.0)</td>
<td>2.1 (1.4–4.83)</td>
<td>7.9 (1.9–28.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Do-not-resuscitate order</td>
<td>310 (54)</td>
<td>161 (45)</td>
<td>149 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-mo mortality*</td>
<td>293 (34)</td>
<td>162 (46)</td>
<td>131 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Midline shift</td>
<td>334 (39)</td>
<td>177 (50)</td>
<td>157 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Herniation</td>
<td>63 (7)</td>
<td>43 (12)</td>
<td>20 (4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All values are median (interquartile range) or n (%). BP indicates blood pressure; CT, computed tomography; EED, edema extension distance; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; and NIHSS, National Institutes of Health Stroke Scale.

*Missing data for mortality in 9 patients (1%), heart failure in 14 patients (2%), dyslipidemia in 10 patients (1%), statin use in 14 patients (2%), and baseline glucose in 14 patients (2%). Baseline INR was available in 740 patients (86%).

†Osmotic agent use indicates use of hypertonic saline, glycerol, or mannitol alone or in combination.
hydrostatic pressure. Clot retraction occurs in response to hemostatic activation designed to limit the primary injury at the site of hemorrhage and increases intraclot pressure leading to shift of serum fluid into the adjacent brain parenchyma. At this acute stage, the blood–brain barrier is relatively intact in contrast to the subacute stage of slower edema growth characterized by vasogenic edema associated with blood–brain barrier breakdown likely mediated by iron-related toxicity and accompanying inflammation. The course of edema progression in previous studies and our model suggests that further growth beyond week 3 is possible, but the significance of late edema on ICH outcome is uncertain.

We found larger baseline ICH volume to be significantly associated with larger-than-expected edema volume. This finding continues to support the consistently reported association of hematoma blood components with edema pathophysiology. Studies have also indicated an association of surrogate markers of iron load such as hematocrit and serum...
Table 2. Multivariable Logistic Regression Analysis of Factors Associated With 6-mo Mortality (n=852)

<table>
<thead>
<tr>
<th>Factor</th>
<th>6-mo Mortality, OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher-than-expected EED</td>
<td>1.60 (1.04–2.46)</td>
<td>0.032</td>
</tr>
<tr>
<td>Baseline hematoma volume</td>
<td>1.02 (1.02–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.06 (1.04–1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.63 (1.67–4.14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>2.56 (1.47–4.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>1.12 (1.08–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline GCs score</td>
<td>0.95 (0.88–1.04)</td>
<td>0.248</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>2.38 (1.55–3.65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; EED, edema extension distance; GCs, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

Conclusions

Edema growth is strongly correlated with time from stroke onset, influenced by baseline hematoma volume and associated with long-term mortality. Edema growth is an important treatment target for strategies to improve patient outcome.
Sources of Funding
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Disclosures
None.

References
Days from intracerebral hemorrhage onset

Absolute edema volume, mL

Supplementary figure*

* 2 outlier scans with >200mL edema volume not presented in this figure
Chapter VII – Impact of early glycaemic status on outcome and oedema growth after intracerebral haemorrhage

7.1 Introduction and summary

Hyperglycaemia has been associated with poor ICH outcome in a number of studies, mostly based on result of single glucose measurement in time (Franke et al., 1992; Schwarz et al., 2000; Passero et al., 2003; Fogelholm et al., 2005a; Kimura et al., 2007; Godoy et al., 2008; Tetri et al., 2009; Lee et al., 2010; Samiullah et al., 2010; Stead et al., 2010; Appelboom et al., 2011; Di Napoli et al., 2011; Qureshi et al., 2011; Wang et al., 2011; Bejot et al., 2012; Feng et al., 2012; Tapia-Perez et al., 2014; Koga et al., 2015; Saxena et al., 2016; Sun et al., 2016; Liu et al., 2017). The impact of subsequent glucose trajectory on outcome and oedema growth is uncertain and not well explored in previous literature. The aim of this study was to assess the association of glycemic trajectory on ICH mortality and acute oedema growth. In the 576 patients with available glucose measurements at baseline (0-24 hour) and on follow up (24-72 hour), patients were considered to have persistent hyperglycaemia if the glucose was ≥8 mMol/L in both epochs. Other glycemic groups were persistent normoglycaemia (glucose <8mMol/L in both epochs), isolated early and isolated late hyperglycaemia. Association between glycemic trajectories and 6-month mortality was analysed in multivariable logistic regression analysis. The relationship between glycemic trajectory and interpolated 72-hour EED (reported in Chapter VI) was also analysed.

The results show that only 52.5% of patients with baseline hyperglycaemia (n=318) remained persistently hyperglycaemic. Patients with persistent hyperglycaemia had a 3.5 fold increased in odds of mortality independent of other known predictors of outcome. There was also no association between glycemic trajectory and oedema at 72-hours. The results suggest that not all patients with baseline hyperglycaemia are at an increased risk of poor outcome, and risk is increased in those with persistently
elevated glucose. Treatment of persistent early hyperglycaemia may improve patient mortality and strategies to achieve persistent normoglycaemia in ICH patients should be assessed in a clinical trial.
Persistent Hyperglycemia Is Associated With Increased Mortality After Intracerebral Hemorrhage

Teddy Y. Wu, MBChB, FRACP; Jukka Putaala, MD, PhD; Gagan Sharma, MCA; Daniel Strbian, MD, PhD; Turgut Tatlisumak, MD, PhD; Stephen M. Davis, MD, FRACP; Atte Meretoja, MD, PhD, FRACP

Background—Hyperglycemia may be associated with worse outcome after intracerebral hemorrhage (ICH). We assessed the association of early glycemic trajectory on ICH mortality and edema growth.

Methods and Results—We included patients from the Helsinki ICH study with glucose measurements at least once between both 0 to 24 and 24 to 72 hours from onset. Hyperglycemia was defined as blood glucose ≥8 mmol/L (144 mg/dL) based on the local threshold for treatment. Glycemic trajectory was defined on maximum values 0 to 24 and 24 to 72 hours after ICH: (1) persistent normoglycemia in both epochs; (2) late hyperglycemia (only between 24 and 72 hours); (3) early hyperglycemia (only before 24 hours); and (4) persistent hyperglycemia in both epochs. Logistic regression with known predictors of outcome estimated the association of glycemic trajectory and 6-month mortality. A generalized linear model assessed the association of glycemic trajectory and interpolated 72-hour edema extension distance. A total of 576 patients met eligibility criteria, of whom 214 (37.2%) had persistent normoglycemia, 44 (7.6%) late hyperglycemia, 151 (26.2%) early hyperglycemia, and 167 (29.0%) persistent hyperglycemia. Six-month mortality was higher in the persistent (51.1%) and early (26.3%) hyperglycemia groups than the normoglycemia (19.0%) and late hyperglycemia (3.6%) groups. Persistent hyperglycemia was associated with 6-month mortality (odds ratio 3.675, 95% CI 1.989–6.792; P<0.001). Both univariate (P=0.426) and multivariable (P=0.493) generalized linear model analyses showed no association between glycemic trajectory and 72-hour edema extension distance.

Conclusion—Early hyperglycemia after ICH is harmful if it is persistent. Strategies to achieve glycemic control after ICH may influence patient outcome and need to be assessed in clinical trials. (J Am Heart Assoc. 2017;6:e005760. DOI: 10.1161/JAHA.117.005760.)

Key Words: edema • glucose • hyperglycemia • intracerebral hemorrhage • mortality

The current American Stroke Association guidelines endorse avoidance of hyperglycemia in patients with intracerebral hemorrhage (ICH). The recommendation was based on association of hyperglycemia and poor outcome in observational studies. The major limitation of these studies is use of single glucose measurement not accounting for potential glucose fluctuations after ICH. Six studies (n=60–295) have utilized multiple glucose measurements in analysis of ICH outcome with mixed results. In preclinical studies, hyperglycemia increases neuronal cell death and brain edema by enhancing breakdown of the blood–brain barrier. It is plausible that hyperglycemia could mediate secondary injury through similar mechanisms in human ICH. There is emerging evidence that secondary injury from perihematomal edema is associated with poor ICH outcome. Edema is strongly correlated with hematoma volume, but other mediators of edema growth including glucose are uncertain. It is possible that glucose and edema evolution are mechanistically related, making them potential modifiable therapeutic targets.

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Accompanying Tables S1 through S6 are available at http://jaha.ahajournals.org/content/6/8/e005760/DC1/embed/inline-supplementary-material-1.pdf

This work was presented as a poster abstract at the International Stroke Conference, February 22–24, 2017, in Houston, TX.

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Hyperglycemia and Cerebral Hemorrhage Mortality

Wu et al

Clinical Perspective

What Is New?

• Only half of intracerebral hemorrhage patients with baseline hyperglycemia remain persistently hyperglycemic.
• Association with mortality was only observed in patients with persistent hyperglycemia.

What Are the Clinical Implications?

• Optimizing glycemic status early after intracerebral hemorrhage may improve outcome after intracerebral hemorrhage.

The aims of this study are to evaluate the impact of early glycemic trajectory on ICH mortality and edema growth. We hypothesized that persistent hyperglycemia is associated with increased mortality and edema growth.

Methods

Patients

Patients from the Helsinki ICH study16 (HICHS) were included. Briefly, HICHS is a retrospective analysis of 1013 consecutive ICH patients admitted to Helsinki University Hospital between January 2005 and March 2010. Data collection was performed retrospectively by chart review.16 Patients were excluded from the current analysis if there was no imaging data available, had missing 6-month mortality data, or had no glucose measurement either within 24 hours and/or between 24 and 72 hours of ICH onset. Stroke onset time was determined from witnessed onset in 363 (63.0%) patients and from last known well time in 213 (37.0%) patients. Institutional approval for the study was granted by the Helsinki University Hospital, and patient consent was not required as there was no patient contact in this observational study registry.

Planimetric ICH and Edema Volume Ascertainment

Hematoma and edema volumes were segmented using semiautomated planimetry.17 Briefly, de-identified computed tomography images were loaded on Analyze 12.0 (Biomedical Imaging Resource; Mayo Clinic). Edematous regions were segmented using a fixed lower Hounsfield Unit (HU) of 5 and a flexible upper limit with a ceiling of 33 Hounsfield Units, comparing with the unaffected hemisphere for visual estimate of edema versus leukoaraiosis. For ICH, Hounsfield Unit range was kept within 44 to 100 Hounsfield Units. T.Y.W. performed segmentation on all scans. The segmented regions of interest were subjected to in-house processing to derive volumes that take into account gantry tilt and true slice thickness as reported in detail elsewhere.17

Glycemic Trajectory Determination

Hyperglycemia was defined as blood glucose ≥8 mmol/L (144 mg/dL) based on the local threshold for treatment. The Helsinki protocol during the study was to provide sliding scale insulin when the glucose was ≥8 mmol/L. Glycemic trajectory was defined on maximum values 0 to 24 and 24 to 72 hours after ICH. Four categories were determined: (1) persistent normoglycemia in both epochs; (2) late hyperglycemia (only between 24 and 72 hours); (3) early hyperglycemia (only before 24 hours); and (4) persistent hyperglycemia in both epochs.

Edema Metric and Interpolated 72-Hour Edema Volume

Edema extension distance (EED), a recently reported edema metric, was used in assessing the association of glycemic trends and edema growth.18 We have previously reported average edema growth trajectory derived from a negative exponential formula (EED growth = 0.162 × days⁻⁰.⁹²⁷, R²=0.82) utilizing data from HICHS.19 This growth rate equates to the average expected EED at any time point from \( ictus = 2.210 \times \text{days}^{0.67331} - 1.478 \). As the patients were scanned at different time points in routine clinical practice, we interpolated the EED from the observed time of an individual’s EED closest to 72-hour time point, assuming the same proportional growth to derive the expected 72-hour EED for the individual patient. In other words, if the patient’s last scan was at 48 hours and was 70% of the average expected EED at this time point, we assumed the patients to also have 70% of average expected 72-hour EED.

Statistical Analysis

Standard descriptive statistics were used. Differences in patient characteristics, stroke severity, and imaging metrics between the glycemic trajectories were assessed on univariate analysis using \( \chi^2 \) or Fisher exact test for categorical variables and Mann–Whitney test for continuous variables. We used mortality at 6 months, the common time point of end point in ICH trials,20,21 Survival differences between the glycemic trajectories were performed using the log rank test and plotted on Kaplan–Meier curve. Association with glycemic trend categories with 6-month mortality was assessed in a logistic regression model adjusted for log-transformed hematoma volume, age, male sex, prior warfarin use, baseline National Institutes of Health Stroke Scale (NIHSS), Glasgow

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Coma Scale (GCS), presence of intraventricular extension, male sex, and infratentorial location, which are factors associated with ICH outcome.\textsuperscript{16} Baseline ICH volume was log transformed before logistic regression analysis to avoid potential confounding by outliers. Collinearity between the covariates in the logistic regression model was checked. The model fit was tested using receiver operating characteristic area under the curve. The impact of glycemic trajectory on model fit was assessed by using a base model with log-transformed ICH volume and age as covariates, a second model with all covariates other than glycemic trajectory, and finally the full model. In the secondary analyses, we repeated the primary analysis by replacing glucose trajectory with the maximum recorded glucose as continuous variable from each epoch (0–24 and 24–72 hours) adjusting for all predefined variables. Correlation between the maximum recorded glucose from the 2 epochs was assessed using Pearson correlation. Further, we assessed the association of absolute change in maximum glucose from 0 to 24 hours to 72 hours and mortality adjusted for 0 to 24-hour glucose and other predefined covariates as listed above. In addition, the logistic regression analysis was also performed adjusting for hematoma growth (defined as 6-mL growth or 33% relative growth on follow-up computed tomography) in the subset of patients with follow-up imaging available. Finally, we performed a propensity-score matching analysis by estimating the propensity score for the covariates included in the primary logistic regression model. Matching was performed to the nearest neighbor with caliper set at 0.1 SD of the log of the propensity scores. The primary analysis was then repeated in the propensity-score-matched population. Association between glycemic trajectory categories and interpolated EED was analyzed using generalized linear model adjusted for factors associated (P<0.1) with increased edema on univariate analysis. A P<0.05 in the multivariable models was considered significant. Propensity-score matching was performed using R 3.1.0 Matchit package while all other statistics were performed using SPSS 23 (IBM, Armonk, NY).

**Results**

Of 1013 HICHS patients, 576 (57%) were eligible for the present analysis. Reasons for excluding 437 patients were the following: no planimetric data (n=19), missing 6-month mortality (n=10), or missing glucose data (n=408) in either or both time windows mostly because of late presentation or early death/palliation, as illustrated in Figure 1. Excluded patients were older (70 versus 65), more likely to have a history of ischemic heart disease (15.8% versus 10.4%) or previous ICH (7.3% versus 3.8%), at baseline had lower GCS (14 versus 15), higher NIHSS (13 versus 10), larger ICH volume (18.0 mL versus 13.4 mL), absolute edema volume (14.4 mL versus 10.1 mL), and EED (0.37 cm versus 0.32 cm), more often irregular hematoma shape (55.4% versus 44.3%), infratentorial location (16.7% versus 12.0%), ventricular extension (45.1% versus 38.0%), and had higher 6-month mortality (39.2% versus 23.8%). In the excluded patients because of early death or palliation (n=167), the highest recorded glucose in the 0 to 24-hour epoch was higher than the included patients (9.40 mmol/L versus 8.30 mmol/L, P<0.001) and they were more likely to be hyperglycemic at 0 to 24 hours [123/167 (73.7%) versus 318/576 (55.2%), P<0.001]. Excluded patients were thus either mild and late, or with characteristics making them prone to early palliation and death (Table S1).

**Baseline Patient Characteristics and Glycemic Trajectory**

Of the 576 patients in the analysis, 214 (37.2%) had persistent normoglycemia, 44 (7.6%) late only hyperglycemia, 151 (26.2%) early only hyperglycemia, and 167 (29.0%) persistent hyperglycemia. In 318 (55%) patients with hyperglycemia within 24 hours of ictus, 167 (53%) remained persistently hyperglycemic (Figure 1). The glycemic trajectory groups differed by presence of hypertension, diabetes mellitus, insulin, antiplatelet, anti-hypertensive medication and statin use, rate of infection, neurosurgery, baseline NIHSS, GCS, ICH and absolute edema volumes, hematoma shape, infratentorial location, and ventricular extension (Table 1). The 6-month mortality rate also differed between different glycemic trajectory groups, with the highest mortality observed in patients with early and persistent hyperglycemia on univariate analysis (Table 1, Figure 2).

**Factors Associated With 6-Month Mortality**

There were 137 (23.8%) deaths by 6 months and factors associated with 6-month mortality on univariate analysis were older age, prior use of warfarin or antihypertensive medication, evidence of infection, lower GCS, higher NIHSS, higher baseline ICH and absolute edema volumes, irregular hematoma shape, ventricular extension, and 72-hour EED (Table 2).

In the multivariable logistic regression model, persistent hyperglycemia was associated with 6-month mortality (odds ratio [OR] 3.675, 95% CI 1.989–6.792; P<0.001) adjusted for log-transformed baseline ICH volume, baseline absolute edema volume, male sex, age, ventricular extension, infratentorial location, NIHSS, and GCS (Table 3). Based on the Wald statistic, glycemic trajectory had the strongest association with outcome of all the covariates. The variance inflation factor was <3.0 between the covariates in the model indicating no significant multicollinearity. The logistic regression model was of good fit (area under the curve 0.877, 95% CI 0.846–0.908) and the addition of glycemic trajectory into
base models containing known predictors of outcome provided the best fit (Table S2).

Neither surgery (OR 0.560, 95% CI 0.247–1.270, P = 0.165) nor presence of infection (OR 0.911, 95% CI 0.546–1.540, P = 0.744) was associated with 6-month mortality when included in the model or influenced the association of persistent hyperglycemia and mortality (with surgery—OR 3.676, 95% CI 1.985–6.807, P < 0.001; with infection—OR 3.693, 95% CI 1.997–6.828, P < 0.001). There was also no interaction of surgery (P = 0.965) or presence of infection (P = 0.594) on the association between glycemic trajectory and mortality. The association with 6-month mortality in the persistent hyperglycemia group remained significant after excluding the 89 patients with diabetes mellitus (OR 5.139, 95% CI 2.545–10.376, P < 0.001).

In the secondary analyses, glucose as a continuous variable was associated with 6-month mortality in both the 0 to 24-hour (OR 1.075 per mmol/L increase, 95% CI 1.018–1.135, P = 0.009) and 24 to 72-hour (OR 1.140 per mmol/L increase, 95% CI 1.050–1.238, P = 0.002) epochs. There was a significant correlation between the maximum glucose measurements in each epoch (Pearson correlation 0.541, P < 0.001). Absolute glucose change between the maximum readings from the 2 epochs was also associated with 6-month mortality (OR 1.101 per mmol/L increase, 95% CI 1.002–1.210, P = 0.046) in the logistic regression analysis adjusting for the predefined covariates and maximum glucose from 0 to 24-hour epoch. In the 184 (31.9%) patients with baseline (<12 hours from ictus) and follow-up computed tomography (12–72 hours from ictus) available, introducing hematoma growth into the logistic regression model did not influence the association of persistent hyperglycemia on mortality (OR 3.674, 95% CI 1.307–10.332, P = 0.014).
Table 1. Baseline Patient Characteristics and Glycemic Trajectory

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total, n=214</th>
<th>Persistent Normoglycemia, n=117</th>
<th>Late Hyperglycemia, n=44</th>
<th>Early Hyperglycemia, n=51</th>
<th>Persistent Hyperglycemia, n=44</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66 (57–84)</td>
<td>69 (58–86)</td>
<td>66 (57–84)</td>
<td>62 (57–85)</td>
<td>66 (58–84)</td>
<td>0.537</td>
</tr>
<tr>
<td>Male sex</td>
<td>342 (59.4%)</td>
<td>128 (59.8%)</td>
<td>24 (54.5%)</td>
<td>85 (56.3%)</td>
<td>105 (62.9%)</td>
<td>0.597</td>
</tr>
<tr>
<td>Hypertension</td>
<td>357 (62.0%)</td>
<td>109 (50.9%)</td>
<td>29 (65.9%)</td>
<td>89 (58.9%)</td>
<td>130 (77.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>89 (15.5%)</td>
<td>5 (2.3%)</td>
<td>2 (4.5%)</td>
<td>14 (9.3%)</td>
<td>68 (40.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>75 (13.0%)</td>
<td>27 (12.6%)</td>
<td>7 (15.9%)</td>
<td>20 (13.2%)</td>
<td>21 (12.6%)</td>
<td>0.942</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>60 (10.4%)</td>
<td>14 (8.5%)</td>
<td>6 (13.6%)</td>
<td>16 (10.6%)</td>
<td>24 (14.4%)</td>
<td>0.081</td>
</tr>
<tr>
<td>Cardiac failure*</td>
<td>30 (5.3%)</td>
<td>7 (3.3%)</td>
<td>2 (4.5%)</td>
<td>12 (7.9%)</td>
<td>9 (5.5%)</td>
<td>0.288</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>121 (21.2%)</td>
<td>42 (19.7%)</td>
<td>12 (27.3%)</td>
<td>22 (14.8%)</td>
<td>45 (27.4%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>22 (3.8%)</td>
<td>8 (3.7%)</td>
<td>3 (6.8%)</td>
<td>7 (4.6%)</td>
<td>4 (2.4%)</td>
<td>0.517</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>138 (24.0%)</td>
<td>48 (22.4%)</td>
<td>6 (13.6%)</td>
<td>22 (14.6%)</td>
<td>62 (37.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>71 (12.3%)</td>
<td>25 (11.7%)</td>
<td>5 (11.4%)</td>
<td>22 (14.6%)</td>
<td>19 (11.4%)</td>
<td>0.810</td>
</tr>
<tr>
<td>Anti-hypertensive medication</td>
<td>267 (46.4%)</td>
<td>80 (37.4%)</td>
<td>19 (43.2%)</td>
<td>66 (43.7%)</td>
<td>102 (61.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin use*</td>
<td>35 (6.3%)</td>
<td>1 (0.5%)</td>
<td>1 (2.3%)</td>
<td>2 (1.3%)</td>
<td>32 (19.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin use*</td>
<td>110 (19.3%)</td>
<td>37 (17.3%)</td>
<td>9 (20.5%)</td>
<td>16 (11.0%)</td>
<td>48 (28.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>64 (11.1%)</td>
<td>14 (6.5)</td>
<td>5 (11.4%)</td>
<td>28 (18.5%)</td>
<td>17 (10.2%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Any infection†</td>
<td>305 (53.0%)</td>
<td>95 (44.4%)</td>
<td>24 (54.5%)</td>
<td>87 (57.6%)</td>
<td>99 (59.3%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>10 (5–34)</td>
<td>7 (3–22)</td>
<td>8 (5–25)</td>
<td>13 (6–35)</td>
<td>13 (7–35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to baseline CT scan</td>
<td>2.7 (1.5–8.1)</td>
<td>3.0 (1.5–11.4)</td>
<td>4.4 (1.8–12.7)</td>
<td>2.3 (1.4–5.4)</td>
<td>2.5 (1.4–6.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Baseline ICH volume, mL</td>
<td>13.4 (5.6–79.2)</td>
<td>10.3 (3.9–57.3)</td>
<td>9.0 (4.3–73.2)</td>
<td>16.1 (7.2–85.3)</td>
<td>17.8 (7.9–96.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline edema volume, mL</td>
<td>10.1 (3.9–61.2)</td>
<td>9.0 (3.5–43.6)</td>
<td>10.6 (3.5–51.4)</td>
<td>10.9 (4.1–51.6)</td>
<td>10.3 (5.1–82.0)</td>
<td>0.047</td>
</tr>
<tr>
<td>Baseline EED, cm</td>
<td>0.32 (0.19–0.44)</td>
<td>0.33 (0.19–0.44)</td>
<td>0.33 (0.18–0.50)</td>
<td>0.30 (0.20–0.41)</td>
<td>0.31 (0.18–0.47)</td>
<td>0.733</td>
</tr>
<tr>
<td>72-h EED, cm</td>
<td>0.87 (0.62–1.20)</td>
<td>0.60 (0.42–0.78)</td>
<td>0.60 (0.46–0.82)</td>
<td>0.65 (0.42–0.91)</td>
<td>0.63 (0.43–0.91)</td>
<td>0.429</td>
</tr>
<tr>
<td>Peak available EED, cm</td>
<td>0.51 (0.32–0.78)</td>
<td>0.51 (0.33–0.75)</td>
<td>0.51 (0.35–0.60)</td>
<td>0.51 (0.30–0.68)</td>
<td>0.54 (0.33–0.80)</td>
<td>0.496</td>
</tr>
<tr>
<td>Irregular hematoma shape†</td>
<td>255 (44.3%)</td>
<td>77 (36.0%)</td>
<td>15 (34.1%)</td>
<td>73 (48.7%)</td>
<td>90 (53.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>69 (12.0%)</td>
<td>18 (8.4%)</td>
<td>2 (4.5%)</td>
<td>28 (18.5%)</td>
<td>21 (12.6%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>219 (38.0%)</td>
<td>65 (30.4%)</td>
<td>11 (25.0%)</td>
<td>65 (43.0%)</td>
<td>78 (46.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>6-m mortality</td>
<td>137 (23.8%)</td>
<td>26 (12.1%)</td>
<td>5 (11.4%)</td>
<td>36 (23.8%)</td>
<td>70 (41.9%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) or n (%). CT indicates computed tomography; EED, edema extension distance; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale.

*Missing data for prior statin (6) and insulin (3) use, history of cardiac failure (9), and dyslipidemia (6).
†Infection was defined as pneumonia, urinary tract infection, sepsis, or other infection treated with antibiotics.
‡Hematoa shape not classified for 1 patient with pure NIH.

Propensity-Score Matching Analysis

Propensity-score matching resulted in a reduced number of patients in each glycemic trajectory group (total n=266; glycemic trajectory groups: persistent normoglycemia n=81, early only hyperglycemia n=71, late only hyperglycemia n=44, and persistent hyperglycemia n=70) with matched baseline characteristics (Table S3). In the multivariable logistic regression analysis, the association between persistent hyperglycemia and mortality remained (OR 3.653, 95% CI 1.357–9.836, P=0.010) (Table S4).

Association Between Glycemic Trajectory and Interpolated 72-Hour EED

In the generalized linear model analyses, there was no association between glycemic trajectory groups and interpolated 72-hour EED in either univariate (P=0.426) or multivariable analyses (P=0.493, Table S5, adjusted for log baseline ICH volume, diabetes mellitus, history of hypertension, irregular hematoma shape, baseline NIHSS, ventricular extension, and infratentorial location).
Discussion

We have shown in a large sample of ICH patients that early hyperglycemia is only associated with ICH mortality if the hyperglycemia is persistent. The association of persistent hyperglycemia with mortality remained robust even after excluding patients known to have diabetes mellitus and adding propensity-score-matching analysis.

A large number of observational studies (21 studies, total number of patients=12 145, Table S6)10–11,22–32 have examined the association between glucose with ICH outcome with the majority (15 studies, total n=11 161) defining hyperglycemia on the basis of single glucose measurement. One notable study was the post hoc analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) II study (n=2653).30 The authors assessed the prognostic significance of admission glucose level on 90-day outcome. This study reported that admission glucose both as a continuous variable and also the highest quartile (>7.9 mmol/L) was associated with combined outcome of death or disability (adjusted OR per mmol/L glucose 1.35, 95% CI 1.01–1.33, P=0.043; adjusted OR for fourth quartile of glucose level 1.34, 95% CI 1.01–1.80, P for trend 0.015).

Six studies (n=984)10–11 reported results for more than single glucose measurement. Although studies by Tapia-Perez et al10 and Koga et al11 reported an association between glucose and outcome (Table S6), these studies (n=298) derived the outcome association from a single glucose measurement, even though multiple time points were reported. Our secondary analyses using glucose as a continuous variable at both the 0 to 24 and 24 to 72-hour epochs are in agreement with these findings. However, we can only report the true natural history of glucose below the cutoff for glucose-lowering treatment and our results do not provide insight into the natural peak of glucose reached in hyperglycemic patients. The results of the secondary analyses therefore need to be interpreted within this context.

Four studies (Table S6) evaluated glycemic trajectory on ICH outcome. In the post hoc analysis of the Antihypertensive Treatment of Acute Cerebral Hemorrhage I (ATACH I, n=60)9 study, increasing glycemic trend in the first 72 hours was associated with 2.5-fold increase in risk of 90-day death or disability on univariate analysis, but this was not significant when adjusted for GCS, ICH volume, and ventricular extension (relative risk 1.19, 95% CI 0.92–1.54, P value not reported). Feng et al assessed the impact of hyperglycemia (mean glucose over 72 hours of ≥150 mg/dL) in 135 ICH patients9 and found no association between hyperglycemia and 90-day death or disability (OR 1.06, 95% CI 0.42–2.66, P value not reported). Godoy et al reported in 295 patients that those with persistent hyperglycemia in the 72 hours after ICH (n=78) had higher 30-day mortality (80%) compared with other glycemic trajectory groups on univariate analysis (P<0.001), but no multivariable analysis was reported.7 Schwarz et al analyzed the impact of persistent hyperthermia at 72 hours on poor outcome (OR for hyperthermia >48-hour duration 13.52, 95% CI 2.22–82.23, P=0.005) in 196 ICH patients.6 In the multivariable analysis, persistent hyperglycemia (defined as ≥11.0 mmol/L for more than 24-hour duration, n=32) was associated with poor discharge outcome (OR 13.54, 95% CI 2.24–81.78, P=0.005). There was no association between hyperglycemia of <24-hour duration with outcome (Table S6). Our results, derived from a significantly larger sample size (n=576), are in concordance with that reported by Schwarz,6 and suggests that hyperglycemia is only harmful after ICH if it persists.

We did not find a significant association with ICH mortality in the subgroup of patients (n=44, 7.7% of cohort) classified with late-only hyperglycemia (OR 0.965, 95% CI 0.298–3.129, P=0.952). These results were derived from a small sample size with a point estimate that approached 1 and a wide confidence interval. The negative association needs to be considered in this context and late hyperglycemia should still be managed as per current best practice guidelines.1 Although our secondary analyses showed increasing glucose levels in both epochs to be associated with mortality, it is likely the outcome association is driven by patients with persistent rather than transient hyperglycemia as demonstrated in the primary analysis.

The mechanism through which hyperglycemia mediates ICH outcome is uncertain. It is plausible that hyperglycemia reflects more severe brain injury resulting from larger baseline

![Figure 2. Kaplan–Meier survival curve according to glycemic trajectory.](image)
hematoma volume (Table 1). However, our logistic regression analyses indicate the robust association of persistent hyperglycemia and mortality even after adjusting for surgery, evidence of infection, and hematoma growth, which are factors that also influence outcome. It is possible that hyperglycemia exacerbates secondary injury. In rat ICH models, hyperglycemia was associated with increased neuronal death and brain edema caused by worsened blood–brain barrier disruption.12,13 However, data from INTERACT II showed no association between baseline hyperglycemia and 24-hour absolute edema growth (glucose ≥6.5 mmol/L versus <6.5 mmol/L, 2.6 mL versus 3.0 mL edema growth, respectively, P=0.293).10 We were also unable to demonstrate an association between hyperglycemia and 72-hour EED. In humans, hyperglycemia induces inflammatory cytokines and the effect persists until return to normoglycemic

Table 2. Baseline Patient Characteristics Associated With 6-Month Mortality

<table>
<thead>
<tr>
<th></th>
<th>Total, n=576</th>
<th>Dead at 180 Days, n=137</th>
<th>Alive at 180 Days, n=439</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per y</td>
<td>66 (57-76)</td>
<td>72 (60-80)</td>
<td>65 (57-75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>342 (59.4%)</td>
<td>90 (85.7%)</td>
<td>252 (57.4%)</td>
<td>0.085</td>
</tr>
<tr>
<td>Hypertension</td>
<td>357 (62.0%)</td>
<td>93 (67.9%)</td>
<td>264 (60.1%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>89 (15.5%)</td>
<td>26 (19.0%)</td>
<td>63 (14.4%)</td>
<td>0.191</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>75 (13.0%)</td>
<td>22 (16.1%)</td>
<td>53 (12.1%)</td>
<td>0.226</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>60 (10.4%)</td>
<td>20 (14.6%)</td>
<td>40 (9.1%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Cardiac failure†</td>
<td>30 (5.3%)</td>
<td>8 (6.0%)</td>
<td>22 (5.1%)</td>
<td>0.670</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>121 (21.2%)</td>
<td>24 (17.5%)</td>
<td>97 (22.2%)</td>
<td>0.305</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>22 (3.3%)</td>
<td>6 (4.4%)</td>
<td>16 (3.6%)</td>
<td>0.695</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>138 (24.0%)</td>
<td>34 (24.8%)</td>
<td>104 (23.7%)</td>
<td>0.787</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>71 (12.3%)</td>
<td>24 (17.5%)</td>
<td>47 (10.7%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>267 (46.4%)</td>
<td>76 (55.5%)</td>
<td>191 (43.5%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Insulin use*</td>
<td>36 (6.3%)</td>
<td>10 (7.5%)</td>
<td>26 (5.9%)</td>
<td>0.520</td>
</tr>
<tr>
<td>Statin use*</td>
<td>110 (19.3%)</td>
<td>26 (19.7%)</td>
<td>84 (19.2%)</td>
<td>0.895</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>64 (11.1%)</td>
<td>15 (10.9%)</td>
<td>49 (11.2%)</td>
<td>0.945</td>
</tr>
<tr>
<td>Any infection</td>
<td>305 (53.0%)</td>
<td>88 (64.2%)</td>
<td>217 (49.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline GCS</td>
<td>15 (12-15)</td>
<td>12 (7-14)</td>
<td>15 (13-15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>10 (5-17)</td>
<td>18 (13-24)</td>
<td>8 (4-13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to baseline CT scan, h</td>
<td>2.7 (1.5-8.1)</td>
<td>2.4 (1.3-6.2)</td>
<td>2.9 (1.5-8.5)</td>
<td>0.087</td>
</tr>
<tr>
<td>Baseline ICH volume, mL</td>
<td>13.4 (5.6-34.2)</td>
<td>33.2 (13.5-62.0)</td>
<td>10.4 (4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline edema volume, mL</td>
<td>10.1 (3.9-21.8)</td>
<td>18.3 (7.4-40.1)</td>
<td>9.0 (3.5-17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline EED, cm</td>
<td>0.32 (0.19-0.44)</td>
<td>0.35 (0.20-0.48)</td>
<td>0.31 (0.18-0.44)</td>
<td>0.134</td>
</tr>
<tr>
<td>72-h EED, cm</td>
<td>0.62 (0.43-0.86)</td>
<td>0.67 (0.49-0.92)</td>
<td>0.60 (0.41-0.85)</td>
<td>0.029</td>
</tr>
<tr>
<td>Irregular hematoma shape†</td>
<td>255 (44.3%)</td>
<td>93 (67.9%)</td>
<td>162 (37.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>69 (12.0%)</td>
<td>18 (13.1%)</td>
<td>51 (11.6%)</td>
<td>0.632</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>219 (38.0%)</td>
<td>83 (60.6%)</td>
<td>136 (31.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycemic trajectory groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent normoglycemia</td>
<td>214 (37.2%)</td>
<td>26 (19.0%)</td>
<td>188 (42.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late hyperglycemia</td>
<td>44 (7.6%)</td>
<td>5 (3.6%)</td>
<td>39 (8.9%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Early hyperglycemia</td>
<td>151 (26.2%)</td>
<td>36 (26.3%)</td>
<td>115 (26.2%)</td>
<td>0.985</td>
</tr>
<tr>
<td>Persistent hyperglycemia</td>
<td>167 (29.0%)</td>
<td>70 (51.1%)</td>
<td>97 (22.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) or n (%). CT indicates computed tomography; EED, edema extension distance; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale.

*Missing data for prior statin (6) and insulin (3) use, history of cardiac failure (9), and dyslipidemia (6).
†Hematoma shape not classified for 1 patient with pure intraventricular hemorrhage.
Hyperglycemia and Cerebral Hemorrhage Mortality

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Table 3. Multivariable Logistic Regression Model on Factors Associated With 6-Month Mortality

<table>
<thead>
<tr>
<th></th>
<th>All Patients, n=576</th>
<th>Excluding Diabetic Patients, n=487</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P Value</td>
</tr>
<tr>
<td>Glycemic trajectories</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late hyperglycemia†</td>
<td>0.965 (0.298–3.129)</td>
<td>0.952</td>
</tr>
<tr>
<td>Early hyperglycemia†</td>
<td>1.290 (0.657–2.535)</td>
<td>0.459</td>
</tr>
<tr>
<td>Persistent hyperglycemia†</td>
<td>3.675 (1.989–6.792)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log of baseline ICH volume, per 1†</td>
<td>3.515 (1.493–8.276)</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline edema volume, mL</td>
<td>0.997 (0.982–1.012)</td>
<td>0.727</td>
</tr>
<tr>
<td>Age, per y</td>
<td>1.054 (1.030–1.078)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.719 (1.033–2.861)</td>
<td>0.037</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>1.981 (0.997–3.935)</td>
<td>0.051</td>
</tr>
<tr>
<td>Baseline NIHSS, per point</td>
<td>1.097 (1.051–1.145)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline GCS, per point</td>
<td>0.954 (0.863–1.055)</td>
<td>0.362</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>1.208 (0.533–2.739)</td>
<td>0.651</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>1.746 (1.060–2.877)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.
†Compared with persistent normoglycemia.

All baseline ICH volume had addition of 1.0 before log transformation to allow inclusion of 3 patients with 0 baseline volume because of pure ventricular hemorrhage.

state. Further, there is evidence of progressive increase in perihematomal glucose metabolism in human ICH peaking at day 3, likely in response to increased perihematomal inflammatory cell infiltrate. It is therefore likely that hyperglycemia contributes to secondary neuronal injury by exacerbating the cerebral inflammatory milieu and oxidative stress, resulting in cellular injury in a process that is difficult to quantify clinically. The effects of hyperglycemia on brain injury are additive to primary injury resulting from the hematoma. Finally, hyperglycemia is also associated with increased risk of cardiac and infectious complications.

Two large randomized controlled trials have examined glycemic control on stroke outcome. The UK Glucose Insulin in Stroke Trial (GIST-UK) enrolled 933 (134 [14.4%] were ICH) stroke patients with admission glucose between 6.0 and 17.0 mmol/L to targeted glycemic control (4.0–7.0 mmol/L) or no intervention. There was no reduction in 90-day mortality in the intervention group (OR 1.14, 95% CI 0.86–1.51, P=0.37). The Quality in Acute Stroke Care (QASC) study randomized 1126 (51 [4.5%] were ICH) acute stroke patients in stroke units to a set of protocolized interventions for managing glucose, fever, and swallowing dysfunction or guideline management. The intervention group had reduced likelihood of 90-day death or disability (42% versus 58%, P=0.002). Interpreting these findings in ICH is difficult because of the small number of patients. In QASC it is unclear which of the 3 interventions contributed to mortality reduction. In GIST-UK >50% of patients had baseline glucose of <8.0 mmol/L, below the threshold for insulin treatment used in the present study. Therefore, our results cannot be interpreted in the light of intervention because only the persistent normoglycemia group (n=214, 37%) received no insulin treatment and in the remaining 362 (63%) patients the glucose was spontaneously elevated before treatment. Although our results are based on a retrospective cohort, the consistent association between hyperglycemia in this study and previous observational data indicate an urgent need to assess glycemic management on ICH outcome in randomized controlled trials.

We acknowledge the study limitations including firstly the potential for bias and chance associations in retrospective studies. We tried to minimize bias by predefining our study population and analysis a priori. Secondly, we had to exclude 43% of the patients in the HICHS predominantly because of early death, early palliation, or late presentation (Figure 1). The excluded patients had worse neurological injury and higher mortality (Table S1), thus the clinical relevance of hyperglycemia in these patients is less clear. Thirdly, we do not have hemoglobin A1C measurements in most patients, and some patients with persistent hyperglycemia may have undiagnosed diabetes mellitus. Although diabetic patients had more persistent hyperglycemia, diabetes mellitus was not associated with mortality in the present cohort. Furthermore, the association of persistent hyperglycemia with mortality remained after excluding patients with known diabetes mellitus and also after propensity-score-matching analysis. Fourthly, the lack of association between glycemic trajectory and 72-hour edema was based on EED derived from interpolating EED volume obtained at a median time of 24 hours from ictus. The EED may
not accurately represent the natural evolution in these patients, and our negative association needs to be interpreted in the context of this limitation. Fifth, we do not have information on functional outcome or medical causes of death and were unable to provide insight into potential associations with hyperglycemia. Finally, the results are derived from a single-center study, which may limit generalizability.

Conclusion
Over half of ICH patients experienced early hyperglycemia, which is only associated with higher mortality when it persists. Strategies to achieve glycemic control after ICH may influence patient outcome and need to be assessed in randomized controlled trials.

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Wu is supported by grants from the Neurological Foundation of New Zealand (grant number 1313-CF) and Royal Melbourne Hospital Neuroscience Foundation; Stbrian is supported by grants from the Helsinki University Central Hospital and the Finnish Medical Foundation; Tatlisumak is supported by the Helsinki University Central Hospital and Sahlgrenska University Hospital grants for ICH research; Meretoja is supported by grants from National Health and Medical Research Council (Australia), Academy of Finland, and the Finnish Medical Foundation.

Disclosures
None.

References


Supplementary table 1. Baseline characteristics between included and excluded patients.

<table>
<thead>
<tr>
<th></th>
<th>Total n=1013</th>
<th>Included n=576</th>
<th>Excluded n=437</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68 (58-78)</td>
<td>66 (57-76)</td>
<td>70 (59-79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>582 (57.5%)</td>
<td>342 (59.4%)</td>
<td>240 (54.9%)</td>
<td>0.159</td>
</tr>
<tr>
<td>Hypertension</td>
<td>637 (62.9%)</td>
<td>357 (62%)</td>
<td>280 (64.1%)</td>
<td>0.512</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>148 (14.6%)</td>
<td>89 (15.5%)</td>
<td>59 (13.5%)</td>
<td>0.419</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>146 (14.4%)</td>
<td>75 (13.0%)</td>
<td>71 (16.2%)</td>
<td>0.150</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>129 (12.7%)</td>
<td>60 (10.4%)</td>
<td>69 (15.8%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>49 (4.9%)</td>
<td>30 (5.3%)</td>
<td>19 (4.4%)</td>
<td>0.558</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>197 (19.7%)</td>
<td>121 (21.2%)</td>
<td>76 (17.7%)</td>
<td>0.173</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>54 (5.3%)</td>
<td>22 (3.8%)</td>
<td>32 (7.3%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>265 (26.2%)</td>
<td>138 (24.0%)</td>
<td>127 (29.1%)</td>
<td>0.071</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>133 (13.1%)</td>
<td>71 (12.3%)</td>
<td>62 (14.2%)</td>
<td>0.399</td>
</tr>
<tr>
<td>Anti-hypertensive medication</td>
<td>489 (48.3%)</td>
<td>267 (46.4%)</td>
<td>222 (50.8%)</td>
<td>0.163</td>
</tr>
<tr>
<td>Insulin use</td>
<td>54 (5.4%)</td>
<td>36 (6.3%)</td>
<td>18 (4.2%)</td>
<td>0.160</td>
</tr>
<tr>
<td>Statin use</td>
<td>191 (19.2%)</td>
<td>110 (19.3%)</td>
<td>81 (19.0%)</td>
<td>0.935</td>
</tr>
<tr>
<td>Baseline GCS</td>
<td>14 (10-15)</td>
<td>15 (12-15)</td>
<td>14 (8-15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>11 (4-20)</td>
<td>10 (5-17)</td>
<td>13 (4-25)</td>
<td>0.008</td>
</tr>
<tr>
<td>Time to baseline CT scan, hours</td>
<td>3.8 (1.6-16.0)</td>
<td>2.7 (1.5-8.1)</td>
<td>9.8 (2.0-43.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline ICH volume</td>
<td>14.25 (5.7-40.1)</td>
<td>13.4 (5.6-34.2)</td>
<td>18.0 (6.1-52.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline edema volume</td>
<td>11.35 (4.1-27.7)</td>
<td>10.1 (3.9-21.8)</td>
<td>14.4 (4.6-37.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline EED, per cm</td>
<td>0.34 (0.19-0.48)</td>
<td>0.32 (0.19-0.44)</td>
<td>0.37 (0.21-0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak EED, per cm</td>
<td>0.48 (0.28-0.71)</td>
<td>0.51 (0.32-0.78)</td>
<td>0.42 (0.22-0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>72 hour EED, per cm</td>
<td>0.60 (0.29-0.86)</td>
<td>0.62 (0.43-0.86)</td>
<td>0.56 (0.36-0.86)</td>
<td>0.021</td>
</tr>
<tr>
<td>Irregular hematoma shape</td>
<td>484 (49.0%)</td>
<td>255 (44.3%)</td>
<td>229 (55.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>142 (14.0%)</td>
<td>69 (12.0%)</td>
<td>73 (16.7%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>416 (41.1%)</td>
<td>219 (38.0%)</td>
<td>197 (45.1%)</td>
<td>0.024</td>
</tr>
<tr>
<td>6-month mortality</td>
<td>347 (34.6%)</td>
<td>137 (23.8%)</td>
<td>210 (39.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) or n (%).
Abbreviations: EED, edema extension distance; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale
**Supplementary table 2.** Model fit with different logistic regression models.

<table>
<thead>
<tr>
<th>Variables in model</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log baseline ICH volume and age</td>
<td>0.761 (0.717-0.808)</td>
</tr>
<tr>
<td>All predefined variables excluding glycemic trajectory</td>
<td>0.863 (0.829-0.897)</td>
</tr>
<tr>
<td>Full model*</td>
<td>0.877 (0.846-0.908)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under curve; ICH, intracerebral hemorrhage.

*Covariates in the full model are log baseline ICH volume, baseline National Institutes of Health Stroke Scale, baseline Glasgow Coma Scale score, baseline edema volume, age, previous warfarin use, infratentorial location and presence of ventricular extension.
**Supplementary table 3.** Baseline characteristics in the propensity score matched population.

<table>
<thead>
<tr>
<th></th>
<th>Total n=266</th>
<th>Persistent normoglycemia n=81</th>
<th>Late hyperglycemia n=44</th>
<th>Early hyperglycemia n=71</th>
<th>Persistent hyperglycemia n=70</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66 (57-76)</td>
<td>69 (57-76)</td>
<td>66 (57-77)</td>
<td>62 (57-77)</td>
<td>65 (58-76)</td>
<td>0.800</td>
</tr>
<tr>
<td>Male sex</td>
<td>144 (54.1%)</td>
<td>40 (49.4%)</td>
<td>24 (54.5%)</td>
<td>40 (56.3%)</td>
<td>40 (57.1%)</td>
<td>0.769</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>31 (11.7%)</td>
<td>8 (9.9%)</td>
<td>5 (11.4%)</td>
<td>9 (12.7%)</td>
<td>9 (12.9%)</td>
<td>0.936</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>9 (4-15)</td>
<td>6 (3-14)</td>
<td>8 (5-13)</td>
<td>10 (6-16)</td>
<td>12 (6-16)</td>
<td>0.066</td>
</tr>
<tr>
<td>ICH volume</td>
<td>12.6 (5.7-27.8)</td>
<td>11.8 (5.8-26.3)</td>
<td>9.0 (4.3-24.4)</td>
<td>15.7 (5.9-33.8)</td>
<td>13.1 (6.2-26.9)</td>
<td>0.363</td>
</tr>
<tr>
<td>Baseline edema volume, mL</td>
<td>10.8 (4.1-21.3)</td>
<td>11.9 (5.2-21.0)</td>
<td>10.6 (3.5-15.2)</td>
<td>12.2 (4.1-24.2)</td>
<td>7.6 (3.9-20.5)</td>
<td>0.318</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>11 (4.1%)</td>
<td>2 (2.5%)</td>
<td>2 (4.5%)</td>
<td>3 (4.2%)</td>
<td>4 (5.7%)</td>
<td>0.795</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>75 (28.2%)</td>
<td>25 (30.9%)</td>
<td>11 (25.0%)</td>
<td>20 (28.2%)</td>
<td>19 (27.1%)</td>
<td>0.909</td>
</tr>
<tr>
<td>6-month mortality</td>
<td>45 (16.9%)</td>
<td>10 (12.3%)</td>
<td>5 (11.4%)</td>
<td>8 (11.3%)</td>
<td>22 (31.4%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) or n (%).

GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale.
**Supplementary table 4:** Multivariable logistic regression model in propensity score matched population on factors associated with 6-month mortality.

<table>
<thead>
<tr>
<th></th>
<th>All patients, n=266</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Glycemic trajectories</td>
<td>-</td>
</tr>
<tr>
<td>Late hyperglycemia*</td>
<td>0.928 (0.250-3.448)</td>
</tr>
<tr>
<td>Early hyperglycemia*</td>
<td>0.608 (0.190-1.944)</td>
</tr>
<tr>
<td>Persistent hyperglycemia*</td>
<td>3.653 (1.357-9.836)</td>
</tr>
<tr>
<td>Log of baseline ICH volume, per 1†</td>
<td>4.000 (0.889-17.991)</td>
</tr>
<tr>
<td>Baseline edema volume, mL</td>
<td>0.997 (0.972-1.022)</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.057 (1.019-1.095)</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.029 (0.887-4.643)</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>2.955 (1.045-8.350)</td>
</tr>
<tr>
<td>Baseline NIHSS, per point</td>
<td>1.126 (1.041-1.218)</td>
</tr>
<tr>
<td>Baseline GCS, per point</td>
<td>1.025 (0.849-2.243)</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>0.933 (0.388-2.243)</td>
</tr>
<tr>
<td>Infratentorial location ‡</td>
<td>-</td>
</tr>
</tbody>
</table>

*Compared with persistent normoglycemia; GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale. †All baseline ICH volume had addition of 1.0 prior to log transformation to allow inclusion of 3 patients with 0 baseline volume due to pure ventricular hemorrhage. ‡ No deaths occurred in patients with infratentorial hemorrhage in the propensity score matched population.
**Supplementary table 5.** Generalized linear model on association of glycemic status on extrapolated 72-hour edema extension distance (EED) in centimeters.

<table>
<thead>
<tr>
<th></th>
<th>beta</th>
<th>SE</th>
<th>Wald</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic trajectory</td>
<td>-</td>
<td>-</td>
<td>2.401</td>
<td>0.493</td>
</tr>
<tr>
<td>Normoglycemia (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Late hyperglycemia</td>
<td>-0.004</td>
<td>0.092</td>
<td>0.002</td>
<td>0.965</td>
</tr>
<tr>
<td>Early hyperglycemia</td>
<td>0.091</td>
<td>0.062</td>
<td>2.203</td>
<td>0.138</td>
</tr>
<tr>
<td>Persistent hyperglycemia</td>
<td>0.050</td>
<td>0.067</td>
<td>0.561</td>
<td>0.454</td>
</tr>
<tr>
<td>Log ICH vol, per 1</td>
<td>0.334</td>
<td>0.066</td>
<td>25.781</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Irregular hematoma shape</td>
<td>0.055</td>
<td>-0.057</td>
<td>0.938</td>
<td>0.333</td>
</tr>
<tr>
<td>Ventricular extension</td>
<td>-0.184</td>
<td>0.051</td>
<td>13.243</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>-0.474</td>
<td>0.074</td>
<td>41.101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS, per point</td>
<td>0.005</td>
<td>0.003</td>
<td>2.893</td>
<td>0.089</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.033</td>
<td>0.502</td>
<td>0.435</td>
<td>0.510</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.205</td>
<td>0.074</td>
<td>7.787</td>
<td>0.005</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SE, standard error
### Supplementary table 6. Studies investigating the association of glucose and outcome after intracerebral hemorrhage.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study size</th>
<th>Proportion diabetic</th>
<th>Timing of glucose measurement</th>
<th>Outcome measures</th>
<th>Main findings</th>
<th>Other adjusted covariates in multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franke1 1992</td>
<td>Netherlands</td>
<td>157</td>
<td>NR</td>
<td>On admission, 96% presented within 24 hours of onset</td>
<td>2 day and 1 year mortality</td>
<td>Hyperglycemia (≥8 mMol/L) was associated with mortality (OR 5.5, P&lt;0.001) at 2 days but not at 1 year</td>
<td>Age, hypertension, eye and motor scores on GCS, ICH volume, pineal gland displacement, modified Rankin score 5</td>
</tr>
<tr>
<td>Passero2 2003</td>
<td>Italy</td>
<td>739</td>
<td>127 (17%)</td>
<td>On admission, all patients presented within 24 hours of onset</td>
<td>30 and 90 day mortality</td>
<td>Hyperglycemia (≥130 mg/dL / 7.22 mMol/L) in non-diabetic, non-comatose patients (n=415) was associated with mortality at 30 days (OR 1.290 95% CI 1.054-1.578, p=0.013) and at 90 days (1.269 (1.051-1.532, p=0.013)</td>
<td>Age, ICH volume, IVH, GCS, mean arterial pressure, surgical evacuation.</td>
</tr>
<tr>
<td>Fogelholm3 2005</td>
<td>Finland</td>
<td>329</td>
<td>39 (11.9%)</td>
<td>On admission, 89% presented within 24 hours of onset</td>
<td>28 day mortality</td>
<td>Increasing admission glucose (OR 1.22 per mMol/L 95% CI 1.07-1.40, p=0.004) was independently associated with 28-day mortality</td>
<td>Coma, midline shift, anticoagulant use, mean arterial pressure</td>
</tr>
<tr>
<td>Kimura4 2007</td>
<td>Japan</td>
<td>100</td>
<td>NR</td>
<td>On admission prior to CT scan. Mean time from onset to scan was 4.6 +/- 5.0 hours</td>
<td>14 day mortality</td>
<td>Hyperglycemia (&gt;150mg/dL / 8.4 mMol/L) was associated with 14 day mortality (OR 35.34, 95% CI 1.40-992.73, p=0.031)</td>
<td>Age &gt;70, systolic blood pressure, leucocytes &gt;8.5, erythrocytes &lt;0.37, potassium &lt;3.5 mMol/L, albumin &lt;4.0g/dL, Sodium &lt;140 mMol/L, ICH volume &gt;20 mL, Mean arterial pressure, sex, ICH volume, IVH, age, GCS, basal ganglia location, thalamus location, infratentorial location, cardiac disease, warfarin use.</td>
</tr>
<tr>
<td>Tetri5 2009</td>
<td>Finland</td>
<td>379</td>
<td>68 (17.9%)</td>
<td>On admission, 94.2% presented within 48 hours of onset</td>
<td>2 and 90 day mortality</td>
<td>Admission glucose was not associated with 2 day (RR 1.04 (95% CI 0.95-1.13, p value not reported) or 90 day mortality (RR 1.04 95% CI 0.99-1.10, p value not reported)</td>
<td>Age, diabetes, systolic and diastolic blood pressure, pontine location, ICH volume, IVH, GCS</td>
</tr>
<tr>
<td>Lee6 2010</td>
<td>South Korea</td>
<td>1387</td>
<td>161 (11.6%)</td>
<td>Fasting morning glucose the day after admission. All patients presented within 48 hours of onset</td>
<td>30 day and mortality on last follow up</td>
<td>Increasing glucose (HR 1.10 per mMol/L 95% CI 1.01-1.19, p=0.03) was associated with 30 day mortality but not long term mortality (HR 1.05 (0.98-1.11, p=0.15)</td>
<td>Age, ICH volume, IVH, NIHSS.</td>
</tr>
<tr>
<td>Stead7 2010</td>
<td>USA</td>
<td>237</td>
<td>47 (19.8%)</td>
<td>On admission. Time of presentation in relation to symptom onset was not reported</td>
<td>7 day mortality</td>
<td>Hyperglycemia (&gt;140mg/dL / 7.7mmol/L) was associated with 7-day mortality in non-diabetic patients (estimate 2.796 SE 1.174, p=0.0172) but not in diabetic patients (estimate 2.590 SE 2.197, p=0.2384)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
patients presented within 24 hours of onset

Di Napoli S 2011 Italy 210 58 (27.6%) On admission. All patients presented within 24 hours of onset 30 day mortality

>200mg/dL/11.1 mMol/L on 2 occasions) was associated with in-hospital mortality (OR 10.9 95% CI 4.72-25.32, p<0.001). However, the proportion of hyperglycemia and duration determined by random glucose testing was not reported.

Model 1: ICH volume, IVH, infratentorial location, age, time to blood test

Model 2: variables in model 1 plus midline shift, hydrocephalus.

Model 3: variables in model 2 and surgery

Appelboom 10 2011 USA 104 26 (23.6%) On admission. Time of presentation in relation to symptom onset was not reported Within 24 hours of hospitalization. Time of presentation in relation to symptom onset not reported

Mortality on discharge and at 90 days

Critical hyperglycemia (>10mMol/L) was independently associated with mortality on discharge (OR 4.381 95% CI 1.186-16.174, p=0.009) and at 90 day (OR 10.85 95% CI 1.886-62.41, p=0.011)

Age, female sex, diabetes mellitus, GCS, AVM, ICH volume, IVH score, midline shift, infratentorial location, ventricular drain, intrathecal IPa, ventriculoperitoneal shunt, early DNR status, length of hospital stay, ICH location, ICH volume and complications.

Wang 11 2011 China 189 31 (16.4%) Within 24 hours of hospitalization. Time of presentation in relation to symptom onset not reported

30 day Barthel’s Index

Hyperglycemia (>6.8 mMol/L) in non-diabetic patients (OR 0.081 95% CI 0.039-0.167, p<0.0001) and diabetic patients (OR 0.056 95% CI 0.022-0.142, p<0.0001) was associated with poor functional recovery.

Bejot Y 2012 France 419 68 (14.8%) On admission. Time of presentation in relation to symptom onset not reported

1 month mortality

Hyperglycemia (≥8.6 mMol/L) was associated with 1 month mortality. (HR 1.76 95% CI 1.23-2.53, p=0.002)

Age, sex, ICH location, IVH, smoking status, aphasia, motor deficit, anticoagulant use, altered consciousness

Saxena 13 2016 INTERACT II 2653 292 (11.0%) On admission, all patients presented within 6 hours of onset.

90 day death, death or major disability (modified Rankin Score 3-6)

Glucose (per mMol/L) was associated with death (OR 1.16 95% CI 1.01-1.33, p=0.043), death or major disability (OR 1.11 95% CI 1.00-1.24, p<0.0001).

Highest quartile of glucose (7.9-25mMol/L) was associated with death or major disability (OR 1.35 95% CI 1.01-1.80, p trend 0.015).

Age, geographic region, sex, heart disease, hypertension, diabetes mellitus, use of aspirin or warfarin, ICH volume, ICH location, IVH, systolic blood pressure, randomized treatment, NIHSS ≥15, age x NIHSS ≥15 interaction, China x IVH interaction, ICH volume deep ICH location interaction and deep ICH x IVH interaction.

Liu 14 2016 China 908 58 (6.8%) On admission. Time of presentation in relation to

Death or disability (modified Rankin Score 3-6) at 3 and 12 months

Baseline glucose (per mMol/L) was associated with reduced odds of good outcome at 3 months (OR 0.914 95% CI 0.857-0.974, p=0.006) but not 12 months (point estimate not reported).

NIHSS, GCS, hematocrit, blood urea nitrogen, previous stroke, stroke complications
On admission, All patients presented within 24 hours of onset

Death or disability (modified Rankin Scale score 3-6) at 3 months

Glucose per mMol/L was associated with death or disability at 3 months (aOR 1.09 95% CI 1.04-1.15, p<0.001).

Highest quartile of glucose (>7.53 mMol/L) was associated with poor 3-month outcome (aOR 1.54 95% CI 1.17-2.03, p=0.002).

Supplementary table 6 (continued)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study size</th>
<th>Proportion diabetic</th>
<th>Timing of glucose measurement</th>
<th>Outcome measures</th>
<th>Main findings</th>
<th>Other adjusted covariates in multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapia-Perez2016</td>
<td>Germany</td>
<td>122</td>
<td>37 (30.3%)</td>
<td>On admission, day 1 and 3. All patients presented within 24 hours of symptoms onset</td>
<td>Mortality at day 7 and 30</td>
<td>Hyperglycemia (&gt;140mg/dL / 7.78 mMol/L) on day 1 was associated with 30-day mortality (HR 2.65 95% CI 1.15-6.12, p=0.02). No association with 7 day mortality was observed (point estimate not reported)</td>
<td>IVH, hydrocephalus, ICH volume, WCC, ventricular drain, age and GCS</td>
</tr>
<tr>
<td>Koga2015</td>
<td>Japan</td>
<td>176</td>
<td>22 (12.5%)</td>
<td>On admission, 24 and 72 hour. All patients presented within 3 hours of symptom onset</td>
<td>3 month outcomes – none to minimal disability, bedridden/death</td>
<td>Admission glucose (per 10mg/dL) was not associated with either none/minimal disability (OR 0.90 95% CI 0.77-1.02 p=0.099) or bedridden/death (OR 1.01 95% CI 0.84-1.19 p=0.892) 24 hour glucose (per 10mg/dL) was associated with none/minimal disability (OR 0.85 95% CI 0.69-0.98 p=0.021) and with bedridden/death (OR 1.14 95% CI 1.00-1.30 p=0.049) 72 hour glucose was associated with none/minimal disability (0.75 95% CI 0.59-0.92 p=0.003) but not with bedridden/death (OR 1.11 95% CI 0.98-1.27 p=0.101)</td>
<td>Sex, age, antithrombotic medication use, systolic blood pressure, initial heart rate, NIHSS, time to initial scan, ICH volume</td>
</tr>
</tbody>
</table>
## Supplementary table 6 (continued)

<table>
<thead>
<tr>
<th>Studies that used glucose trajectory (4 studies, n=886)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author, year</strong></td>
<td><strong>Country</strong></td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Schwarz 18 2000 Germany 196 NR</td>
<td>Admission to 72 hours. All patients presented within 24 hours of symptom onset</td>
</tr>
<tr>
<td>Godoy 2008 Argentina, Italy 295 148 (50.2%)</td>
<td>Daily blood glucose for 72 hours. All patients presented within 24 hours of symptom onset</td>
</tr>
<tr>
<td>Qureshi 2011 ATACH I study 60 10 (16.7%)</td>
<td>Glucose trend over first 72 hours. All patients presented within 6 hours of symptom onset</td>
</tr>
<tr>
<td>Feng 2012 USA 135 26 (19.3%)</td>
<td>Mean glucose within 72 hours. All patients presented within</td>
</tr>
<tr>
<td>Current study</td>
<td>Finland</td>
</tr>
</tbody>
</table>

*Likely error in reporting 95% Confidence Interval in the published manuscript.
AVM indicates arteriovenous malformation; DNR, do not resuscitate; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; NIHSS, National Institutes of Health Stroke Scale; NR, not reported.
References:


Chapter VIII

General discussion

This work has provided further insights into the complex processes contributing to outcome after intracerebral haemorrhage. From a technical perspective it was shown that methods employed to calculate haematoma and oedema volume significantly influenced the volume output. There were also strong independent associations between early oedema growth and persistent hyperglycemia with long-term mortality. Pre-stroke use of metformin appeared to be protective in diabetic ICH patients and patients with simultaneous intracerebral haemorrhages had similar aetiology and outcome to patients with single ICH.

The results of this work support the notion that multiple dynamic processes contribute to ICH injury in addition to primary injury from the haematoma. Previous Phase III clinical trials have focused predominantly on one specific treatment target – the haematoma – without concurrent therapy for other potentially modifiable outcome correlates (i.e. concurrent anti-oedema therapy and optimisation of metabolic profile such as glucose and temperature control). There are many clinical and imaging factors contributing to ICH outcome (figure 22) and ICH management in the future is likely to involve a multi-pronged approach targeting both primary and secondary injury in addition to optimising individual patient’s metabolic profile.
Figure 22. Contributions to brain injury and outcome after intracerebral haemorrhage.

- **Primary injury**
  - ICH volume,
  - ICH growth
  - Ischaemic injury

- **Rapid oedema growth**
  - Clot retraction
  - Hydrostatic pressure
  - Thrombin

- **Secondary injury**
  - Subacute oedema growth
    - Thrombin
    - Inflammation
    - Blood brain barrier breakdown
  - Neuronal injury
    - Iron toxicity
    - Oxidative damage

- **Secondary injury**
  - Delayed oedema growth
    - Inflammation
    - Blood brain barrier breakdown
  - Neuronal injury
    - Delayed massed effect
    - Iron toxicity
    - Oxidative damage

- **Haematoma resorption and resolution of oedema**
- **Residual neurological deficit**

Oedema growth trajectory

Days from ICH onset

Percentage of maximal oedema reached

0 25 50 75 100
0 5 10 15 50
8.1 Significance of accurate volume estimation

Both haematoma and oedema influence outcome after ICH in a volume dependent manner (Broderick et al., 1993; Yang et al., 2015). It is therefore vitally important that accurate volume estimation is obtained in assessing impact of a therapeutic agent. Although ABC/2 provides an easy to use bedside clinical tool for estimating haematoma volume (Kothari et al., 1996), its accuracy is limited in large or irregularly shaped haematomas (Huttner et al., 2006; Yang et al., 2013b). Studies have demonstrated significant variance with manual or computer assisted planimetry generated volumes (Huttner et al., 2006). Furthermore, the ABC/2 method cannot be used to estimate oedema volume because the boundary between oedema and normal background brain parenchymal is difficult to determine visually. Threshold based semi-automated planimetry using pre-determined thresholds (Volbers et al., 2011) for haematoma (44-100 HU) and oedema (5-33 HU) is increasingly being used for haematoma and oedema segmentation and is likely to be the gold standard for accurate planimetric segmentation in future ICH research. Following segmentation, volume is generated by the software used for segmentation and a number of commercially available softwares are available for this purpose. The volume derivation from segmentation performed on CT images is influenced by gantry tilt, slice thickness and potential inter-slice gap or overlap. This is an area that has not been discussed in detail in available literature.

In Chapter III an analysis was performed comparing the performance of two softwares Analyze and Osirix for haematoma and oedema segmentation. The segmentation was performed on CT images from two comprehensive stroke centres and contained sequences with both uniform and variable image slice thickness. The study demonstrated excellent inter-rater and intra-rater reliability for haematoma and oedema segmentation, although the variance was higher in large volume oedema. The presented study also investigated the impact of gantry tilt and varying slice thickness on accuracy of volume output. The results indicated that software generated volumes in both Analyze and Osirix can underestimate true volume by up to 41% in images with variable slice thickness due to the software assuming equal thickness for all images. Our method for volume calculation used in the study accurately accounted for the impact of gantry tilt, variable slice thickness and potential gaps or overlap.
between slices. The technical code and a ready-to-use plugin for Osirix software were made available for download with the publication of the study manuscript (http://link.springer.com/article/10.1007/s00234-016-1720-z).

The study in chapter III represents an important contribution to ICH research. It emphasises the importance of using the best practice approach for volume calculation. Given that both haematoma and oedema influence ICH outcome in a volume dependent manner, 40% variance in volume output will influence results of observational and interventional studies. It is vital that future ICH research involving volumetric output utilises the best practice approach for evaluation of haematoma and oedema and that the method used for calculation is reported clearly.

8.2 Insight into simultaneous multiple intracerebral haemorrhages

Haematoma growth is a known poor prognostic feature (Davis et al., 2006) resulting from active bleeding from single or multiple bleeding sources. Fisher’s pathological studies postulated an ‘avalanche’ of secondary haemorrhages triggered by the mechanical stress of the primary haematoma leading to haematoma growth (Fisher 1971). Additionally, autonomic dysregulation associated with haemorrhage may lead to rupture of at-risk Charcot Bouchard microaneurysms resulting in secondary haemorrhage and haematoma expansion. This may account for the observation of multi-lobular and simultaneous multiple intracerebral haemorrhages (SMICH).

Previous studies of SMICH were derived from small single centre series without detailed reporting of aetiology and outcome (Chen et al., 2016; Laiwattana et al., 2014; Maurino et al., 2001; Sorimachi et al., 2007b; Stemer et al., 2010; Takeuchi et al., 2011; Weisberg 1981; Yeh et al., 2014; Yen et al., 2005). In Chapter IV, the presence of SMICH on baseline imaging in patients presenting to the Royal Melbourne Hospital and Helsinki University Hospital was analysed. The study found an overall SMICH prevalence of ~6%, presenting in approximately 1 in 20 ICH patients. This is also consistent with single centre case series (see Table 1 from the published work in Chapter IV). The aetiological association with SMICH was analysed and compared to patients with single ICH. The results indicate a widely distributed aetiology for SMICH with cerebral amyloid angiopathy and hypertensive aetiology being the most common causes of SMICH, similar to that found in single
ICH. However, SMICH itself was not associated with increased mortality compared with patients with single ICH, even after propensity score matching and excluding patients with very small (<5mm) secondary haematoma. In SMICH, the prognostic indicators for mortality were baseline ICH volume and presence of ventricular haemorrhage, similar to the prognostic factors in single ICH. The study contributes to understanding of ICH evolution in illustrating the varied aetiologies found in SMICH and that management in these patients should target the underlying pathology. The results are limited by lack of MRI imaging to refine aetiological classification and allow analysis of the association between microhaemorrhages and SMICH. Future prospective studies with MRI imaging and standardised aetiological classification are needed to improve understanding of this entity.

8.3 Oral diabetic medications – potential avenue for ICH treatment?

The sulphonylurea inhibited non-selective ion channel – SUR1-TRPM4 – mediates oedema growth after ischaemic stroke by allowing influx of sodium into the intracellular space resulting in ionic fluid shift into the cell and oedema (figure 8). Previous observational studies have reported improved outcome in ischaemic stroke patients pre-treated with sulphonylurea (Kunte et al., 2007; Kunte et al., 2012), possibly through reduced post-stroke oedema. A phase II randomised controlled trial in patients with large volume ischaemic infarction demonstrated treatment with intravenous sulphonylurea (glyburide) significantly reduced midline shift compared to routine care (Sheth et al., 2016). SUR1-TRPM4 is also expressed in the peri-haematomal tissue of human ICH and is postulated to contribute to early oedema formation (figure 8) (Urday et al., 2015b). In addition, metformin, another commonly used oral diabetic agent, has also been associated with improved ischaemic stroke outcome (Horsdal et al., 2012), possibly through improved glycaemic control and reduced metabolic stress mediated by reduced lactate generation (Li et al., 2010). The study presented in Chapter V assessed the impact of pre-stroke use of oral anti-diabetic agents (metformin and sulphonylureas) on ICH outcome. The results indicated that pre-stroke use of metformin was independently associated with nearly halved odds of death at 90 days while sulphonylurea use was not associated with
outcome. Although there was no difference in baseline glucose levels between users and non-users of metformin, it is possible that pre-stroke exposure to metformin resulted in improved glycaemic control and reduced medical complications. It is also possible that metformin treatment could have resulted in reduced secondary neuronal injury through reduced metabolic stress as demonstrated in ischaemic stroke animal models.

The study in Chapter V contributes to ICH research by reporting a novel association between metformin and ICH outcome, which has not been previously reported. Metformin is accessible and economical and is safe to use in non-diabetic patients (Preiss et al., 2014). The results of this study generate hypotheses that could be assessed in a randomised controlled trial, following further validation in other cohorts. An interesting finding in the study presented in Chapter V was the lack of association between pre-stroke use of sulphonylurea and peri-haematoma oedema at baseline and 72 hours. The results could suggest a lack of significant contribution of the SUR1-TRPM4 channel in early oedema, which is most likely the result of hydrostatic pressure and clot retraction as discussed in the previous passages (Wu et al., 2017a). However, this lack of association between pre-stroke sulphonylurea use and oedema should be considered in the context of the majority of patients having sulphonylurea withheld after hospitalization. Therefore there may not have been active drug in circulation to inhibit the SUR1-TRPM4 channel during the period of oedema development.

The only preclinical study to have examined SUR1-TRPM 4 channel expression in ICH was published following the publication of data presented in Chapter V. It demonstrated expression of SUR1-TRPM 4 in male Sprague Dawley rats began 12 hours after stereotactic injection of autologous blood into the basal ganglia and reached a peak at 24 hours before declining (Jiang et al., 2017). Treatment with glyburide resulted in less brain water content due to decreased blood-brain-barrier disruption and resulted in improved neurological outcome (Jiang et al., 2017). A phase III study (CHARM, NCT02864953) of intravenous glyburide in large territory ischaemic stroke is anticipated to start recruitment shortly. Although promising clinical results in ischaemic stroke and pre-clinical ICH data have been shown, the role of SUR1-TRPM4 channel in early ICH oedema growth requires further research.
8.4 Impact of peri-haematomal oedema on outcome after intracerebral haemorrhage

Much emphasis in ICH management has been placed on minimising primary injury from the haematoma. Recent studies have implicated oedema growth in the first 72 hours as a mediator of outcome (Murthy et al., 2015; Yang et al., 2015), likely resulting from mass effect and secondary injury associated with inflammation and oxidative injury (Urday et al., 2015b). Unlike oedema evolution after ischaemic stroke, oedema after ICH is more complex and dynamic, and often does not reach a peak until 2 to 3 weeks after onset (Staykov et al., 2011). Data from the INTERACT studies and a single centre study indicated doubling of oedema volume within the first 24 hours after ICH onset (Gebel et al., 2002a; Yang et al., 2015). However, natural history data on subacute oedema growth is limited with the majority of the published reports originating from a single centre (University of Erlangen-Nuremberg) in Germany.

The study presented in Chapter VI advances current knowledge in oedema evolution. The growth trajectory derived from a large dataset with a well-defined patient cohort indicated a 2-stage growth trajectory consistent with postulated oedema growth pathophysiology – an initial rapid acute stage followed by subacute slower growth. The analysis indicated that nearly 60% of the oedema growth as measured by the EED was completed within the first 24 hours of symptoms onset, followed by slow stage of subacute growth that progressed into the second and third weeks after onset. The expected 72-hour EED was calculated for each patient using the mathematical formula derived from the growth trajectory. Patients with larger than expected oedema growth at 72-hours were associated with significantly increased odds of death at 6-months, independent of other robust predictors of ICH outcome. This study supports recent publications that early oedema growth is an important determinant of outcome after ICH.

Factors associated with increased early oedema growth were higher baseline haematoma volume, elevated glucose, previous warfarin use and worse baseline stroke severity. The association of baseline haematoma volume is consistent with previously reported correlation between haematoma volume and oedema (Arima et al., 2009). This likely reflects the contribution of haematoma to oedema growth in both acute and subacute stages of oedema evolution. In the hyperacute stage,
haematoma volume contributes to oedema growth through hydrostatic pressure associated with haematoma growth. Once haematoma growth ceases, clot retraction results in further oedema growth (Majidi et al., 2016). In the subacute phase, the contribution of blood degradation products in haemoglobin and iron to oedema growth results from associated inflammation and enhanced breakdown of the blood-brain-barrier (Keep et al., 2012; Urday et al., 2015b). Iron toxicity is thought to additionally contribute to direct neuronal damage. The ongoing minimally invasive surgery MISTIE III study (NCT01827046) and the iron chelation Hi-DEF study (Yeatts et al., 2013) are likely to provide important insights into different methods to reduce haemorrhage-related iron toxicity and may impact outcome and oedema formation. Other potential contributors to oedema evolution are temperature, glucose, sex, anticoagulant use and markers of inflammation with the effect of hypothermia on ICH outcome being assessed in ongoing trials (Kollmar et al., 2012; Rincon et al., 2014).

An easily modifiable potential therapeutic target is serum glucose, which has been associated with increased oedema and blood-brain-barrier breakdown in preclinical models (Song et al., 2003). In Chapter VII, the impact of serum glucose on oedema was assessed. The study used interpolated EED calculated from the analysis performed in chapter VI and examined for an association in a multivariable model between glycaemic trajectory within the first 72 hours of ictus and 72-hour EED. The results suggested no association between glycaemic control and acute oedema growth and found that baseline haematoma volume was a significant predictor of acute oedema, consistent with reported literature. The lack of association is consistent with data from INTERACT 2, which found no association between baseline serum glucose level and 24-hour absolute oedema (Saxena et al., 2016), and also results from a post hoc analysis of ATACH 1 (Qureshi et al., 2011). Potential explanations for the lack of association found here and that demonstrated in pre-clinical studies could be two fold. Firstly the analysis is based on acute oedema formation at 24 hours in the INTERACT 2 and ATACH 1 analysis while Chapter VII used 72-hour oedema volumes. The acute phase of oedema evolution is driven predominately by pressure effects from hydrostatic pressure and clot retraction at the stage of oedema pathogenesis where the blood-brain-barrier is relatively intact. Studies assessing the relationship between
oedema and glucose, including the study presented in Chapter VII do not have or have not reported comprehensive imaging or glucose data in the subacute period between day 3 and week 2 after stroke onset. Secondly, the negative association between 72-hour oedema volume and glucose was based on retrospective analysis, a prospective study is required to validate these results. The negative association reported in Chapter VII and other studies on glucose and acute oedema growth do not preclude a potential impact of glucose on subacute oedema growth. However as ~75% of EED growth has already occurred by 72 hours (Chapter VI), the significance of delayed oedema is uncertain. The impact of delayed oedema growth, its relevance to patient outcome and the potential contribution of glucose to its evolution deserves further research.
8.5 Serum glucose as a modifiable target for improving ICH outcome

The current major targets for translational research in ICH are haematoma and oedema. However glucose is an easily modifiable laboratory marker and has been associated with outcome after both ischaemic stroke and ICH. In a large number of ICH studies (supplementary table 6 from published paper in Chapter VII, 21 studies, n=12,145), increased glucose level was associated with poor outcome. Glucose is intrinsically associated with systemic inflammation through activation of inflammatory cytokines which can enhance neuronal injury and mediate blood-brain-barrier breakdown (Esposito et al., 2002). The current American Heart Association/American Stroke Association guidelines recommend avoiding hyperglycaemia (Hemphill et al., 2015), based on observational studies using a single time point glucose measurement. However, it is likely that a proportion of patients with baseline hyperglycemia will become normoglycaemic and the impact of transient hyperglycaemia on ICH outcome is uncertain.

The study in Chapter VII contributed important observations to the ICH literature. The study results indicated that only approximately 50% of patients with hyperglycaemia in the first 24 hours would remain persistently hyperglycaemic in the subsequent 48 hours. Patients with persistent hyperglycaemia had a 3.5 fold increased risk of death after ICH, even after adjusting for factors associated with mortality including baseline haematoma volume and haematoma growth. Similar results were confirmed in propensity score matching analysis. The association remained even after excluding diabetic patients. This observation suggests that patients with persistent hyperglycaemia are at the greatest risk of mortality. Although the study in Chapter VII did not find a significant association in patients with baseline-only hyperglycemia or late-only hyperglycaemia, the results do not definitively exclude potential harm in these patient groups. Furthermore, the neutral findings noted in the group with late-only hyperglycaemia were based on a small sample size with limited statistical power. Hyperglycaemia at any time point after ICH onset should be managed as per current practice guidelines (Hemphill et al., 2015).

The mechanism through which hyperglycaemia mediates outcome after ICH is uncertain. It is likely that hyperglycaemia is associated with increased medical
complications such as infection and increased risk of cardiovascular events. It is also likely that hyperglycaemia directly causes damage at a cellular level as noted in pre-clinical studies (Song et al., 2003). The increased injury burden on neurons is likely to negatively influence functional recovery which, in turn, increases mortality risk due to complications associated with immobility. The impact of hyperglycaemia is likely additive to that caused by primary injury from the haematoma. However, the alternative consideration is that hyperglycaemia is a marker of more severe initial brain injury rather than a cause of subsequent injury. Prospective interventional studies optimising glycaemic control in stroke are required to assess the potential benefit of glycaemic control on outcome.

A large (proposed sample size n=1400) phase III trial – the Stroke Hyperglycemia Insulin Network Effort (SHINE, NCT01369069) of tight glucose control (target glucose range 4.5-7.2mMol) in acute ischaemic stroke using insulin infusion is underway. A randomised controlled trial of tight glycaemic control in ICH patients is urgently needed to investigate this very treatable clinical target.

8.6 Limitations

Although this thesis has reported a number of clinically relevant findings and potential translational targets, a number of limitations need to be acknowledged.

8.6.1 Retrospective analyses

Almost all the analyses reported in this thesis are retrospective from previously published datasets. The only study performed prospectively was reported in Chapter III with performance and analysis of semi-automated segmentation of ICH and oedema. The major limitation associated with retrospective studies is potential for misclassification / information bias and the accuracy of the data required accurate record keeping and accurate interpretation and collection of information. In the Helsinki ICH study, data ascertainment was performed on ‘diligently’ kept ‘chart notes’ with every patient been seen and diagnosed by a neurologist. All the other medical information including information on medical history was derived from comprehensive province-wide notes from both hospital specialties and general practice referrals. In the RMH ICH study, most of the data was collected
prospectively as part of the ongoing stroke database. Chart and electronic laboratory information review was required to obtain certain missing information such as baseline NIHSS, glucose level and medication use. The VISTA-ICH data were derived from prospectively collected data from international randomised controlled trials performed according to good clinical practice, including regular independent monitoring of the data collection and follow up. Only limited clinical information was required for analysis in patients from the Salford ICH registry. Although a number of significant associations with ICH outcome were noted, these were based on retrospective analyses and should be confirmed in prospective studies. Further, the reported results such as the association of metformin and outcome will require further validation and testing in preclinical settings before consideration is given to a clinical trial.

8.6.2 Generalisability

The Helsinki University Hospital treats approximately two-thirds of all ICH patients within the province of Uusima (population catchment 1.5 million) and had similar 3-month mortality (32%) to the rest of Finland (35%) when the study was published in 2012 (Meretoja et al., 2012). The Royal Melbourne Hospital is located at the northern border of the Melbourne central business district and has a local catchment in addition to acting as a statewide referral centre. There are a number of other tertiary hospitals in Melbourne with stroke unit care and RMH receives approximately 10% of all strokes treated in Victoria. The overall 30-day mortality rate for patients in the RMH cohort was 35%, which is lower than 45% noted in the previous North Melbourne study (Thrift et al., 2001) performed a decade earlier but comparable to the 35% mortality noted in the contemporaneous Adelaide city (Leyden et al., 2013) and 37.5% mortality in a statewide analysis of New South Wales data (Gattellari et al., 2014). In both these cohorts therefore there is a potential for referral bias as ICH patients may have been admitted to other centres in southern Finland and in Melbourne. The slightly lower mortality rate observed in the Helsinki and Melbourne cohorts compared to the rest of Finland and New South Wales may be due to referral bias but may also be a result of differences in patient care.

In terms of demographic differences between ICH and RMH, the median age of presentation was lower in the Helsinki cohort (68 vs 73 years) while 57% of patients
in both cohorts were male. In terms of stroke severity, the RMH cohort did not record NIHSS for all patients but the GCS of 14/15 was the same in both cohorts. Baseline haematoma volume was smaller in the Helsinki cohort (14.25 vs 16.20mL) which may account for the discrepancy in the mortality rates between the cohorts. Another important difference to be considered is the ethnic make up of these populations as ICH outcome is associated with ethnicity (van Asch et al., 2010). However, the Helsinki population is predominantly European with non-European immigrants making up a small proportion of the population (Saukkonen and Pyykkönen 2008). This is in contrast to the Melbourne population which is predominately European but with nearly 25% of the population comprised of Asian and Middle Eastern ethnicities (Australian Bureau of Statistics 2011). The ethnic composition and the ICH characteristics in these two cohorts may not necessarily reflect the patient characteristics from other regions and may limit the generalisability of the findings presented in this thesis.

The placebo treated patients (n=987) from the VISTA-ICH database had a 90-day mortality rate of 20.4%, significantly lower than the Helsinki and RMH ICH cohorts. The lower mortality is noted in the setting of comparable baseline ICH volume (15.3mL vs 14.25mL Helsinki and 16.20mL RMH), younger age (66 vs 68 Helsinki and 73 RMH), higher GCS (15 vs 14 for both Helsinki and RMH) and higher proportion of male patients (63.2% vs 57% for both Helsinki and RMH) compared to Helsinki and RMH cohorts. There was proportionally more lobar ICH (63.6%) than RMH (31.8%) or Helsinki (26.1%) cohorts, which may explain the reduced mortality rate (Samarasekera et al., 2015) in the VISTA-ICH cohort. The VISTA-ICH patients all had to meet selection criteria for randomised controlled trials, which would have excluded patients with poor premorbid function and poor prognostic features such as massive haematoma volume and very low GCS. This is also reflected in the differences in the mortality of diabetic patients included in the analysis presented in Chapter V (VISTA-ICH 22.5%, Helsinki 38.4% and RMH ICH 32.9%). Further, the results from Chapter V were also based on diabetic patients and the results may not be generalisable to all ICH patients.
8.6.3 Ascertainment bias

The planimetric segmentation of ICH and oedema used for analyses presented was performed by the author of this work and therefore may be at risk of ascertainment bias. In Chapter III, the reliability of the semi-automated planimetric method used was compared between 3 raters involved in stroke research, including the author of this work, with different levels of expertise in neuroimaging. The study demonstrated excellent inter-rater and intra-rater intraclass correlation coefficients for both ICH and oedema (all intraclass correlation coefficients >0.931) (Wu et al., 2016).

The study presented in Chapter IV required imaging review and selection of patients with simultaneous multiple ICHs. This was performed by the author of this work and an experienced stroke neurologist. There was a potential for selection bias but we minimised the risk of bias by pre-specifying the diagnostic criteria for SMICH. Further, the patients deemed to have SMICH were selected after a second review performed by another author experienced in stroke imaging research.

8.6.4 Outcome data, early limitation of care and repeat imaging

8.6.4a Mortality

The outcome used for analysis in the chapters was mortality as follow up of functional status for stroke patients during the study period was not routine at Helsinki University Hospital and RMH. In Helsinki, comprehensive vital status data was kept by Statistics Finland. For RMH patients, survival was evidenced by clinical visits, laboratory or radiological investigations beyond the 90-day period and if no vital status data was available the patients were considered lost to follow up. The VISTA-ICH patients had comprehensive follow up data as part of the pre-specified individual trial study protocol. Detailed functional outcome data for all the patients would have been preferred to enable assessment for an association between a test variable and functional recovery. It is likely that the true impact of the associations reported in the studies was underestimated using mortality only as an endpoint. However, mortality is a concrete outcome and also a robust indicator for the burden of stroke (Wang et al., 2016b).
8.6.4b. Early limitation of care

A further limitation with mortality only endpoint is the potential for poor prognostic indicators to influence management decisions regarding early institution of do-not-resuscitate orders or care limitation as discussed in Chapter I. For instance a patient with rapid early oedema growth (Chapter VI) may still benefit from aggressive management despite having statistically increased risk of death. Previous published studies examining the impact of early limitation of care have indicated a significant minority of patients with poor baseline prognostic features such as large ICH volume and low baseline GCS may still benefit from aggressive treatment with reasonable functional recovery (Becker et al., 2001; Zahuranec et al., 2007; Morgenstern et al., 2015). The aim of the mortality analyses presented in this thesis was to explore potential treatment strategies and not intended to produce prognostic indicators to influence clinical decisions on early palliation. The readers of this thesis need to interpret the study findings in light of this. Clinical decision-making regarding care limitation needs to be individualised to avoid creating “self-fulfilling prophecies” (Becker et al., 2001).

8.6.4c Routine follow up CT

The major limitation to the imaging data presented is the lack of routine follow up scans at regular intervals in the Helsinki cohort, which was used to describe the natural history of oedema growth. It would have been preferable to have follow up imaging at set time points up to 3 weeks from ictus, but this is not possible outside of trials and performing routine CT multiple times in every patients is not justified clinically, expensive and exposes patients to unnecessary radiation. A mathematical equation created in Chapter VI based on oedema growth rates from all available scans enabled assessment of oedema natural history and also calculation of oedema at 72-hours. This method was also used to analyse for potential association of glucose and oedema growth in Chapter VII. As the oedema equation is derived from the Helsinki cohort, the growth rate may not be applicable to other ICH populations.

8.6.5 Potential sources of statistical errors

In most studies presented in this thesis, the independent association between a test variable and patient outcome was assessed in multivariable logistic regression models. Over-specification or modeling can be present when too many variables are included
in a model and, in general, a variable to outcome event ratio of at least 1:10 avoids this issue of over-modeling (Peduzzi et al., 1996). The covariates in the logistic regression models used in the studies were pre-defined and limited largely to age, male sex, NIHSS, GCS, baseline ICH volume, ventricular extension and infratentorial location. Over-modeling was not an issue in all the multivariable analyses presented. There was also no multicollinearity as indicated by the low variance inflation factors between the covariates contained in the logistic regression models presented in this thesis.

One potential cofounding factor is imbalance of baseline characteristics. A method to account for potential confounding is propensity score matching analysis. This was performed as a secondary analysis in Chapters IV, V and VII. The sample size in Chapter V was significantly reduced following propensity score matching, this resulted in a non-significant association of metformin and outcome although the point estimate remained in the same direction. In Chapters IV and VII, the result of the primary analysis was unchanged following propensity score matching.

Adjustment for multiple hypothesis testing was not performed in the studies presented in this thesis, potentially exposing the results to type I statistical error. However the hypotheses presented and tested in the studies were independent analyses with different patient inclusion criteria. Furthermore in 3 studies the study population was derived from combining patients from other ICH cohorts with the Helsinki ICH study. Although the risk of type I statistical errors is considered low, the readers should consider the results in light of this limitation and further validation from other independent ICH cohorts would strengthen and support the statistical validity of the published findings.

8.6.6 Strengths

This thesis has a number of strengths. Firstly the ICH cohorts consisted of well characterised patients and had follow up data for nearly all patients (100% in VISTA-ICH, 99% in Helsinki and 95% in RMH). Mortality data was also derived from reliable sources of information. Secondly, the planimetric method and the post processing used to derive the haematoma and oedema volumes utilised a ‘gold standard’ approach by accounting for the individual slice thickness and adjusting for
impact of gantry tilt (Wu et al., 2016). Obtaining the best estimate of haematoma and oedema volume added to the confidence and reliability of the associations reported in the studies given the volume dependent impact on outcome of haematoma and oedema. Thirdly, all the reported analyses were defined a priori and advanced statistical methods such as propensity score matching analysis were used to confirm the findings from the preliminary analysis. Finally this thesis reported on a number of promising potential translational targets that could be used for research to improve ICH outcome.

8.7 Future directions

8.7.1 Automated segmentation - the future approach to volumetric segmentation

Automated volume segmentation of the ischaemic penumbra and core is available through programs such the RAPID software (iSchemaView, Menlo Park, CA) for management of acute ischaemic stroke (Campbell et al., 2015). As presented in Chapter III, planimetric haematoma and oedema segmentation requires an average time of between 6 and 9 minutes. An automated algorithm to segment haematoma and oedema is likely to improve research productivity, reduce cost and training time. Since completion of Chapter III, a study presenting a method for fully automated haematoma segmentation and volume output was published using the Medical Imaging and Interaction Toolkit (MITK). The MITK software is available for download as a freeware. The authors used machine learning and random forest based methodology to devise an automated algorithm and compared the volume output to volumes derived from ABC/2 and manual segmentation. The authors reported the machine-learning algorithm was able to account for slice thickness variation in addition to excluding non-haemorrhage brain regions such as bone. The results presented indicated excellent correlation between automated output and manual segmentation (concordance correlation coefficient 0.95, 95% CI 0.91), although there was a mean volume difference of 3.1 mL (~10%) between manual segmentation and the automated algorithm (p=0.06) (Scherer et al., 2016). The automated algorithm is yet to be made available (personal communication with Dr Scherer) at the time of thesis submission. The author of this thesis plans to perform a validation study.
comparing the volume and time taken for segmentation of haematoma volume using
the methodology presented in Chapter III to this new method when it becomes
available for use.

8.7.2 Oedema management

The mechanisms of oedema formation remain poorly understood. Further research is
required to elucidate other, non-haematoma related factors contributing to oedema
evolution. Potential research questions in this area include association of
hypertension/haemodynamic parameters and haematoma expansion with oedema
evolution. In addition, the contribution of pro-inflammatory factors such as fever,
peripheral leucocyte count and other markers of systemic inflammation, and iron to
delayed oedema growth need further research. The impact of delayed oedema growth
on patient outcome remains uncertain and not well studied. The full results of Safety
of Pioglitazone for Hematoma resolution in Intracerebral Hemorrhage (SHRINC)
study (n=84) are expected to shed more light on the evolution of oedema as each
patient had 5 brain MRIs performed serially within 56 days from ictus (Gonzales et
al., 2013).

There are also other unanswered questions including mechanisms behind the reported
impact of oedema on functional recovery (Murthy et al., 2015) and its potential
influence on neural network recovery and functional connectivity.

Results of ongoing ICH medical management trials including hypothermia (Kollmar
et al., 2012; Rincon et al., 2014) and iron chelation (Yeatts et al., 2013) may shed
further light into potential modifiers of oedema.

8.7.3 Combined approach to ICH treatment

Although there are many unanswered questions in ICH, it is clear that the brain injury
after ICH is an evolving and dynamic process. The ongoing clinical trials target one
facet of ICH management, with most studies assessing strategies to limit injury
cased by the haematoma. It is likely that management of ICH in the future will
require management of different contributing facets to primary and secondary injury.
A likely management paradigm is represented in figure 23.
Figure 23. Potential approach to future ICH management.

- Intracerebral haemorrhage
  - Acute blood pressure lowering
  - Anticoagulant reversal if indicated
  - Imaging markers of haematoma expansion
    - No
      - Surgery in select patients
        - minimally invasive surgery
    - Yes
      - Haemostatic agents
      - Stroke unit care
        - Assess for haematoma growth and monitoring of oedema growth
        - Allied health input
          - Rehabilitation and recovery
          - Secondary prevention
        - Blood pressure control
          - Glycaemic control
          - Temperature monitoring
        - Potential oedema therapy
          - Hypothermia
          - Iron chelation
          - Anti-inflammatory
          - Decompression
  - Blood pressure control
  - Glycaemic control
  - Temperature monitoring
  - Potential oedema therapy
  - Acute blood pressure lowering
  - Glycaemic control
  - Temperature monitoring
  - Allied health input
    - Rehabilitation and recovery
    - Secondary prevention
  - Potential oedema therapy
    - Hypothermia
    - Iron chelation
    - Anti-inflammatory
    - Decompression
  - Stroke unit care
    - Assess for haematoma growth and monitoring of oedema growth

8.8 Conclusions

Management of intracerebral haemorrhage is challenging due to the evolving and dynamic nature of the mechanisms affecting patient outcome. This thesis has contributed to advancing understanding of the mechanisms in the evolution of prognostic factors after intracerebral haemorrhage. The major conclusions of the thesis are summarised in table 7.

Table 7. Thesis conclusions

- Simultaneous intracerebral haemorrhages are a relatively common presentation of intracerebral haemorrhage with widely distributed aetiologies. Management of these patients needs to target the underlying pathologies.
- Threshold-based semi-automated planimetric estimation of haematoma and oedema volumes are reliable but volume output can be significantly underestimated if appropriate adjustments for gantry tilt, slice thickness and interslice distance are not made. The results of clinical trials may be influenced by these errors.
- Oedema evolution is a two-stage dynamic process with rapid acute stage followed by slower subacute growth. Increased rate of oedema growth is independently associated with mortality and is influenced by baseline haematoma volume and increased baseline glucose level.
- Only 50% of patients with hyperglycaemia within 24 hours of onset remain persistently hyperglycaemic between 24 and 72 hours. Mortality after intracerebral haemorrhage is associated with persistent hyperglycaemia, even after adjusting for other known prognostic indicators.
- Metformin use before onset of intracerebral haemorrhage was associated with halved odds of death in diabetic patients. Metformin may provide neuroprotection through reduced metabolic stress and secondary injury and is a potential translational target.
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