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Treatment and prognosis in posterior circulation ischaemic stroke

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Abstract

Acute ischemic stroke is caused by a blocked blood vessel in the cerebral circulation. It is the most common form of stroke worldwide and a major cause of disability and death. One in five ischaemic strokes affects the posterior circulation. This type of stroke is associated with high risk of recurrence, disability and mortality. Diagnosing posterior circulation stroke can be challenging, as it often presents with non-specific or fluctuating symptoms. Several aspects of posterior circulation stroke are poorly understood compared to anterior circulation stroke. Treatments to re-open the blocked blood vessel and reperfuse the brain are available but patients with posterior circulation stroke were excluded from most of the randomized controlled trials which showed the benefit of reperfusion therapies in ischaemic stroke.

This thesis examines the natural history, clinical and neuroimaging prognostic factors of outcome and treatment response in patients with posterior circulation stroke. We created the Basilar Artery Treatment and MANagement (BATMAN) collaboration, an international multicentre prospective registry aiming to answer clinical questions regarding this devastating and under-researched form of stroke. The overarching aim of this registry is to identify clinical and neuroimaging prognostic factors of outcome and treatment response in patients with posterior circulation stroke.

This thesis examines clinical and imaging predictors of outcome in patients with posterior circulation stroke and how they may be applied in clinical practice. The ultimate aim is to push boundaries of treatment in patients with posterior circulation stroke allowing treatment in extended time windows when favourable imaging profiles are present and identify the optimal treatment management for these patients.

Declaration

This is to certify that:

(i) the thesis comprises only my original work towards the degree of Doctor of Philosophy except where indicated in the preface,

(ii) due acknowledgement has been made in the text to all other material used,

(iii) the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Dr Fana Alemseged 26/02/2021

Preface

Contribution to thesis

Projects in this thesis were carried out in collaboration with multiple institutions worldwide, principally the Department of Neurology, Royal Melbourne Hospital, Department of Medicine, The University of Melbourne. Supervisors and collaborators assisted in project design, ethics submission, data collection, data analysis and manuscript preparation. For all projects listed in this thesis I remain the primary investigator with >50% of original work contributed.

Contribution to publications

In all publications arising from the work undertaken in this thesis, co-authors provided supervisory assistance and input for drafting and revision of manuscripts. I remain the primary contributor with >50% of effort towards publication. The work presented in this thesis was undertaken in the Department of Neurology, Royal Melbourne Hospital in association with the Departments of Medicine and Radiology, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne. A substantial component of the work presented in this thesis has been published or is currently in submission for publication. Additionally, this work has been presented at various national and international scientific conferences.

Publications relevant to this thesis:

Alemseged F, Shah DG, Bivard A, Kleinig TJ, Yassi N, Diomedi M, Di Giuliano F, Sharma G, Drew R, Yan B, Dowling RJ, Bush S, Sallustio F, Caltagirone C, Mercuri NB, Floris R, Parsons MW, Levi CR, Mitchell PJ, Davis SM, Campbell BC. Cerebral blood volume lesion extent predicts functional outcome in patients with vertebral and basilar artery occlusion. *International Journal of Stroke*. 2019 Jul;14(5):540-547.

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Acknowledgements

When I decided to move from Italy to the "other side of the world" to commence a PhD, I was only partially aware of the life-changing adventure I was about to start. Living in a new country (with a different language and culture) and working as an academic stroke neurologist at one of the most prestigious stroke centres in the world, has been such an exciting and rewarding experience both personally and professionally.

During this time, I discovered an incredible passion for stroke research. This was inspired by some of the finest minds in the field. I am extremely grateful to these fine minds, my supervisors Prof. Bruce Campbell, A/Prof. Nawaf Yassi, Prof. Stephen Davis and Prof. Peter Mitchell. Their invaluable support together with their tremendous knowledge and experience have encouraged me in all the time of my academic research and clinical fellowship.

I cannot owe enough thanks to my primary supervisor Prof. Bruce Campbell. I remember sending him an email a few years ago, when I was still a registrar in Rome, asking If I could come to the Melbourne Brain Centre for a research fellowship. It was night-time in Melbourne, so I was surprised when after a few minutes I received his reply "Sure! What do we need to do to make that happen?" This has been Bruce for me over the past 5 years. Whether I had an ambitious research idea, a problem with one of my research projects or a complex stroke case to discuss, he was always there offering unwavering support, tremendous clinical knowledge, brilliant insight and hyper-intelligent suggestions. As true leaders know, the most powerful way of inspiring people is leading by example. I saw his unrelenting pursuit of practice-changing research and mission of treating every single patient with the best care possible inspiring so many young minds in these years. Being one of the youngest world-recognised stroke leaders ever, while remaining such a humble and down to earth person is again so inspiring both on a professional and personal level. I want to especially thank Bruce, "the Almighty" (as we used to call him among stroke fellows) for his mentorship in the past year. During this challenging time, in a global pandemic, he has never failed to give all the support needed to finalise my PhD and build my future career as an academic stroke neurologist.

Nawaf has not only been a mentor but also a friend. I was lucky enough to be constantly enlightened by his tremendous clinical knowledge and research acumen. Together we worked *very hard to design a research project at the interface of stroke and Alzheimer's disease that I believe has great potential to give a significant contribution to the dementia field.*

I have been so honoured to be a PhD student of Prof. Stephen Davis, one of the fathers of stroke treatment as we know it today. For me, Stephen Davis is the King Midas in the stroke field. He turned everyone who worked at the Melbourne Brain Centre into an outstanding academic neurologist with his golden touch. I hope I will be no exception.

I would like to thank everyone at the Melbourne Brain Centre for their support but especially Prof. Leonid Churilov for his help with statistical analyses, Amy McDonald for her knowledge of research, Lauren Pesavento for her help with data and Gagan Sharma for his assistance with image processing.

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Finally, I want to dedicate this achievement to my parents and my sister. They taught me and showed me in so many ways that regardless of who you are, where you come from and how many challenges you face in life, hard work, determination (and a bit of luck) will take you wherever you want. I was lucky enough to meet an incredible team at the Melbourne Brain Centre who made my PhD journey successful. My luck continued when I met my partner Leone, one of the most precious gifts this incredible Australian adventure has given to me.

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List of Abbreviations

ASPECTS	Alberta Stroke Program Early CT Score
pc-ASPECTS	Posterior circulation Acute Stroke Prognosis Early CT score
BAO	Basilar artery occlusion
BATMAN	Basilar Artery on Computed Tomography Angiography
	Basilar Artery Treatment and Management
CI	Confidence interval
CT	Computed tomography
DWI	Diffusion weighted imaging
ENDOSTROKE	The Endovascular Stroke Treatment registry
e-NIHSS	Expanded National Institutes of Health Stroke Scale
EVT	Endovascular therapy
HINTS	Head Impulse—Nystagmus—Skew Test
ICA	Internal carotid artery
IQR	Inter-quartile range
IVBSS	Israeli Vertebrobasilar Stroke Scale
MCA	Middle cerebral artery
M1	First segment of the middle cerebral artery
M2	Second segment of the middle cerebral artery
MELAS	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
NIHSS	National Institutes of Health Stroke Scale
PICA	Posterior-inferior cerebellar artery
PCA	Posterior cerebral artery
PFO	Patent foramen ovale
PRES	Posterior reversible encephalopathy syndrome
RCVS	Reversible cerebral vasoconstriction syndrome
SCA	Superior cerebellar artery

SWI Susceptibility-weighted imaging

VA Vertebral artery

Trial abbreviations

AcT Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke

ANGIOCAT Evaluation of Direct Transfer to Angiography Suite vs. Computed Tomography Suite in Endovascular Treatment: Randomized Clinical Trial

ATLANTIS Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke

ATTEST Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis

DAWN Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo

DEFUSE-3 Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3

DIRECT-SAFE A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval

DIRECTANGIO Effect of DIRECT Transfer to ANGIOsuite on Functional Outcome in Severe Acute Stroke

ECASS European Cooperative Acute Stroke Study

ENDOLOW Endovascular Therapy for Low NIHSS Ischemic Strokes

EPITHET Echoplanar Imaging Thrombolytic Evaluation Trial

ESCAPE Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke

ETERNAL-LVO Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion

EXTEND Extending the Time for Thrombolysis in Emergency Neurological Deficits

EXTEND-IA Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial

EXTEND-IA TNK Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke

FASTEST Recombinant Factor VIIa (rFVIIa) for Hemorrhagic Stroke Trial

IMS-3 Interventional Management of Stroke III Trial

IST-3 Third international stroke trial

MERCI Mechanical Embolus Removal in Cerebral Ischemia

MOSTE Minor Stroke Therapy Evaluation

MR CLEAN Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

MR CLEAN NO IV Intravenous treatment followed by intra-arterial treatment versus direct intra-arterial treatment for acute ischaemic stroke caused by a proximal intracranial occlusion

MR RESCUE Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy

NINDS The National Institute of Neurological Disorders and Stroke Trial

PISTE Pragmatic Ischaemic Stroke Thrombectomy Evaluation

REVASCAT Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours

SWIFT DIRECT Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke

SWIFT PRIME Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment Trial

SYNTHESIS Local Versus Systemic Thrombolysis for Acute Ischemic Stroke

TASTE Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation Trial

TASTE-A Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance

TEMPO-2 A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion

THAWS THrombolysis for Acute Wake-up and Unclear-onset Strokes With Alteplase at 0.6 mg/kg Trial

THRACE Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke

TWIST Tenecteplase in Wake-up Ischaemic Stroke Trial

WAKE-UP Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke

Literature review and Introduction

Definitions

Acute ischemic stroke is a focal infarction of brain tissue, spine or retina due to a reduction or interruption of blood supply. This is usually caused by an arterial occlusion or critical stenosis in the anterior or posterior cerebral circulation. The American Heart Association/American Stroke Association definition describes acute stroke as a neurological dysfunction due to injury from a vascular cause that can either be demonstrated through neuro-pathology, neuro-imaging and/or clinical evidence of permanent injury. (1) Transient ischaemic attack was traditionally defined as a sudden, focal neurological deficit lasting < 24 hours due to a vascular origin. (2) This definition was subsequently changed to a transient episode of neurological dysfunction caused by ischaemia and without acute infarction, (3) so that patients with evidence of infarction on brain imaging are re-classified as having had a stroke, regardless of their symptom duration.

Epidemiology

Stroke is the second leading cause of death and the most common cause of adult disability in the developed world. (4) Ischemic stroke comprises ~80% of stroke in Australia (5) and most Western countries. Intracerebral haemorrhage comprises 10%-15%, subarachnoid haemorrhage 5%, and the remainder are due to other rare causes of stroke. (6) In a study from 1990-2016, the lifetime risk of stroke was estimated to be 24.9% (95% CI 23.5-26.2) from age 25 when adjusted for other causes of death, with the risk of ischaemic stroke being 18.3%. Therefore, one in four people globally will have a stroke in their lifetime. (7) There were 27,428 Australians who experienced stroke for the first time in their lives in 2020, which equates to one stroke every 19 minutes, (8) with Australians in regional areas 17% more likely to have a stroke than those in metropolitan areas. (9) In 2020, the estimated cost of stroke in Australia was $6.2 billion (Australian dollars) in direct financial impact (productivity costs including healthcare costs, welfare and carer costs), and a further $26.0 billion in long-term disability and mortality. (9)

Pathophysiology of acute ischemic stroke

Blood flow restriction causes regional hypoxia that initially induces electrical failure of the affected neurons. (10) The term "ischaemic penumbra", first used in the 1970s, describes this phase in which the hypoperfused brain has become electrically non-functional but can recover if blood flow is rapidly restored through vessel recanalisation. Below a critical threshold, the ion pumps and the intracellular mechanisms that provide cellular energy start to fail. (10) This causes neuronal death from apoptosis or necrosis and triggers pathways of excitotoxicity and inflammation that further damage the tissue. The term "ischaemic core" describes this phase, when localised hypoxia has crossed the critical threshold and the irreversible cascade of cellular death has been initiated. Restoration of blood flow will no longer avoid neuronal death and may cause greater harm by leading to secondary haemorrhagic transformation of areas of infarction.

The time window for blood flow restoration through vessel recanalisation to prevent the ischemic penumbra transitioning into the ischaemic core is highly dependent on the collateral blood flow. (11) Collateral circulation has a key role in the dynamic compensation that allows the existence of ischaemic penumbra and the success of reperfusion therapies, through secondary anastomotic networks that provide backup blood supply when an arterial blood flow is disrupted. In large vessel occlusions proximal to the circle of Willis, anterior and posterior communicating arteries (when present and not hypoplastic) allow collateral blood flow to potentially supplement all of the major intracerebral arteries (anterior, middle and posterior). (12) The posterior communicating arteries may supply collateral blood flow in either direction between the anterior and posterior circulation. Distal branches of the major cerebellar arteries provide collateral links across the vertebral and basilar arteries. Significant variability and asymmetry exist in the anatomy of the circle of Willis, with a "textbook" configuration present in only a minority of cases. (12) Other collateral pathways include retrograde flow through the ophthalmic artery contributed by branches of the external carotid artery. In occlusions distal to the circle of Willis, dural and leptomeningeal anastomoses that are highly variable between individuals form the main collateral pathways, and may fluctuate over time. Other collateral pathways may be created in specific pathological conditions. For instance, a patient with occlusion of the internal carotid artery may have a dominant collateral pathway from the posterior circulation through an enlarged anterior choroidal artery. (13)

Posterior circulation stroke

A posterior circulation ischemic stroke is an infarction in the territory supplied by the vertebrobasilar system. The vertebrobasilar arterial system supplies blood flow to the cerebellum, medulla, pons, midbrain, thalamus, mesial temporal and occipital cortex. Posterior circulation stroke accounts for about 20-25% of all ischemic strokes, but it is associated with a high risk of disability, recurrence and mortality. (14)

Posterior circulation anatomy

The posterior circulation is constituted by the two vertebral arteries (VAs), the basilar artery (BA), the posterior cerebral arteries (PCAs) and their branches (Figure 1).

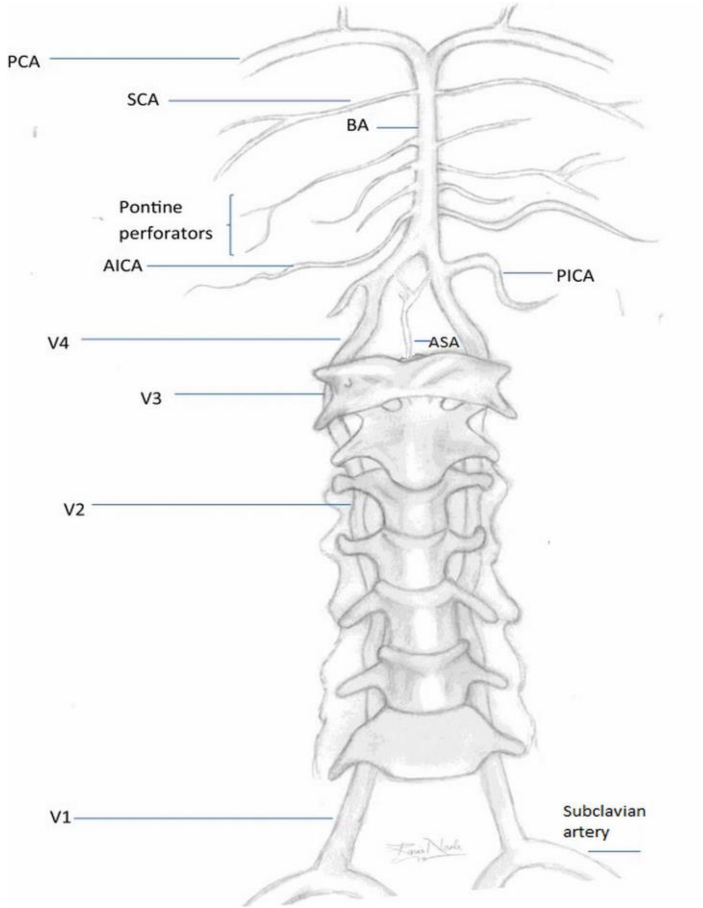

Figure 1. Vertebrobasilar system. The figure illustrates the four segments (V1-V4) of the vertebral arteries from their origin at the level of the subclavian arteries. From the vertebral arteries, the posterior-inferior-cerebellar (PICA) arteries and the anterior spinal artery arise. The basilar artery (BA) arises from the confluence of the left and right vertebral arteries at the base of the pons. Before terminating at the upper pontine border where it divides into the two posterior cerebral arteries, it provides several paired branches: the anterior inferior cerebellar artery (AICA), the pontine arteries and the superior cerebellar artery (SCA).

The vertebral arteries originate from the subclavian arteries, although they can occasionally arise directly from the aortic arch. Ascending in the neck, they supply the posterior fossa and occipital lobes, and provide segmental vertebral and spinal column blood supply. The origin of the vertebral arteries is usually from the posterior superior part of the subclavian arteries bilaterally, although sometimes this can arise from the brachiocephalic artery on the right and in 6% of cases from the aortic arch, mostly on the left. The caliber of the vertebral artery is 3-5 mm in diameter, with the ostium being the most common site of stenosis. The vertebral artery is typically divided into 4 segments: V1 pre-foraminal segment (origin to the transverse foramen of C6); V2 foraminal segment (from the transverse foramen of C6 to the transverse foramen of C2); V3 atlantic, extradural segment (from C2, where the artery loops and turns lateral to ascend into the transverse foramen continues through C1 to pierce the dura); V4 intradural or intracranial segment (from the dura at the lateral edge of the posterior atlanto-occipital membrane to their confluence on the medulla to form the basilar artery). Numerous muscular branches, that can anastomose with occipital branches of the external carotid artery, are given off as the artery ascends. The posterior inferior cerebellar artery (PICA), the largest branch of the vertebral artery, is one of three main arteries supplying the cerebellum. Other branches include the segmental cervical muscular and spinal branches (V1 segment); the anterior meningeal artery, muscular and spinal branches (V2 segment); the posterior meningeal artery (V3 segment), the anterior and posterior spinal arteries (V4 segment) and perforating branches to the medulla. The basilar artery arises from the confluence of the left and right vertebral arteries at the base of the pons. (15) The basilar artery runs cranially in the central groove of the pons towards the midbrain within the pontine cistern and bifurcates at the upper pontine border, where it divides into the two posterior cerebral arteries. The basilar artery provides the anterior inferior cerebellar artery (AICA), the labyrinthine artery (variable origin; more commonly a branch of AICA), the pontine arteries and the superior cerebellar artery (SCA).

Anatomical variants

Anatomical variants are common in the posterior circulation. Although often asymptomatic, anatomical variants may contribute to the risk of ischaemic stroke and be relevant for the stroke pathogenic mechanism.

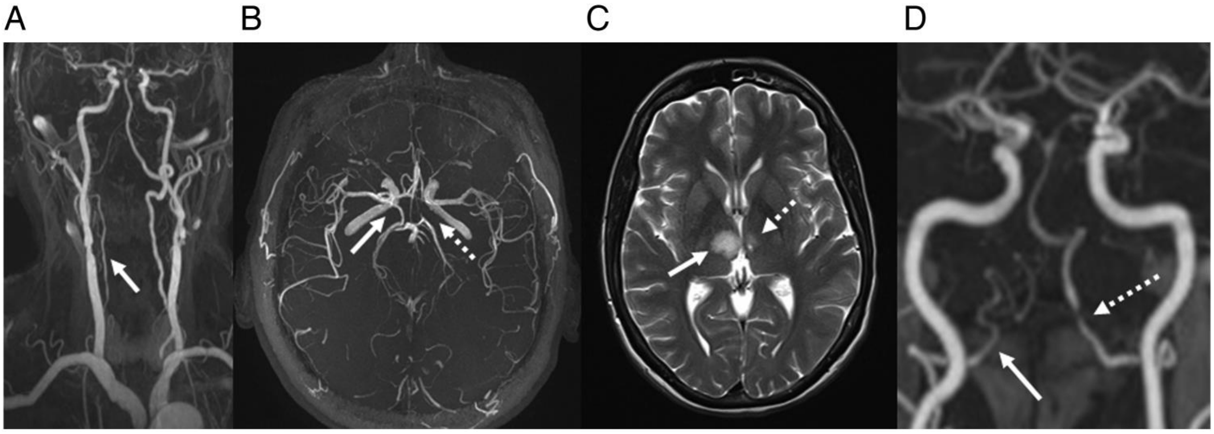

Figure 2. Example of anatomical variants in the posterior circulation (A) Hypoplastic vertebral artery (arrow); (B) Fetal posterior communicating artery on the right (arrow in bold), absent posterior communicating artery on the left (dashed arrow); (C) bilateral thalamic infarcts, consistent with the presence of a Percheron artery; (D) right vertebral artery terminating in the posterior inferior cerebellar artery (arrow in bold), stenosis of the V4 segment on the left (dashed arrow).

Hypoplastic vertebral artery (Figure 2A) is present in one-quarter of the population, but it appears to be more common in patients with posterior circulation ischaemic stroke. (16) The ischaemic risk may be increased due to asymmetric flow dynamics which would lead to vessel shear stress and the formation of atheroma. A fetal origin of the posterior cerebral artery is a common anatomical variant, estimated to occur in 20-30% of individuals. (17) The posterior communicating artery (PCOM) is larger than the P1 segment of the posterior cerebral artery (PCA) and supplies the bulk of the blood to the PCA. Although the term is typically used to refer to the situation where the PCOM is larger than the P1 segment of the PCA, the P1 can be either hypoplastic or absent (Figure 2B). In these cases, an infarct in the PCA territory may indicate a symptomatic stenosis or occlusion of the internal carotid artery. A small (<1 mm in diameter) or absent ipsilateral posterior communicating artery is a risk factor for ischemic cerebral infarction in the posterior circulation territory in patients with internal-carotid-artery occlusion. (18) In case of occlusion of the basilar artery, a large posterior communicating artery may allow collateral flow from the anterior circulation and improve clinical outomes. (19, 20) If a fetal origin is present bilaterally, the basilar artery is significantly smaller than normal.

The artery of Percheron is characterized by a solitary arterial trunk that branches from one of the proximal segments of either of the posterior cerebral arteries and supplies blood to the paramedian thalami. This type of variation is present in 4%-12% of the population. (21) Occlusion of this artery results in a bilateral paramedian thalamic infarction (Figure 2C) that may extend to the midbrain. (21) Other variants include hypoplasia or aplasia of the intracranial segment of the vertebral artery, terminating into the PICA (Figure 2D). Hypoplasia of the basilar artery is rare and is often associated with bilateral fetal PCAs. The persistent trigeminal artery is the most common and most cephalic of the persistent carotid-vertebrobasilar anastomoses. Its reported prevalence is 0.1%–0.6%. (22) This artery originates from the internal carotid artery immediately after its exit from the carotid canal and anastomoses with the mid basilar artery. The part of the basilar artery that is caudal to the anastomosis with the trigeminal artery is usually hypoplastic. (22)

Collateral pathways of the basilar artery

When the trunk of the basilar artery is occluded, a drop in perfusion pressure at the confluence of the posterior cerebral arteries leads to reverse filling through posterior communicating arteries, if they are present. This reversed flow may supply flow distal to the clot and generate residual flow in the ischemic region, by maintaining the patency of the perforating arteries and the SCA branches. Goyal et al. (20) showed in n=21 individuals with basilar artery occlusion that patients with bilateral posterior communicating arteries have more favorable 3-month outcome than those with unilateral/absent posterior communicating artery (modified Rankin Scale 0-2, 72.7% vs 0% respectively, p=0.001). Furthermore, Hong et al. (19) demonstrated in n=95 patients with acute brainstem infarction due to at least 50% stenosis of the basilar artery, that fetal posterior communicating arteries were predictors of good prognosis in basilar artery occlusion (modified Rankin Scale 0-2, odds ratio 5.1; 95% CI 1.4–18.8). Posterior communicating arteries, therefore, seem to be the main collateral pathways involved in the pathophysiology of basilar artery occlusion. Fetal posterior communicating arteries may be protective in basilar artery occlusion because of the smaller territory at ischemic risk and the preservation of penetrating arteries to the midbrain and thalamus that arise from the anterior circulation-supplied fetal posterior communicating arteries. (19, 23) Because time is a critical variable in the development of collateral circulation, chronic pathology of the basilar artery resulting from atherosclerosis may allow for more extensive development of collateral flow via the posterior communicating arteries. (19) A second collateral pathway can flow via the posterior inferior cerebellar arteries which can be supplied by the anterior spinal artery; thus, if vertebral arteries remain patent at the origin, they may generate flow through the posterior inferior cerebellar artery into the AICAs, the SCAs, and the perforating arteries. (23)

Aetiology of posterior circulation ischaemic stroke

Cardiac embolism, atherosclerosis, small vessel disease (lacunar infarcts) and vertebral artery dissection are the most common causes of posterior circulation stroke. Even after thorough investigations, a definite cause cannot be established in up to 30% of patients – so-called “cryptogenic stroke”. By the TOAST classification, which is the one most commonly used in clinical practice, cryptogenic stroke (or stroke of undetermined origin in TOAST terminology) is defined as brain infarction that is not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation. (24)

The New England Medical Center Posterior Circulation registry, (22) including 407 patients with posterior circulation stroke, demonstrated that embolism was the commonest stroke mechanism, accounting for 40 to 54% of cases. Cardiac-origin embolism accounted for 24 to 33% of strokes, whereas artery-to-artery embolism accounted for 14 to 18%. Intraarterial embolism was the commonest mechanism of brain infarction in patients with vertebral artery occlusive disease. Cardioembolic stroke has been identified as the stroke subtype with the highest morbidity and mortality burden. (25) It is most often due to atrial fibrillation but can also occur with segmental hypokinesis following myocardial ischemia or valvular disorders. Infective endocarditis and cardiac tumours (fibroelastoma or myxoma) are less common. Atrial fibrillation is responsible for ~20% of ischemic stroke (26) and has a considerable risk for recurrence. (27) Stasis in the left atrium allows thrombus to form with subsequent risk of cerebral or systemic embolisation. The risk of stroke is present regardless of whether the patient has permanent, persistent or paroxysmal atrial fibrillation, but several studies have suggested that the risk is higher in patients with increased atrial fibrillation burden. (28, 29) Patients with atrial fibrillation have larger strokes with worse outcomes than other stroke mechanisms. (30) Given the high embolic risk, oral anticoagulation with warfarin is recommended for all patients with valvular atrial fibrillation and with warfarin or the non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, edoxaban for patients with non-valvular atrial fibrillation. (31) However, such therapy is associated with an increased risk of bleeding and its use must take both benefit and risk into account. Among patients with nonvalvular atrial fibrillation, the vast majority of thrombus material is formed within the left atrial appendage. The importance of the left atrial

appendage in thromboembolic risk among patients with atrial fibrillation provides the rationale for ligation, amputation, or occlusion of the left atrial appendage, especially in patients who are candidates for but cannot receive oral anticoagulation, or those at high risk of bleeding with oral anticoagulation. The WATCHMAN device (Boston Scientific), a self-expandable nitinol cage deployed in the left atrial appendage using a transseptal approach, is the most commonly implanted percutaneous left atrial appendage occlusion device, given the available data supporting its use. However, approximately 10% of embolic thrombus is not generated in the left atrial appendage (e.g. the clot originates from the left atrial cavity) and therefore closing the left atrial appendage may not eliminate the risk of embolism. (32)
Segmental hypokinesis, a common consequence of myocardial infarction, can cause abnormal wall motion and the development of mural thrombus with subsequent embolisation. (33) Severe cardiomyopathy can also trigger the development of mural thrombus. Other potential causes of cardiac embolism are patent foramen ovale (PFO), aortic arch atheroma, and mitral valve strands, as well as potential prothrombotic disorder. (24) PFO is a congenital variant which is found in ~25% of the general population and is over-represented in stroke patients with cryptogenic stroke. (34) Closure of a PFO can prevent paradoxical embolism and thereby reduce the risk of recurrent stroke. While early trials were neutral, more recent evidence from randomized controlled trials indicated that PFO closure is effective in reducing the risk of recurrent stroke for selected patients with presumed PFO-associated stroke. Percutaneous PFO closure is more effective for preventing recurrent ischemic stroke than antiplatelet therapy alone for highly selected patients (age ≤60 years) who have a likely embolic ischemic stroke and a PFO. (35-37)

About one-third of posterior circulation strokes are caused by occlusive disease within the extracranial and intracranial vertebral arteries and the basilar artery. Large artery atherosclerosis is related to age, hypertension, diabetes mellitus, smoking, hypercholesterolemia, and polygenic inheritance. (38) Rupture of the fibrous cap of plaques, made of cholesterol-laden macrophages accumulated in the arterial wall, may lead to platelet aggregation and thrombus formation that can subsequently embolise causing more distal arterial occlusion.

The most common site for large artery atherosclerosis in Western populations is the internal carotid artery just beyond the bifurcation. The aortic arch is another high-risk site of thromboembolism from atherosclerotic disease. (39) Asian and African populations are more prone to intracranial atherosclerosis. (40) In the posterior circulation, atherosclerotic plaques are often found at the origin of the vertebral arteries, in the intracranial or intradural segments of the vertebral arteries, or at the confluence where they form the basilar artery. Atherosclerotic plaques can cause distal embolisation or haemodynamic hypoperfusion if a severe stenosis is present. Atherosclerotic lesions in the intracranial segment of the vertebral artery and the PICA can cause a bulbar or cerebellar infarct, and those in the proximal-mid segment of the basilar artery can cause pontine or midbrain infarcts. (41, 42) Embolic occlusions more often affect the distal basilar artery and the posterior cerebral arteries. Emboli can originate from the aortic arch, the subclavian artery, and the origin of the vertebral arteries.

Recurrent ischaemic events affecting the brainstem can be caused by haemodynamic phenomena due to a severe occlusive vascular lesion (so-called vertebrobasilar insufficiency). The subclavian steal syndrome refers to a vascular disorder in which occlusion or stenosis of the subclavian artery proximal to the vertebral artery origin causes altered vascular haemodynamics. This results in retrograde blood flow in the ipsilateral vertebral artery toward the upper arm, distal to the subclavian artery narrowing, where the decreased blood pressure had been established. In some cases, patients may develop upper-limb ischemic symptoms due to reduced arterial flow in the setting of subclavian artery occlusion, or they may develop neurologic symptoms due to posterior circulation ischemia associated with exercise of the ipsilateral arm. (43) Bow-hunter syndrome is an uncommon cause of vertebrobasilar insufficiency that results from occlusion or injury to the vertebral artery during neck rotation. The cause is often a skeletal abnormality that may compress the vertebral artery compromising distal flow or lead to vessel wall injury resulting in thromboembolism. (44)

Arterial dissection (a tear in the arterial wall with intramural hematoma) is a common cause of stroke in young patients. (45) The lumen may be narrowed by the intramural hematoma and superadded luminal thrombus which can also embolise to more distal vessels. Although some dissections have an identifiable traumatic precipitant, including neck manipulation, often there is no clear reason for the dissection and recognisable underlying connective tissue disorders are relatively rare. (46) Vertebral dissections most often occur in either V2, where the artery travels within the transverse foramen, or V3, where the artery runs around the lateral masses of cervical vertebrae 1 (C1) and C2. Vertebral artery dissections extend intracranially in 10% of cases; intracranial dissection can occasionally result in subarachnoid haemorrhage. (47)

Small vessel disease in the deep penetrating arteries of the brain, pathologically described as lipohyalinosis, (48) can lead to lacunar infarction. The epidemiological risk factors are traditionally described as diabetes and hypertension. The pathological changes underlying lacunar infarction appear to be heterogeneous. Lipohyalinotic thickening of the wall of these arteries can occur, usually in the presence of hypertension, which results in diffuse small vessel disease. (47) Alternatively, focal atherosclerosis, either at the mouth or along the length of the penetrating vessel, can block these arteries, leading to lacunar infarction. (42)

Dolichoectasia (dilatative arteriopathy) is a vascular pathology, preferentially involving the vertebral and basilar arteries, characterized by marked elongation, widening, and tortuosity of arteries. Flow in dilated arteries can become bidirectional, resulting in reduced antegrade flow and thrombus formation that can occlude the origin of perforating arteries or embolise distally. Elongation and angulation of arteries can stretch and distort the orifices of arterial branches, leading to decreased blood flow, especially in penetrating branches. Symptoms can also occur due to mass effect from the dilated artery with progressive compression of cranial nerves, the brainstem, or the third ventricle; and catastrophic outcome can occur if there is vascular rupture. (49)

Fabry disease is a rare, X-linked lysosomal storage disease. Deficiency of the enzyme alpha-galactosidase A leads to deposition of glycolipid in arteries, tissues, and organs. In this condition, stroke can occur and is more frequent in the posterior circulation than in the anterior circulation. Vertebrobasilar dolichoectasia can be present and could serve as an early marker of neurovascular involvement. (50) The treatment of patients with Fabry disease primarily focuses upon replacing the missing or deficient enzyme alpha-galactosidase A with enzyme replacement therapy, as well as treating the various symptoms and disease complications. However, enzyme replacement therapy does not significantly reduce the risk of stroke and cerebrovascular disease.

Giant cell arteritis is the most common of the systemic vasculitides. It is a granulomatous large vessel vasculitis that virtually never occurs in individuals younger than 50 years of age. Patients with giant cell arteritis present with headache, abrupt onset of visual disturbances (especially transient monocular visual loss), jaw claudication, unexplained fever or anemia. Cerebral ischaemic events occur in the period of active disease and mainly affect the vertebrobasilar territory. This topography of stroke is more common in patients with active giant cell arteritis than in the general population of the same age. (51) The diagnosis of giant cell arteritis should be premised on histopathologic proof or evidence from imaging exams. Temporal artery biopsy is the cardinal diagnostic procedure. Though never studied in a placebo-controlled manner, the effectiveness of glucocorticoids for the management of giant cell arteritis has been well established by decades of clinical experience. Glucocorticoids produce prompt improvement in systemic symptoms and signs and, if expeditiously administered, can prevent the most sinister potential complication of giant cell arteritis, that of visual loss.

Clinical presentation

Posterior circulation strokes can present with a wide variety of symptoms and signs due to the proximity of brainstem nuclei and large afferent and efferent tracts. Some of these symptoms may be non-specific or fluctuating. The onset and duration of symptoms in vertebrobasilar stroke depend, in large part, upon the etiology. Patients with atherosclerotic lesions in the vertebral arteries or proximal segment of the basilar artery typically have a stuttering course of symptoms, with up to 50% of patients experiencing transient ischemic attacks several days to weeks prior to the acute occlusion. (52) In contrast, embolic events (e.g affecting the distal basilar artery or the posterior cerebral arteries) are sudden, without prodrome, with acute and dramatic presentation. In the 407 patients from the New England Medical Centre Posterior Circulation Registry (NEMC-PCR), (41) the most frequent presenting symptoms were dizziness (47%), unilateral limb weakness (41%), dysarthria (31%), headache (28%) and nausea or vomiting (27%). The most frequent signs were unilateral limb weakness (38%), gait ataxia (31%), unilateral limb ataxia (30%), dysarthria (28%) and nystagmus (24%). The following paragraphs describe the clinical syndromes associated with stroke topography.

<u>Intracranial vertebral artery, posterior-inferior cerebellar artery</u>

The occlusion of the intracranial vertebral artery and the PICA causes ischaemic infarcts in the lateral medulla and the portion of the cerebellum supplied by the PICA.

Lateral medullary (Wallenberg) syndrome

The Lateral medullary (Wallenberg) syndrome is due to a vertebral artery or PICA occlusion. Patients present with nausea, vomiting, and vertigo (due to the involvement of the vestibular system), limb ataxia and dysmetria, Horner syndrome, facial pain and temperature loss, nystagmus, hypoacusis, dysarthria, dysphagia, paralysis of the pharynx, palate, and vocal cord, loss of taste from the posterior third of the tongue. Contralateral findings include loss of pain and temperature sense, indicating an involvement of the lateral spinothalamic tract. Other findings such as tachycardia and dyspnea and delayed-onset palatal myoclonus may be present. The prognosis of patients with Wallenberg syndrome is usually quite good. However, the presence of dysphagia is a strong prognostic factor of poor outcome in patients with lateral medullary syndrome. (53) Dysphagia can lead to serious complications such as aspiration pneumonia and malnutrition. (54) It has been associated with prolonged hospital stay, higher admission rates to residential care facilities and increased mortality. (55)

Cerebellar infarction

A cerebellar stroke may cause dysmetria, dysdiadochokinesia, intention tremor, gait or limb ataxia, dysarthria, and difficulties with memory and motor planning. PICA infarcts are the most common cerebellar infarcts. (56) Patients most commonly present with acute vertigo, vomiting, headache, gait disturbances, and horizontal nystagmus ipsilateral to the lesion. Vertigo is more frequent in PICA strokes (due to the involvement of the midline vermis) as compared with SCA infarcts. In patients with SCA territory infarcts, gait or limb ataxia, dysarthria, and horizontal nystagmus are more pronounced, and fewer patients have headache and vomiting. Gait ataxia is almost always present in posterior circulation stroke involving the cerebellum (57) and nearly all patients with cerebellar ataxia fall toward the lesion side. (56) Lack of gait evaluation in patients during a bedside examination is a common cause of misdiagnosis of cerebellar infarction. (58) Patients with cerebellar infarcts (in particular large PICA infarcts) need close neurological monitoring because of the risk of developing oedema with mass effect that may result in pontine compression, acute hydrocephalus secondary to obstruction of the fourth ventricle, or both. Cerebellar infarcts may develop mass effect in 10% to 25% of all cases. (59) These patients might require neurosurgical intervention, because of the potentially fatal consequences of cerebral oedema in the posterior fossa. (60) Clinically significant cerebellar oedema usually manifests with reduced level of consciousness and occurs within 1 to 7 days from the stroke, with a mean of 3 days. (58)

Medial medullary (Dejerine) syndrome

This syndrome results from occlusion of a vertebral artery or its branch to the anterior spinal artery. It usually presents with ipsilateral paresis of the tongue with deviation toward the lesion, contralateral hemiplegia and loss of ipsilateral vibration and proprioception.

Babinski-Nageotte syndrome

Babinski–Nageotte syndrome occurs when there is damage to the dorsolateral or posterior-lateral medulla oblongata. It was first described in 1902 and later named after the neurologists who initially investigated it, Joseph Babinski and Jean Nageotte. Symptoms include ipsilateral cerebellar ataxia, sensory deficits of the face, and Horner's syndrome, along with contralateral weakness and loss of sensation. (61)

Basilar artery occlusion

Basilar artery occlusion (BAO) comprises ~1% of all strokes but is one of the most devastating neurological conditions associated with a high risk of disability and mortality (up to 80-90%), if recanalization does not occur. (23, 62, 63) The clinical syndrome associated with basilar artery occlusion is variable, depending on the location and etiology of the occlusive lesion, on the vascular anatomy and collateral flow. Traditionally, basilar artery occlusion has been divided into 3 major clinical types of presentations: (1) sudden onset of severe motor and bulbar symptoms (e.g. quadriplegia, ophthalmoplegia, and anarthria) combined with reduced consciousness- more frequent in cardioembolic stroke (e.g. distal occlusion of the basilar artery due to an embolus) (2) gradual or stuttering course of posterior circulation symptoms (e.g. visual and balance disturbances, dysarthria, paresthesiae, or motor weakness) which subsequently become disabling and reduce consciousness- usually more frequent in basilar artery occlusion stroke of atherosclerotic etiology (e.g. lesions in the proximal basilar artery or bilateral vertebral arteries); (3) transient prodromal symptoms (double vision, dysarthria, vertigo, paresthesiae), which precede the monophasic symptoms by several days or weeks, Figure 3 (63, 64)

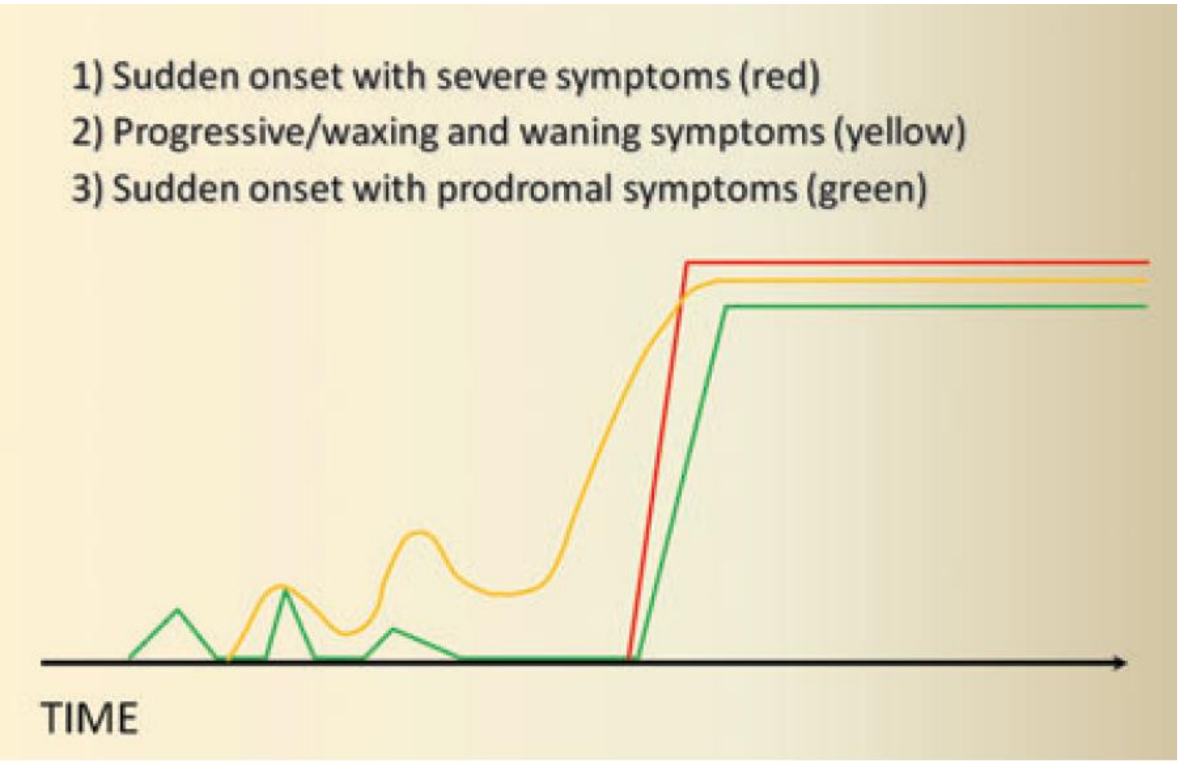

Figure 3. Basilar artery occlusion three main phenotypes. Figure from "Current treatment of basilar artery occlusion. Lindsberg PJ, Sairanen T, Strbian D, Kaste M. Ann N Y Acad Sci. 2012;1268:35-44".

In the Basilar Artery International Cooperation Study (BASICS) registry, (65) the first large prospective registry including 592 patients with basilar artery occlusion, 19% of patients had prodromal transient ischaemic attacks and 19% had prodromal minor ischaemic strokes. Vertigo, nausea and headache have been reported as the most common prodromal symptoms. (66) Other prodromal signs include: altered consciousness, diplopia, visual disturbances, facial palsy, dysarthria, dysphagia, sensory symptoms, hemiparesis, tinnitus, hypoacusis, drop attack, convulsive-like movements, "Fourire prodromique" (a rare form of pathological laughter) and peduncular hallucinosis. (67) Coma may occur with bilateral involvement of the pontine tegmentum or with lesions of the midbrain reticular formation. In the BASICS registry (65), 59% of patients had severe deficits (defined as presence of coma, tetraplegia, or in a locked-in syndrome). Of these patients, 50% died and 33% had severe disability at one month. (65) Coma at onset has been reported as a strong prognostic factor for poor outcome.

(62) In several studies, patients with distal basilar artery occlusion have been reported to have better functional outcomes than those with proximal occlusion. (62, 68, 69) This may be explained by the fact that distal basilar occlusions are more likely embolic and may have a more favourable response to thrombolysis compared to atherosclerotic thrombi in the more proximal segments of the basilar artery. (70)

Locked-in syndrome

Locked-in syndrome results from occlusion of the proximal and middle segments of the basilar artery, leading to infarction of the upper ventral pons. Bilateral ventral pontine lesions involving corticospinal and corticobulbar tracts lead to quadriplegia, anarthria and impairment of horizontal eye movement due to a lesion of bilateral CN VI nuclei, with preserved consciousness (because the tegmentum of the pons is spared), vertical eye movements and blinking. Three categories of locked-in syndrome have been described: the classic in which the patient has intact vertical eye movements, the incomplete locked-in syndrome which is similar to the classic with remnants of some voluntary motor control, and total locked-in syndrome in which the patient is fully conscious but has complete immobility including eye movements. (71)

Top-of-the-basilar syndrome

The "top of the basilar" syndrome is an occlusion of the rostral basilar artery that can cause ischemia of the midbrain, thalami, and temporal and occipital lobe hemispheral territories supplied by the posterior cerebral artery branches. In most patients, infarction in this region is caused by embolism from a more proximal source such as the heart (e.g atrial fibrillation), the aortic arch, the extracranial or intracranial vertebral arteries in the neck. In many patients, infarction is limited to the rostral brainstem. Patients with the top-of-the basilar syndrome may present with sudden changes in the level of consciousness, confusion, behavioural abnormalities, amnesia, vivid hallucinations and dreamlike behaviour. (67) Hemianopia, cortical blindness, CN III palsy, pupillary and oculomotor abnormalities (e.g. vertical gaze palsy, skew deviation, convergence-retraction nystagmus) and motor dysfunction can also be present. (67)

Internuclear ophthalmoplegia

Internuclear ophthalmoplegia (INO) is a horizontal gaze palsy, resulting from a brainstem lesion affecting the medial longitudinal fasciculus between the nuclei of CN VI and III, most commonly in the pons, due to an occlusion of the basilar artery or its paramedian branches. A patient with internuclear ophthalmoplegia shows no adduction of the ipsilateral eye and full abduction of the contralateral eye with nystagmus. Convergence is preserved. No adduction to either side with nystagmus of the abducting eye in both directions suggests bilateral internuclear ophthalmoplegia.

One-and-a-half syndrome

This syndrome is caused by a lesion affecting the paramedian pontine reticular formation and medial longitudinal fasciculus simultaneously, resulting in ipsilateral conjugate gaze palsy and internuclear ophthalmoplegia. A patient with this syndrome is unable to move the ipsilateral eye and can only abduct the contralateral eye with nystagmus. Vertical gaze and convergence generally are preserved.

Upper dorsal pontine (Raymond-Cestan) syndrome

Raymond-Cestan syndrome is due to obstruction of the long circumferential branches of the basilar artery and characterised by ipsilateral ataxia and coarse intention tremor, weakness of the muscles of mastication, sensory loss in the face and contralateral loss of all sensory modalities with or without facial weakness and hemiparesis. Horizontal gaze palsy may also occur.

Lower dorsal pontine (Foville) syndrome

Foville syndrome may result from lesions to the dorsal tegmentum of the lower pons. Ipsilateral paresis of the upper and lower face muscles, horizontal gaze palsy on the ipsilateral side, and contralateral hemiplegia can be present.

Ventral pontine (Millard-Gubler) syndrome

This syndrome occurs after paramedian infarction in the pons and results in ipsilateral CN VI palsy with diplopia, CN VII palsy, and contralateral motor weakness.

Ventral midbrain (Weber) syndrome

Weber syndrome may result from occlusion of the median and/or paramedian perforating branches of the basilar artery. Clinical findings include ipsilateral CN III palsy, ptosis, and mydriasis with contralateral hemiplegia.

Dorsal midbrain (Benedikt) syndrome

Benedikt syndrome occurs after infarction in the midbrain tegmentum from occlusion of paramedian branches of the basilar artery, the PCA, or both. The patient may present a Weber syndrome associated with contralateral involuntary movements (e.g. intention tremor, ataxia, or chorea) due to the involvement of the red nucleus.

Posterior cerebral artery occlusion

Most posterior cerebral artery occlusion (PCA) territory infarcts are due to embolism from the heart, aortic arch or vertebral arteries. Atherosclerosis and dissection of the PCAs are not common. Depending upon the location and severity of the occlusion, signs and symptoms vary. Occlusion of the proximal portion of the vessel may cause only minor deficits due to the collateral blood flow from the opposite hemisphere via the posterior communicating artery. The most common clinical finding is homonymous hemianopia, caused by a lesion in the contralateral occipital lobe. Macular or central field sparing can occur if the occipital pole remains intact through blood supply from a branch of the middle cerebral artery. Cortical blindness results from bilateral PCA infarcts. Other clinical symptoms associated with PCA infarcts may include hemisensory loss or central post-stroke pain (due to thalamic infarction), colour blindness, headache and hallucinations**.** Lesions in the more distal territories can also cause involuntary movements (chorea, intention tremor, hemiballismus), contralateral hemiplegia, Weber’s syndrome and Bálint's syndrome (oculomotor apraxia, optic ataxia, simultanagnosia). Approximately one-quarter of patients with PCA infarcts have neuropsychological symptoms. Most common are language-related disorder as aphasia, dyslexia, dyscalculia and colour dysnomia with PCA infarcts in the dominant hemisphere. Less frequent are disorders of visual cognitive functions with spatial disorientation, visual agnosia, prosopagnosia, dyschromatopsia, and palinopsia in patients with non-dominant hemisphere infarcts. Memory dysfunction is also frequently seen. (72)

Differential diagnosis

Posterior circulation strokes are misdiagnosed three times more often than anterior circulation strokes, as they frequently present with non-specific symptoms, including vertigo, disequilibrium or headache. (73) Furthermore, several conditions present with signs and symptoms that can mimic a posterior circulation stroke. The advance of neuroimaging techniques has allowed detecting ischaemic lesions in the posterior fossa with increasing accuracy (74) (see Section “Cerebral imaging in suspected acute stroke patients”). A suspected posterior circulation stroke may be confirmed using non-contrast CT brain but magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) sequences is more sensitive. However, the sensitivity of MRI in the posterior circulation is not as high as in the anterior circulation and some patients with tiny ischaemic lesions in the brainstem may have a negative DWI scan. (75) Still, in the brainstem, where efferent and afferent white matter fibers, as well as nuclei of cranial nerves, are so close to each other, these small infarcts may lead to severe symptoms and poor prognosis. Therefore, posterior circulation stroke should remain a clinical diagnosis. An acute onset should always suggest a possible vascular event. A stuttering or progressive course usually suggests other pathologies (e.g. a mass lesion in the posterior fossa) but may also be present in posterior circulation strokes (e.g. prodromal symptoms due to an atherosclerotic lesion in the proximal basilar artery) which can sometimes make the clinical diagnosis more challenging.

In patients presenting with vertigo, a peripheral vestibulopathy should be differentiated from a cerebellar or brainstem infarct. In a study of n=1666 patients presenting to the emergency department with dizziness, vertigo, or imbalance, stroke or TIA was found in only 3.2% of subjects, predominantly in older patients with two or more stroke risk factors. (76) In contrast, in n=240 patients with a clinical diagnosis of vestibular neuritis due to vertigo lasting >24 hours with a reported normal neurologic examination, cerebellar strokes were found in 10% of patients, predominantly within the PICA territory. (76) Provocative maneuvers (e.g. the head thrust and Dix–Hallpike maneuvers) can help differentiate between central and peripheral causes. The Head Impulse—Nystagmus—Skew Test (HINTS) is a useful bedside test to differentiate between peripheral vestibulopathy and posterior circulation stroke with a reported sensitivity of 100% and specificity of 96% for stroke. (77) Basilar migraine may sometimes mimic a brainstem infarct and can be differentiated due to the gradual onset and history of migraine attacks. Central pontine myelinolysis and Wernicke encephalopathy may present with brainstem symptoms. A history of rapid correction of the patient's serum sodium or possible thiamine deficiency (including alcohol intake or malnutrition states) may help in these cases. In the posterior reversible encephalopathy syndrome (PRES), 10-15% of patients develop focal deficits along with the headache and visual disturbances that can simulate a PCA infarct. (78) A history of severe hypertension, immunodepression, kidney disease or eclampsia and the presence of vasogenic oedema in the posterior territory bilaterally on imaging can assist clinicians in the differential diagnosis. Reversible cerebral vasoconstriction syndrome (RCVS) presenting with sudden onset headache and focal neurological deficits is another possible differential diagnosis of PCA infarct. (15) Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) also have a predilection for the posterior circulation. For other conditions such as a subarachnoid haemorrhage and intracranial haemorrhage in the posterior fossa, thunderclap headache and hypertension may direct clinicians towards the correct diagnosis but this can only be confirmed by neuroimaging. Other differential diagnostic conditions are non-convulsive epileptic seizures, hypoxic-ischemic encephalopathy, and different causes of coma such as hypoglycemia or other forms of metabolic coma. (63)

Cerebral imaging in suspected acute stroke patients

The acute stroke imaging protocol for patients with suspected ischaemic stroke (including posterior circulation stroke) in Australia includes non-contrast CT brain, CT perfusion and CT Angiography. This stroke protocol allows clinicians to quickly ascertain if the stroke is ischaemic or haemorrhagic, the size and the location of the stroke, possible aetiology and if the patient is a candidate for reperfusion therapies.

Non-contrast CT brain

The advent of non-contrast CT brain, invented by Nobel Prize winners Cormak and Hounsfield in 1973, revolutionized stroke care. For the first time in history, diagnosing a brain condition was possible and intracranial haemorrhage and infarction could be distinguished. This technique utilises ionising radiation coupled with a digital detector array to quantify the attenuation of X-ray projections through various tissue. CT brain is now available in all emergency departments around the world. It is the first imaging modality used to assess patients presenting with neurological deficits and provides sufficient diagnostic information to commence time-critical treatment in most eligible patients. However, CT provides suboptimal visualization of the posterior fossa structures due to the artifacts produced by bone structures such as the temporal bones. Thus, early ischemic changes may not be easily visible, particularly in the brainstem.

Ischaemic stroke- acute phase

Loss of grey-white matter differentiation (attenuation difference between normal grey and white matter due to the development of ionic oedema) is the first sign of an ischaemic infarction on CT brain. Changes in the lentiform nucleus are seen as early as 1 hour after an occlusion and are visible in 75% of patients at 3 hours. (79) Ionic oedema is followed by vasogenic oedema when the breakdown of the blood-brain barrier occurs, resulting in more established hypodensity. (80) Cortical hypodensity with associated parenchymal swelling and resultant gyral effacement is another early sign in ischaemic stroke. This is usually due to increased cerebral blood volume within the ischaemic lesion and can be potentially reversible with prompt reperfusion. Hemorrhagic transformation is part of the natural evolution of stroke. It can range from minor haemorrhagic infarction with no clinical consequences to significant parenchymal haematoma with mass effect and associated clinical deterioration, especially after reperfusion therapies.

The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point scoring system that provides a standardized topographic assessment of acute ischemic changes in the middle cerebral artery territory on non-contrast CT brain. (81) Although the interrater reliability of this score has been questioned, (82) ASPECTS score is strongly associated with 3-month functional outcomes in patients with anterior circulation strokes. (81)

Ischaemic stroke- subacute phase

As time goes on the swelling starts to subside and small amounts of cortical petechial result in reduced infarct visibility that can occur around 2-3 weeks post-infarction. This is known as the CT fogging phenomenon. (83) As the blood-brain barrier loses integrity in the days following stroke, surrounding vasogenic oedema and contrast enhancement in a subacute infarct can be observed. In these cases, the subacute infarct can mimic a tumour and MRI may be necessary to reach a definitive diagnosis.

Ischaemic stroke- chronic phase

After the initial oedema resolves, atrophy takes place and gliosis sets in, eventually appearing as a region of low density with negative mass effect. Cortical mineralization can also sometimes appear.

Hyperdense arteries

The earliest CT sign visible is the hyperdense vessel sign which is a manifestation of the thrombus or embolus within a segment of the artery and as such is immediately visible. This appears as a focal hyperdensity within the artery, asymmetrical compared to the controlateral vessel segment, likely due to red blood cell predominant clots. (84) The hyperdense vessel sign has been described in the middle cerebral artery both proximally and in the Sylvian fissure (MCA "dot" sign), the basilar artery, the carotid artery and the posterior cerebral arteries. (85-87) Although the sensitivity of the hyperdense vessel sign is low on 5mm thick non-contrast CT images, this can be significantly improved using thin slices (~1mm) which can increase the sensitivity up to 100%. (88) The presence of a hyperdense basilar artery sign (Figure 4) in the setting of acute posterior circulation stroke has been reported to have 71% sensitivity, 98% specificity, and 94% accuracy for basilar artery occlusion with a positive predictive value of 83% and negative predictive value of 95%. It is also a strong predictor of functional outcome (89) and treatment response to intravenous thrombolysis.

Figure 4. Hyperdense basilar artery in a patient with basilar artery occlusion.

Stroke mimics

Due to the subtlety of early ischemic changes, the main use of non-contrast CT in selection for thrombolysis has traditionally been to exclude differential diagnoses. Acute intracranial haemorrhage and most extra-axial bleeding (e.g. acute subdural haematoma) can usually be easily identified as areas of focal hyperdensities on non-contrast CT brain, as acute blood is markedly hyperdense compared to brain parenchyma. However, more subacute to chronic extra-axial haemorrhages may appear isodense or hypodense, becoming more difficult to detect. Focal convexal subarachnoid blood can be a pathognomonic sign of amyloid angiopathy in elderly patients presenting with transient migratory sensory symptoms. In contrast, in young patients presenting with thunderclap headache, subarachnoid haemorrhage may be suggestive of vascular malformations, cortical vein thrombosis or reversible cerebral vasoconstriction syndrome. Tumours usually appear as hypodense lesions with or without mass effect and can be easily differentiated from vascular events based on the patient's clinical features and the temporal course of symptoms.

CT Angiography

CT Angiography (CTA) is a non-invasive imaging technique that allows visualisation of the cerebral arterial filling at peak arterial phase, using a moderate dose of radiation and iodinated contrast. CTA is the non-invasive gold standard technique to determine the presence of extracranial or intracranial vessel stenosis or occlusion in patients with suspected ischaemic stroke. Ideally, it should be acquired from the aortic arch to the cerebral vertex to cover the entirety of the vasculature relevant to stroke. Many cases of arterial dissection are identifiable using CTA. Anatomical variants, alternative collateral pathways, atherosclerotic plaques and the degree of the stenosis can be characterised in 3D reconstructions of CTA.

In intracerebral haemorrhage, CTA has a critical role in screening for the presence of an underlying vessel abnormality such as an aneurysm, arterio-venous malformation or dural arterio-venous fistula. CTA results are used to guide acute and chronic therapies, including medical, surgical, and endovascular treatments.

CT Angiography source images (CTA-SI), prior to any 3D reformatting, can provide additional information for acute stroke imaging assessment. In acute ischemic stroke, hypoattenuation on CTA-SI reflects the extent of tissue hypoperfusion. On early CT scanners the CTA-SI abnormality reflected reduced cerebral blood volume and correlated with DWI abnormality (90) and the final infarct volume more accurately than non-contrast CT. However, faster modern scanners produce a cerebral blood flow-weighted CTA-SI abnormality that tends to overestimate the extent of irreversible injury.(91, 92)

CT Perfusion imaging

CT perfusion is a multiphasic acquisition technique that enables differentiation of salvageable ischemic brain tissue (the ischaemic penumbra) from the irrevocably damaged infarcted brain (the ischaemic core), by tracking a single bolus of iodinated contrast arriving in the brain and subsequently being washed out. When a vessel occlusion occurs, collateral blood flow is delayed and reduced compared to the contralateral structures and the tissue downstream to the occlusion shows delayed contrast arrival and prolonged bolus washout. The contrast in each image voxel creates a time-concentration curve that can be manipulated through a deconvolution algorithm, a complex mathematical procedure that models the concentration-time curve that would occur after an instantaneous bolus of contrast. (93) This process enables the computation of perfusion maps representing different hemodynamic properties, based on the relationship between the bolus shape in the feeding vasculature, the arterial input function, and the contrast passage observed in each voxel. (94) The perfusion parameters developed as aforementioned are: cerebral blood flow (CBF), cerebral blood volume (CBV), time-to-peak (TTP), time to peak of the deconvolved tissue residue function (Tmax) and mean transit time (MTT). Time to Peak (TTP) and Tmax represent the delay to peak concentration in the raw and deconvolved curves respectively and are increased in hypoperfused regions. They are markedly increased in regions of collateral flow due to an arterial occlusion or (more mildly) distal to a severe stenosis. Therefore, a prolonged TTP (or Tmax) may be a good indicator of the site of vessel occlusion and can direct the clinician where to look for an occlusion even in more distal arterial branches, when a consistent pattern exists. Because TTP is usually affected by extra-cerebral factors such as cardiac output and injection timing, it needs to be normalized to the normal contralateral hemisphere. The ischaemic penumbra, salvageable tissue at risk of infarction without reperfusion, is generally defined as a Tmax (or relative TTP) >6 seconds (95, 96) or delay time >3 seconds (97), depending on the processing software used. Milder prolonged Tmax or TTP can be observed in the context of partial vessel occlusions or stenoses and spontaneous reperfusion (e.g. distal clot migration). CBV is the area under the concentration-time curve for each voxel. Normal CBV differs in grey matter (~4%) versus white matter (~2%) and is reduced in an irreversibly damaged brain. CBF is proportional to the peak height of the tissue residue function. The most commonly validated parameter to estimate ischaemic core is CBF<30% of the contralateral hemisphere, which had better concordance with contemporaneously-acquired diffusion magnetic resonance imaging than CBV-based thresholds. However, inaccuracies with overestimation of ischemic core in white matter can sometimes occur. (94, 98, 99) MTT can be calculated as CBV/CBF and is prolonged in ischemic lesions. (100)

CT perfusion increases diagnostic confidence in ischaemic stroke, helps to identify patients with salvageable tissue who may benefit from reperfusion therapies, (101, 102) and can identify potential stroke mimics. (103) Although CTP diagnostic accuracy in anterior circulation stroke is well established, (104) its application remained challenging in posterior circulation stroke until recently due to limited spatial coverage and the presence of beam hardening artefact. (105) The introduction of whole-brain CTP coverage has enabled the assessment of infratentorial structures and CT Perfusion has been shown to improve diagnostic sensitivity compared to non-contrast CT. (106) In recent studies, a protocol including non-contrast CT, CT Angiography source images (CTA-SI) and CT Perfusion predicted a posterior circulation infarct with higher accuracy than non-contrast CT or combined non-contrast CT and CTA-SI. (107, 108) However, although CT Perfusion sensitivity for ischaemic lesions is high in the cerebellum, it is low in the brainstem. (76, 105) Importantly, CT perfusion must be interpreted alongside the non-contrast CT-brain, as this may assist distinguishing real CT perfusion abnormalities from artefacts, particularly in the brainstem. Moreover, in some cases such as distal clot migration or spontaneous recanalization, an improvement in collateral circulation can affect perfusion maps and a subacute infarction may not be detected as ischemic core.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a technique that uses a powerful magnetic field to provide high-resolution images, without the use of ionizing radiation or radioactive tracers. In Australia, MRI is not routinely used in the acute stroke imaging protocol due to its limitations in a time-critical setting, such as difficulties performing rapid safety screening for possible contraindications (e.g. presence of metallic foreign bodies, non-MRI compatible pacemaker) and the fact that MRI is more time-consuming due to its longer acquisition times. This may constitute an even bigger issue in potentially unstable or agitated patients. Furthermore, movement artefacts can more easily affect the quality of MRI images in comparison with CT perfusion. However, MRI provides better visualization of the soft tissue structures (49) and can detect early evidence of infarction with DWI sequences with high accuracy, especially in the posterior fossa.

Diffusion MRI

Diffusion weighted imaging (DWI) measures the net movement of molecules of water in random Brownian motion, usually restricted by cell structures. The average diffusivity, which can be detected by measuring diffusion in different vectors, is reduced in acute ischemic stroke due to the cytotoxic oedema with extracellular to intracellular shift of water. DWI, currently the most sensitive modality for ischemic injury, shows hyperintense (high signal intensity) ischemic tissue changes within minutes after arterial occlusion, (109) which can remain up to a few weeks after the stroke. (110) Apparent diffusion coefficient maps (ADC) represent the quantitative diffusion values of the tissue without T2 effects. ADC maps appear hypo-intense (low signal) within minutes of the occlusion, with pseudo-normalisation after 5-10 days (111) due to increasing vasogenic oedema. In a phenomenon called T2 shine-through, some tissues that are bright on T2 will appear bright on DWI images without having abnormal restricted diffusion because the DWI image has T2-weighting. However, they will have increased ADC. Although lesions are less conspicuous on ADC than the B1000 diffusion image, when a lesion appears bright on DWI it is important to check whether the ADC is reduced in the corresponding region. This may become difficult to determine in very small lesions such as in the brainstem. A small but significant percentage of patients with ischaemic stroke may have a negative DWI scan. DWI-negative ischaemic strokes are reported in up to 7% of stroke patients. Patients with posterior circulation ischemia are 5 times more likely than patients with anterior circulation ischemia to present with a negative DWI scan (75, 112), in particular for brainstem lesions. Image quality is limited in the brainstem due to susceptibility artifacts caused by the proximity to the skull base and the mastoid. The signal of small infarcts may be blurred by the low spatial resolution of the conventional DWI. The detection rate and accuracy for ischaemic lesions in the posterior fossa, particularly the brainstem, can be improved by high-resolution imaging with thinner sections and combined axial and coronal DWI sequences. (74, 113)

T2 FLAIR MRI

T2 fluid-attenuated inversion recovery (FLAIR) is an MRI technique that shows areas of tissue T2 prolongation as bright while suppressing (darkening) the cerebrospinal fluid signal (CSF). The FLAIR sequence is part of almost all protocols for imaging the brain and it is particularly useful in detecting subtle changes or ischaemic lesions (e.g. lacunar infarcts) in the periventricular region close to CSF. The ischaemic lesions appear on FLAIR with a different timing compared to DWI. Whilst it takes minutes for the cytotoxic oedema to develop causing a net decrease in water diffusion as visualized by an increased signal on DWI, hours are needed for the vasogenic oedema to gradually appear and cause a visible hyperintensity on FLAIR imaging. However, in contrast to DWI lesions, FLAIR abnormalities remain visible for an extended time with progressive evolution in gliosis and atrophy. Interestingly, the development of a FLAIR lesion is less dependent on time from symptom onset in patients with good collaterals as compared with those with poor collaterals. (114) Therefore, a mismatch between DWI and FLAIR may be suggestive of an acute infarct occurred within a few hours from stroke onset or good collateral pathways that have prevented the ischaemic lesion to progress. Due to technical factors such as CSF motion, FLAIR may be less accurate in the posterior fossa. (115)

Magnetic resonance perfusion

Magnetic resonance perfusion involves administering gadolinium contrast to obtain perfusion maps. The thresholds used for estimated ischaemic penumbra are similar to CT-perfusion, in particular for the time-to-maximum parameter. (94)

Susceptibility-weighted imaging

MRI offers several techniques that are sensitive to blood products. These sequences exploit what is referred to as T2* which is highly sensitive to small perturbations in the local magnetic field. The most sensitive of these sequences is the susceptibility-weighted imaging (SWI), a sequence useful in detecting blood products and distinguishing calcium from blood. The blood products appear hypointense, due to the susceptibility artifact induced by iron in the hemoglobin. In ischaemic stroke, the most common use of SWI is for the identification of small amounts of haemorrhage/blood products within an area of infarction. Intravascular thrombus is also hypointense, analogous to the CT hyperdense artery sign.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is an alternative to CT angiography to visualise the cerebral vascular anatomy, eliminating the need for ionizing radiation and iodinated contrast media. Contrast-enhanced MR angiography is a technique involving 3D spoiled gradient-echo sequences, with administration of gadolinium-based contrast agents. However, this is contraindicated in patients with allergy to gadolinium contrast or poor renal function. In contrast, time-of-flight (TOF) MRA is an MRI technique to visualize flow within vessels, without the need to administer contrast. It is based on the phenomenon of flow-related enhancement of spins entering into an imaging slice. TOF sequences can achieve high resolution but tend to overestimate the degree of stenosis due to flow-related signal drop-out in low-flow conditions (e.g. trickle flow states, tortuous vessels, flow from a vessel parallel to the scan plane).

Cerebral catheter angiography

Cerebral catheter angiography is a dynamic imaging technique that provides high-resolution and three-dimensional visualisation of the cerebral vasculature and allows real-time analysis of the blood flow. (116) A catheter is inserted through a minimally invasive vascular access, followed by injection of the iodinated contrast under fluoroscopic guidance. Typically the transfemoral route is used, although radial or brachial artery catheterisation may also be performed. (117) Digital subtraction techniques (subtracting a pre-contrast baseline image) are then used to obtain images of the cerebral vascular anatomy. The dynamic acquisition allows assessment of the collateral circulation (which is not possible with standard CTA or MR Angiography but can be derived from perfusion acquisitions). However, this requires a three-vessel cerebral arteriogram (both common carotid arteries and a vertebral artery). Furthermore, catheter angiography provides precise luminal characterization, visualisation of vessels of small calibre, and may help with identification of pseudo-occlusion (apparent occlusion of the proximal end of a vessel on CT or MR Angiography due to a stagnant column of unopacified blood caused by a distal obstruction) or intravascular dissection. Despite all these advantages, cerebral angiography has a minimal (<1%) but real risk of peri-procedural stroke. Additionally, highly specialised equipment and team are required. Given all these reasons and the increasingly accuracy for detection of major vessel pathologies of CTA and MRA, catheter angiography is mostly reserved for acute stroke patients who are intended to undergo endovascular therapy or cases of vascular abnormality where the diagnosis remains unclear after non-invasive imaging.

Recently, a new direct transfer to angiography-suite protocol has been proposed as a promising measure to improve onset to recanalization time in patients who undergo endovascular treatment. This approach is based on ruling out an intracranial haemorrhage or a large established infarct using a cone-beam CT, bypassing conventional multimodal imaging. Preliminary data (including a small percentage of patients with posterior circulation stroke) would suggest that this approach may be a feasible and safe strategy in patients who undergo endovascular treatment, within 3 hours from symptoms onset, (118) but further evidence is warranted. Randomized controlled trials are ongoing (ANGIOCAT, Clinicaltrials.gov registration: NCT04001738; DIRECTANGIO, Clinicaltrials.gov registration: NCT03969511).

Imaging prognostic factors of outcome in patients with basilar artery occlusion

Posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS)

Similarly to the ASPECTS score for anterior circulation strokes, Puetz et al. (119) have developed a posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS) to predict functional outcome in patients with basilar artery occlusion. The pc-ASPECTS is a 10-point scoring system, based on hypoattenuation on non-contrast CT brain or CTA-SI. Beginning with 10 points for a normal CT scan, regional abnormalities were scored and one point subtracted for involvement of each of the left or right thalamus, cerebellum or posterior cerebral artery territory, and two points subtracted for involvement of each of the midbrain or pons. This scoring system has been built on the concept that infarction size in the posterior fossa may not correlate well with stroke severity, whereas stroke location can be more critical for prognostication, due to the proximity of vital tracts and nuclei. (120) In a retrospective cohort of 130 patients with suspected vertebrobasilar artery occlusion, the sensitivity of pc-ASPECTS for early ischemic changes was higher when calculated on CTA-SI compared to non-contrast CT brain [65% (95% CI, 0.57-0.73) versus 46% (95% CI 0.37-0.55), respectively]. pc-ASPECTS on CTASI but not non-contrast CT brain was associated with functional independence (modified Rankin scale 0-2, odds ratio 1.58; p=0.005 versus odds ratio 1.22; p=0.42, respectively). Among n=46 patients with basilar artery occlusion, patients with a pc-ASPECTS score of 8–10 were more likely to have a favourable outcome (modified Rankin Scale 0-3, risk ratio 12.1; 95% CI 1.7–84.9) compared to those with a pc-ASPECTS 0–7. Furthermore, a pc-ASPECTS ≤7 was an independent prognostic factor of mortality (risk ratio 0.4; 95% CI 0.2–0.9). This result was confirmed in a small subgroup of patients (n=21 patients) who achieved angiographic recanalization (risk ratio 7.7; 95% CI 1.1-52.1). (119)

The pc-ASPECTS on CTA source images was also evaluated in the BASICS registry. (121) A CTA-SI pc-ASPECTS ≥8 was associated with reduced mortality (risk ratio 0.7; 95% CI 0.5–0.98) and functional independence (risk ratio, 2.0; 95% CI 1.1–3.8). (122)

Therefore, CTA-SI pc-ASPECTS may help to identify patients with basilar artery occlusion who are unlikely to benefit from reperfusion therapies. However, CTA-SI pc-ASPECTS does not discriminate between the ischemic core and penumbra and it has not been routinely adopted in treatment decision-making. In a study from the BASICS group, Pallesen et al. (123) explored the prognostic value of pc-ASPECTS on CT Perfusion but were limited by the small sample size (n=27) and incomplete CT Perfusion coverage, with the pons being imaged in only 19% of patients. Despite this, they found that an extensive lesion on CBV maps (pc-ASPECTS < 8) was associated with high case fatality (3/3 patients with CBV pc-ASPECTS< 8 died at 1 month compared to 6/23 patients with a CBV pc-ASPECTS ≥ 8; risk ratio 3.8; 95% CI, 1.9-7.6). (123)

The pc-ASPECTS has also been applied to diffusion-weighted imaging. In a retrospective study of n=132 patients with posterior circulation stroke, Tei et al. found that the diffusion-weighted imaging pc-ASPECTS was independently associated with favourable functional outcomes (modified Rankin Scale 0-3, odds ratio 0.40; 95% CI 0.23–0.67). (124) In another retrospective study of n=50 patients with acute basilar artery occlusion, diffusion-weighted imaging pc-ASPECTS≥8 was independently associated with favourable outcome (odds ratio 3.9; 95% CI 1.4–11.7). (125)

<u>Pons–Midbrain Index</u>

Schaefer and colleagues (126) developed a CTA-SI score, the pons-midbrain index. In an analysis of n=16 patients with vertebrobasilar occlusion treated with intra-arterial thrombolysis, baseline CTA-SI hypoattenuation in the pons and midbrain was graded as 0=no hypoattenuation, 1= <50% hypoattenuation, and 2=>50% hypoattenuation. A score of 0 implies no hypoattenuation in the brainstem and a score of 8 implies >50% hypoattenuation bilaterally in the pons and midbrain. Pons-midbrain index was independently associated with 3-month functional outcome (cumulative r=0.81, p<0.001) and mortality (p=0.004). (126)

Vascular scores

Posterior circulation collateral flow has been evaluated as imaging prognostic factor of functional outcome in basilar artery occlusion, predominantly on CT Angiography and catheter angiography.

Posterior Circulation Collateral Score (PC-CS)

The Posterior Circulation Collateral score (127) is a 10-point CTA scoring system that allocates collaterals a maximum of 10 points; 1 point for each patent posterior inferior cerebellar artery, anterior inferior cerebellar artery, and superior cerebellar artery, 1 point for each patent posterior communicating artery smaller than the ipsilateral P1 segment of the posterior cerebral artery, and 2 points for each posterior communicating artery with a calibre equal or larger than the ipsilateral P1 segment. The PC-CS was categorized into poor (0–3), intermediate (4–5), and good (6–10) collateral scores. Patients with a poor PC-CS were more likely to have poor outcomes at 1 month (modified Rankin scale score 4-6, risk ratio 0.74; 95% CI 0.58–0.96). Furthermore, the presence of at least 1 patent posterior communicating artery was associated with a lower risk (risk ratio 0.79; 95% CI 0.66–0.95) of poor outcome, as well as the presence of a posterior communicating artery with a calibre larger than the ipsilateral P1 segment (risk ratio 0.76; 95% CI 0.61–0.96).

Posterior Circulation Computed Tomography Angiography (pc-CTA) Vascular Score

The Posterior Circulation Computed Tomography Angiography (pc-CTA) score is a 6-point scoring system which allocates 1 point for each occluded segment of the vertebrobasilar system (the proximal, middle and distal segment of the basilar artery and the two posterior cerebral arteries). In a retrospective analysis of n=15 patients with vertebrobasilar stroke, patients with good outcome had a lower pc-CTA (median 2, IQR 1-2 versus median 3 IQR 3-4 p= 0.02). The authors described an excellent interobserver agreement for this score, although no specific kappa statistic or intraclass coefficient was reported.

Basilar Artery on Computed Tomography Angiography (BATMAN) Score

In 2017, our group developed and published a novel vascular score for basilar artery occlusion, the Basilar Artery on Computed Tomography Angiography (BATMAN). (128) This 10-point CTA scoring system evaluates both the extent of the occlusive thrombus in the vertebrobasilar system and the presence of collateral flow through the posterior communicating arteries. We allocated 1 point for each segment of the vertebrobasilar system, including the vertebral arteries (considered as 1 segment), each posterior cerebral artery (considered separately), and the 3 segments (proximal, middle and distal) of the basilar artery. We allocated 2 points for each posterior communicating artery and 1 point for a hypoplastic posterior communicating artery (defined as smaller than 1 mm), if in continuity with the top of the basilar artery via a P1 PCA segment, or 3 points for each fetal posterior communicating artery (to incorporate the point otherwise attributed to a patent P1 segment). Therefore, a score of 10 suggests normal arterial filling of the vertebrobasilar system with no occlusion and a score of 0 suggests no filling of the vertebrobasilar system. In n=83 patients in the derivation cohort and n=41 patients in the validation cohort, multivariable analyses showed that BATMAN score of <7 was significantly associated with poor outcome in the derivation cohort (modified Rankin Scale 4-6, odds ratio 5.5; 95% CI, 1.4–21; p=0.01), in the validation cohort (odds ratio 6.9; 95% CI, 1.4–33; p=0.01). These results were confirmed in a sensitivity analysis of n=73 endovascular patients (odds ratio, 4.8; 95% CI, 1.2–18; p=0.01). Interrater agreement was substantial (intraclass coefficient correlation, 0.85; 95% CI, 0.8–0.9). The BATMAN score has subsequently been externally validated in basilar artery occlusion patients treated with endovascular thrombectomy (129) and appears to have good prognostic accuracy and substantial reliability when evaluated on catheter angiography. (130)

The American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR)

In the ENDOSTROKE study, Singer at al. (131) evaluated the collateral status in patients with basilar artery occlusion treated with endovascular therapy on catheter angiography images. They used the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral grading system, although this score is more frequently used in anterior circulation stroke. This scoring system grades 0 for no collaterals visible at the ischemic site; 1 for slow collaterals to the periphery of the ischemic site with persistence of some of the defect; 2 for rapid collaterals to the periphery of the ischemic site with persistence of some of the defect, and to only a portion of the ischemic territory; 3 for collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase; and 4 for complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion. (132) In the ENDOSTROKE study, collateral scores were categorized into ASITN/SIR grades 0–1, 2, and 3–4. Among n=124 patients evaluated, 20% had poor collaterals (grades 0–1), 47% had moderate collaterals (grade 2), and 33% had good collaterals (grades 3–4) prior to endovascular therapy. In multivariable analysis, collateral status was significantly associated with successful recanalization (odds ratio 3.09, 95% CI 1.51–6.31 p=0.002) and good outcomes (modified Rankin scale 0-2, odds ratio 2.1, 95% CI 1.11–4.06, p=0.02). (131)

Clinical measurements in stroke

National Institutes of Health Stroke Scale

The National Institutes of Health Stroke Scale (NIHSS) is a non-linear scale widely-used to assess neurologic deficits in acute stroke patients, (133) (Table 1). The first version of the scale, a 15-item scale, was published in 1989 (134) and used to assess neurological deficits in the pilot study of the first positive clinical trial of intravenous alteplase (the NINDS trial). (133) Since then, the NIHSS has become an indispensable tool in clinical practice, treatment-decision-making and stroke research, and is strongly associated with outcomes after stroke in all stroke patients, including those with basilar artery occlusion. (135) The current version of the NIHSS ranges from 0 (no deficits) to 42 (death) and contains 13 sub-items, each scoring from 0 (normal) to a maximum of 4 (most severe) points.

A mild stroke is traditionally defined as a score of <5, following the licensing guidelines for intravenous alteplase, (136) while a severe stroke can be defined as 15-25 and very severe as >25. (137) However, of the elements present on the current scale, motor function and cortical signs (especially language) receive the highest priority. Symptoms such as limb ataxia and cranial nerve palsies receive fewer points and other posterior circulation findings such as truncal ataxia, eye movement abnormalities (nystagmus, internuclear ophthalmoplegia and vertical gaze palsy) and bulbar symptoms (palatal paralysis and tongue deviation) are not measured. The NIHSS cut-off for favourable outcomes is lower in patients with posterior circulation stroke compared to patients with anterior circulation stroke, suggesting that the NIHSS may underestimate clinical severity in posterior circulation stroke. (138) Previous studies have reported that more than 75% of patients with posterior circulation stroke present with a baseline NIHSS 0-5. (138, 139)

To date, there is no validated alternative scale to the NIHSS for posterior circulation stroke patients. The Israeli Vertebrobasilar Stroke Scale (IVBSS) is a 44-point scoring system developed in a cohort of n=43 patients with vertebrobasilar stroke. The 11 items (including dysphagia and gait ataxia) contained in the score were chosen using an arbitrary weighting system based on clinical experience. (140) Excellent reliability (kappa > 0.75) between examiners was demonstrated. The IVBSS score was strongly associated with the concurrent NIHSS and modified Rankin scale ($r = 0.80$ and 0.76, respectively; $p < 0.0002$). (140) More recently, Olivato et al. (141) developed an extended version of the NIHSS (the expanded NIHSS, e-NIHSS) in 22 patients with posterior circulation stroke and 25 with anterior circulation stroke to improve the NIHSS diagnostic accuracy in posterior circulation stroke. This scale included additional items such as trunk ataxia, nystagmus, Horner's syndrome, IX and XII cranial nerve deficits, which were weighted using an arbitrary scoring system. They found that patients with posterior circulation stroke evaluated with e-NIHSS had an average of 2 points higher than patients evaluated with the NIHSS ($p <0.05$). (141)

Both the e-NIHSS and the IVBSS score were developed in small cohorts, used arbitrary scoring systems, and did not demonstrate higher prognostic or diagnostic accuracy in comparison with the NIHSS.

Table 1. National Institutes of Health Stroke Scale.

Sub-item	**Description**
1a. Level of Consciousness	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best Gaze	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial Palsy	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor Arm	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement.

6. Motor Leg	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement.
7. Limb Ataxia	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs.
8. Sensory	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9. Best Language	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.

11. Extinction and Inattention	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Modified Rankin Scale score

The modified Rankin Scale (mRS) is a 7-point scale ranging from 0 (no residual evidence of stroke) to 6 (death) to measure functional outcome in patients after stroke. (Table 2) It was first described as a measure of the prognosis of stroke patients. (142) The current scale measures disability by assessing post-stroke deficits, limitations in the activities of daily living and the need for supervision, assistance or nursing care. In clinical practice, the scale is used to assess post-stroke disability (usually at 3 months), but also to measure the level of function of patients prior to the stroke, although several limitations of its use in this setting exist. (143)

In most clinical trials in ischaemic stroke, the 3-month modified Rankin Scale is used as an outcome measure. Outcomes may be analysed either through ordinal analysis of shifts in distribution of all grades of the modified Rankin Scale, or as a dichotomised measure. Excellent functional outcome (no disability) is defined as mRS 0-1 at 3 months and good functional outcome (return to independence) as mRS 0-2 at 3 months. Given the dismal prognosis of basilar artery occlusion, mRS 0-3 (moderate disability) has been accepted and used as a favourable outcome in the BASICS registry (65) and several subsequent studies. (127, 128)

Table 2. Modified Rankin Scale score.

Grade	Description	Key differentiator to previous grade
0	No symptoms at all	
1	No significant disability despite symptoms; able to carry out all usual duties and activities	Presence of residual deficits
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	Inability to carry out all pre-morbid activities
3	Moderate disability; requiring some help, but able to walk without assistance	Unable to be left at home alone for two weeks
4	Moderately severe disability; unable to walk and attend to bodily needs without assistance	Unable to walk unassisted
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention	Requires constant care
6	Dead	

Reperfusion and recanalization scales for vessel occlusion status

The modified Treatment in Cerebral Ischemia (mTICI) and the Arterial Occlusive Lesion (AOL) scales are recommended as the standard assessments of reperfusion and recanalization respectively in the angiographic evaluation of anterior circulation stroke. The modified TICI scale grades the severity of vessel occlusion from 0 (no perfusion) to 3 (complete reperfusion), Figure 5. A modification with the introduction of a "grade 2c" ("near complete perfusion except for slow flow or distal emboli in a few distal cortical vessels") has been recently suggested for anterior circulation strokes with the expanded TICI (e-TICI) scale. (144) Although mTICI has never been formally validated in the posterior circulation, it is used routinely to assess reperfusion status after endovascular therapy in basilar artery occlusion in both clinical practice and stroke research. (131)

The AOL score is a recanalization score that grades the severity of vessel occlusion from 0 (no recanalization of the arterial occlusion) to 3 (complete recanalization with any distal flow), Figure 3. In a small study of n=49 patients with basilar artery occlusion, Jung et al. showed that inter- and intraobserver agreement for the Arterial Occlusive Lesion scale was reliable, while the modified Treatment in Cerebral Ischemia failed to achieve substantial interobserver agreement. (145) Despite this, mTICI remains the revascularization scale mostly used to assess reperfusion status after endovascular therapy in basilar artery occlusion patients, both in clinical practice and stroke research.

Figure 5. Modified Treatment in Cerebral Ischemia (mTICI) and the Arterial Occlusive Lesion (AOL) scales.

	mTICI	AOL
0	No perfusion	Complete occlusion of the target artery
1	Antegrade reperfusion past the initial occlusion but limited distal branch filling with little or slow distal reperfusion	Incomplete or partial local recanalization at the target artery with no distal flow
2		Incomplete or partial local recanalization at the target artery with any distal flow
2a	Antegrade reperfusion of less than half of the previously occluded target artery ischemic territory	
2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory	
3	Complete antegrade reperfusion of the previously occluded target artery territory, with absence of visualized occlusion in all distal branches	Complete recanalization and restoration of the target artery with any distal flow

Radiological classification of haemorrhagic transformation

The European Co-operative Acute Stroke Study (ECASS) radiological classification categorizes haemorrhagic transformation as haemorrhagic infarction (HI) or parenchymal haematoma (PH). (146) Haemorrhagic infarction describes petechial haemorrhage within the infarct and can be scattered (HI1) or confluent (HI2). PH describes blood clot with mass effect and can be categorized into PH1 (occupying <30% of the infarcted territory) and PH2 (occupying >30% of the infarcted territory with substantial mass effect). These radiological classifications were subsequently incorporated in the Heidelberg bleeding classification with addition of PH remote to the ischemic lesion, subarachnoid, subdural and intraventricular haemorrhage. (147)

Definition of symptomatic intracerebral haemorrhage (SICH)

Early definitions of symptomatic haemorrhage (e.g. as used in the NINDS trial**)** (148) included any type of bleeding with any degree of neurological deterioration. The Safe Implementation of Thrombolysis - Monitoring Study (SITS-MOST) definition (149) aims to reduce false attribution of neurological deterioration to minor hemorrhagic transformation. It combines a radiological criterion of ECASS PH2 (defined above) combined with a clinical criterion of ≥4 point increase in NIHSS from baseline, or the lowest subsequently recorded score, within <36 hours from treatment. The Heidelberg bleeding classification (147) subclassifies SICH as definite (if any intracranial haemorrhage is the dominant brain pathology on imaging causal for deterioration), probable (in the presence of PH2, even if the ischemic infarct may have contributed to deterioration) and possible (in the presence of HI2, PH1, PH remote to the ischemic lesion, subarachnoid, subdural and intraventricular haemorrhage, even if the ischemic infarct may have contributed predominantly to the deterioration). The clinical criterion requires ≥4 point increase in NIHSS from baseline, or ≥2 point in one NIHSS category, or need for major medical or surgical intervention.

Interventions in stroke

Stroke care

Stroke unit care involves treatment provided by a specialised multidisciplinary team consisting of stroke physicians /neurologists, nursing and allied health staff in an organised geographically defined unit. In a meta-analysis of 20 trials (n=4127) (150), stroke unit care decreased both mortality and poor outcome through prevention and management of post-stroke complications, and these benefits are durable in long-term follow-up. (151) Post-stroke complications include venous thromboembolic prophylaxis and pressure ulcer prevention due to immobility, management of dysphagia, hyperglycemia, prevention and treatment of infection and prevention of recurrent stroke. (152, 153) For every 100 patients receiving stroke unit care, there were two extra survivors, six more living at home, and six more living independently. Stroke unit care benefitted the full spectrum of patients regardless of age, stroke severity and stroke type. (150)

Intravenous thrombolysis

Intravenous thrombolysis for acute ischemic stroke aims to restore cerebral blood flow by dissolving blood clots in the blocked artery. Recombinant tissue plasminogen activator (tPA) is a serin-protease that catalyzes the conversion of plasminogen to plasmin which breaks the crosslinks between fibrin molecules to destabilise the structural integrity of blood clots. It has been now 25 years since the publication of the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial (148), the first large positive clinical trial of recombinant tissue plasminogen activator (tPA or alteplase). Several randomized trials (including the ECASS I, II, III and ATLANTIS part A and B trials) were subsequently conducted to compare alteplase and placebo in 0 to 6 hours (149, 154-157) from stroke symptom onset. Individual patient meta-analysis emphasized the generalized efficacy of tPA in the 0- to 4.5-hour time window, regardless of baseline stroke severity or age, but all confirming a striking relationship with treatment time, with the greatest benefit seen within 90 min from symptom onset. (158, 159) A meta-analysis of all alteplase trials, (160) concluded that treatment within three hours was most beneficial (odds ratio 0.65, 95% CI 0.54 to 0.80, p<0.0001; 6 trials, 1779 participants) but that the odds of a favourable 3-month outcome were still significantly increased in the 3-4.5 hour time window (odds ratio 1.4 [95% CI 1.1-1.9]). Subsequently the ECASS III trial in patients aged 18-80 years demonstrated the benefit of 0.9 mg/kg alteplase between 3 and 4.5 hours after symptom onset using only non-contrast CT brain to exclude patients with haemorrhage or oedema. As a result, many countries have amended the license for stroke treatment with rtPA up to 4.5 hours, (161) which is the current recommended time window for alteplase in unselected stroke patients, although this remains off-label in the USA.

The IST-3 trial enrolled n=3035 patients (n=1515 in the tPA group and n=1520 in the control group) treated within 4.5 hours of symptom onset, of whom n=1617 (53%) were older than 80 years of age. (162) This study showed a shift towards improved functional outcomes at 6 months on ordinal shift analysis of the Oxford Handicap Score (a variant of the Modified Rankin scale (163), common odds ratio 1.27, 95% CI 1.10–1.47; p=0.001) in favour of the tPA arm, although there was an increased risk of symptomatic intracranial haemorrhage within 7 days (adjusted odds ratio 6.94, 95% CI 4.07–11.8). The treatment effect in patients older than 80 years of age was at least as large as in patients younger than 80 years of age. (162) Meta-analysis of all available randomized data, including the IST-3 trial (162), and large observational registries (164, 165) indicated that patients aged over or under 80 years benefited equally, particularly if treated within three hours of onset. (166)

The rates of early recanalization with alteplase in patients with large vessel occlusion is low, being 6% to 9% for terminal internal carotid occlusions, 30% to 35% for proximal middle cerebral artery occlusion and 44% for distal middle cerebral artery occlusion and only ~4% for basilar artery occlusion. (167, 168)

The main complication of intravenous thrombolysis with alteplase is symptomatic intracranial haemorrhage, which is associated with a high risk of death and disability. In the largest meta-analysis of tPA trials, symptomatic intracranial haemorrhage within 7 days of stroke was increased in the treatment compared to the placebo group (7.7% versus 1.8%, odds ratio 3.72, 95% CI 2.98–4.64; p<0.0001) and accounted for most of the deaths within a week. (95) However, the definition of symptomatic haemorrhage used in the first trials included any clinical deterioration associated with any amount of intracerebral bleeding. In contrast, the SITS definition used in the ECASS-III trial (161) and SITS-ISTR registry (169) requires a significant neurological deterioration (≥4 point increase in NIHSS) combined with a large parenchymal hematoma (PH2 – blood clot occupying >30% of the infarcted area with substantial mass effect). Using this refined definition of symptomatic haemorrhage, both the ECASS-III trial and the real-world SITS-ISTR registry have reported symptomatic haemorrhage rates of around 2%.

A meta-analysis of randomized trials has confirmed the powerful efficacy of tPA in reducing disability with a number needed to treat (NNT) of 4.5, 9 or 14 within 90, 180 and 270mins respectively. (170) A pooled analysis of nine alteplase trials (n=6756) reported an overall odds ratio of achieving independence at 3 months (modified Rankin scale 0-1) of 1.75 (95% CI 1.35-2.27) for administration <3 hours, 1.26 (95% CI 1.05-1.51) for administration in 3-4.5 hours and 1.15 (95% CI 0.95-1.40) for administration >4.5 hours, with a strong linear trend between earlier treatment and improved outcomes even in the 0-3 hours. (159) In particular, the first hour (the “golden hour”) following the onset of symptoms appears important, with treatment ≤60 minutes associated with improved freedom from disability.

(171) There appears to be no clear benefit of earlier treatment on symptomatic haemorrhagic transformation in meta-analyses of the alteplase trials. (166, 170)

Dosing

Alteplase is administered at a dose of 0.9mg/kg (10% bolus and 90% infusion) in most countries, as it was used in the positive NINDS trial. However, given concerns of increased haemorrhagic transformation in Asian patients, Japan licensed 0.6mg/kg and this dose is sometimes used in other Asian countries, particularly when patients are required to directly pay for alteplase. A recent large trial compared alteplase 0.6mg/kg to 0.9mg/kg in n=3310 patients, of whom 63% were Asian. (172) The trial did not achieve the primary endpoint of non-inferiority for death or disability (modified Rankin score 2-6, 53.2% versus 51.1%, non-inferiority p=0.51), but reported non-inferiority if that same margin was applied to the modified Rankin Scale ordinal analysis (p=0.04). Symptomatic haemorrhage was reduced in the low-dose arm (1.0% vs 2.1%, p=0.01). (172) Although some parts of Asia routinely use the lower 0.6mg/kg dosing, this trial has not led to changes in alteplase dosing in most countries.

<u>Intravenous thrombolysis in posterior circulation stroke</u>

Patients with posterior circulation stroke were under-represented in most of the positive clinical trials of alteplase. Despite accounting for 20% of all strokes, (14) only 5% of patients from the NINDS study had a posterior circulation stroke, (148) the European Cooperative Acute Stroke Study (ECASS) I and II trials included only patients with anterior circulation stroke, (154, 155) and the ATLANTIS (156, 157) and ECASS III trials did not report on the number of patients with posterior circulation stroke. (161) These trials have largely included anterior circulation stroke patients because posterior circulation stroke patients are relatively rare. Moreover, these trials had strict selection criteria (in some cases the intention was to increase the likelihood of a positive trial rather than individual risk-benefit analysis) and excluded patients with mild or fluctuating symptoms which can occur in patients with posterior circulation stroke. However, several observational studies have demonstrated a comparable efficacy and safety profile in patients with anterior and posterior circulation stroke treated with alteplase, (173, 174) with few studies suggesting a lower risk of haemorrhagic complications in posterior circulation stroke. (175) In a recent meta-analysis including 21 studies (n=10.175 patients with anterior circulation stroke and n=1.393 patients with posterior circulation stroke treated with alteplase), posterior circulation stroke was associated with a broader time-window for intravenous thrombolytics, milder stroke symptoms at onset, and greater delay from onset to treatment. (176). In this study, good functional outcomes were significantly associated with posterior circulation stroke (modified Rankin Scale 0–2, odds ratio 1.36, 95% CI 1.08–1.71), although few patients with basilar artery occlusion were included. Symptomatic intracerebral haemorrhages were significantly less frequent in posterior circulation strokes than in anterior circulation strokes (odds ratio 0.32, 95% CI 0.21–0.49). (176) Several other studies suggested that the risk of hemorrhagic transformation in posterior circulation stroke is lower than in anterior circulation stroke. (175, 177) A recent meta-analysis, including patients from the SITS-ISTR registry, reported a relative risk for symptomatic haemorrhage in posterior circulation stroke versus anterior circulation stroke of 0.49 (95% CI, 0.32–0.75). (178) The lower risk of hemorrhagic transformation in posterior circulation stroke may be explained by a stronger tolerance to the ischemic insult in the posterior circulation territory, likely due to its greater white matter structure and collateral pathways, particularly in the brainstem. (179) This may slow the progression to irreversible ischemia and make the infarction less prone to haemorrhagic complications after reperfusion therapies. Furthermore, because the volume of the infarct lesion predicts the risk of haemorrhagic complications after intravenous thrombolysis, the lower infarct volume in posterior circulation stroke compared to anterior circulation stroke may result in lower bleeding risk in posterior circulation stroke patients. (180) The risk of symptomatic intracerebral haemorrhage appears to remain lower in comparison with anterior circulation stroke across different definitions (NINDS, ECASS II and SITS-MOST). (177) The rate of patients with posterior circulation stroke treated with intravenous thrombolysis has been reported to range from 12 to 19% in clinical practice. (175, 181) Although underrepresented in the first pivotal randomized controlled trials, there has been an increase in the rate of treatment with intravenous thrombolysis among these patients in the recent years. (182)

Intravenous thrombolysis in basilar artery occlusion

Clinical outcomes in basilar artery occlusion improve if recanalization is achieved. The BASICS registry reported that 96.3% of patients who did not receive any treatment died within 1 month. (65) Despite its proven efficacy in ischemic stroke more generally, alteplase only achieves rapid reperfusion in ~4% of basilar artery occlusion patients. (167) Previous studies indicate that the success of recanalization after alteplase in basilar artery occlusion depends on clot length and location, with odds ratio of unsuccessful recanalization significantly increased by 1.06 (95% CI 1.01–1.12) for each 1 mm of thrombus length. (183) Sairanen et al. (173) demonstrated that the highest frequency for recanalization was found in a small group of patients with top-of-the basilar occlusion, where 87% of patients achieved successful recanalization. Recanalization was thus associated with clot location at the top of the basilar (odds ratio 4.8, 95% CI 1.1–22; p= 0.048) (173), consistent with previous evidence. (184) In top-of-the -basilar occlusions, the branches penetrating into the brainstem and cerebellum are likely to remain patent due to retrograde flow from the posterior communicating arteries which may augment residual blood flow in the branches, which usually is not the case in proximal basilar artery occlusions. (64) Furthermore, top-of-the basilar occlusions generally do not have an underlying vessel pathology, as it occurs for proximal-mid basilar artery lesions with underlying atherosclerotic pathology, and are more likely to have smaller basilar thrombi which may be more responsive to intravenous thrombolysis. (183). Overall, the recanalization rate at 24 hours after intravenous thrombolysis in these studies was up to 65%. Presence of mid-basilar occlusion tended to be associated with unsuccessful recanalization (odds ratio 4.76, 95% CI 0.91–24.84; p=0.06), whereas occlusion of embolic origin decreased the likelihood of unsuccessful recanalization (odds ratio 0.21, 95% CI 0.06–0.81). (183) Patients who achieved successful recanalization had better functional outcomes than patients who did not achieve successful recanalization (modified Rankin scale score 0-3 64.1% versus 28.2%, respectively). (183)

Alternative thrombolytic agents

The first thrombolytic agent tested in acute ischemic stroke was streptokinase, an antigenic compound isolated and derived from purified streptococci bacteria. (185) Streptokinase resulted in increased risk of bleeding and mortality (8, 186) in several large clinical trials, including an Australian-led one. (187) Another promising thrombolytic agent was desmoteplase, a drug with high fibrin-specificity derived from vampire bat saliva. The early phase trials of desmoteplase were promising with increased reperfusion in extended time window (3-9 hours) and a safe profile in terms of symptomatic haemorrhage and trends to improved outcome. (188, 189) However, phase 3 trials failed to show improvement in outcomes in patients selected using penumbral imaging (DIAS-2 trial) (190) or who had large vessel occlusion or high-grade stenosis (DIAS-3 trial). (190, 191) The prematurely terminated DIAS-4 trial together with a post hoc pooled analysis of the concomitant DIAS-3, DIAS-4, and DIAS-J (Japan), demonstrated that treatment with intravenous 90 µg/kg desmoteplase is safe, increases arterial recanalization, but does not significantly improve functional outcome at 3 months.(192) In a subsequent meta-analysis of six trials evaluating the safety and efficacy of intravenous desmoteplase in a 3-9 hours time window, Li et al. (193) reported increased reperfusion rates (odds ratio 1.57,95% CI 1.10-2.24; p =0.01) with no increase in symptomatic intracerebral haemorrhage and death. However, there was no difference in functional outcomes at 90 days (odds ratio 1.14, 95% CI 0.88-1.49; p=0.31 vs control).

Tenecteplase is the most promising alternative thrombolytic agent. It is a genetically modified tPA agent that can be administered by intravenous bolus, without the need for the additional 1-hour infusion of alteplase through an infusion pump, with a half-life of 22 minutes. (194) Tenecteplase also only requires one drug vial compared to potentially multiple for alteplase and is cheaper than alteplase in most countries. Tenecteplase has been approved for acute myocardial infarction and was demonstrated to be superior to alteplase. (195, 196) The first trial testing tenecteplase in stroke was an open-label, dose-escalation safety study comparing 0.1, 0.2, 0.4, 0.5mg/kg in 88 ischemic stroke patients within 3 hours. (197) Enrollment into the dose used for myocardial infarction (0.5 mg/kg) was closed prematurely due to the high risk of symptomatic intracranial haemorrhage. However, they found that doses of 0.1 to 0.4 mg/kg were safe in ischemic stroke. (197) A subsequent efficacy trial was prematurely terminated due to slow recruitment after only 112 patients had been randomized: the 0.4-mg/kg dose was discarded as inferior and the optimal dose between 0.1mg/kg and 0.25mg/kg could not be identified at the time the trial was stopped. (198) In 2012, Parsons et al. completed a randomised phase IIb study in which they compared tenecteplase 0.1mg/kg (n=25 patients) and 0.25mg/kg (n=25 patients) to alteplase 0.9mg/kg (n=25 patients) in a cohort of ischemic stroke patients with large vessel occlusion and salvageable tissue on CT perfusion, within 6 hours of symptom onset. (199) In this trial, the pooled tenecteplase groups had greater reperfusion (p=0.0004) and better outcomes (modified Rankin Score 0-2, 72% vs 44%, p=0.02) than the alteplase group. (199) Tenecteplase was associated with increased reperfusion, early neurological improvement and improved 3-month functional outcome with a strong dose-dependent relationship, with the 0.25 mg/kg dose achieving better efficacy outcomes compared to 0.1 mg/kg, with no increase in symptomatic intracerebral haemorrhage.(199) A subsequent phase II trial compared tenecteplase 0.25mg/kg to alteplase 0.9mg/kg in n=104 ischemic stroke patients within 4.5 hours of symptom onset. No significant differences were found for the primary endpoint of percentage of penumbral salvaged (68% [SD 28] in the tenecteplase group vs 68% [SD 23] in the alteplase group; mean difference 1.3% [95% CI −9.6 to 12.1]; p=0·81). (200) However, a subsequent pooled analysis of these two trials demonstrated that treatment with tenecteplase was associated with greater early clinical improvement (median National Institutes of Health Stroke Scale score change: tenecteplase, 6; alteplase, 1; p<0.001) and better functional outcomes (modified Rankin scale score 0–1: odds ratio, 2.33; 95% CI, 1.13–5.94; p=0.032) than those treated with alteplase, with the greatest benefit seen in patients with a CT perfusion-defined target mismatch (201). Furthermore, patients with large vessel occlusion treated with tenecteplase had higher recanalization rates at 24 hours (71% for tenecteplase vs 43% for alteplase, p=0.001) and tended to have better functional outcomes (modified Rankin scale score 0–1: odds ratio 4.82, 95% confidence interval 1.02–7.84, p=0.05) than patients treated with alteplase.(202) Patients with basilar artery occlusion were not included in these trial.

The Australian-led Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial compared tenecteplase 0.25mg/kg to alteplase prior to endovascular therapy in n=202 patients with large vessel occlusion. (203) In this trial, tenecteplase led to higher reperfusion rates prior to endovascular therapy (22% vs 10%, non-inferiority p=0.002, superiority p=0.03) and improved functional outcomes (ordinal analysis of the modified Rankin Scale, common odds ratio 1.7,95% CI 1.0-2.8, p=0.04) compared with alteplase in large vessel occlusion ischemic strokes. Subsequently, the EXTEND-IA TNK part 2 trial compared tenecteplase 0.25mg/kg with 0.4mg/kg and did not find any further benefit with the higher dose for vessel recanalisation or improved outcomes. (204) These results clarified that the optimal dose of tenecteplase for large vessel occlusion stroke is 0.25mg/kg. This came after a large Norwegian phase III trial compared tenecteplase 0.4mg/kg to alteplase in n=1107 stroke patients recruited within 4.5 hours of onset or of awakening from sleep with symptoms. (205) In this trial, tenecteplase did not show superiority in improving excellent outcome (modified Rankin Scale 0-1, 64% vs 63%, odds ratio 1.08 [95% CI 0.84-1.38, p=0.52]). The dose of tenecteplase 0.4mg/kg was considered safe as the rate of symptomatic haemorrhagic transformation was not increased (p=0.70). However, this cohort of patients had a very low median baseline severity (National Institutes of Health Stroke Scale score of 4) with a high number of stroke mimics (17%), which significantly reduced the power to detect a meaningful difference between the two thrombolytic agents.

A subsequent meta-analysis of non-inferiority including five trials of tenecteplase versus alteplase, (206) found that tenecteplase was non-inferior to alteplase for all clinical efficacy measures (modified Rankin Scale 0-1, 0- 2 and ordinal analysis) as well as symptomatic haemorrhagic transformation, regardless of the dose being 0.25mg/kg or 0.4mg/kg or the need for endovascular therapy for large vessel occlusion. (206)

In summary, tenecteplase appears superior at 0.25mg/kg dose to alteplase for large vessel occlusion and non-inferior at either 0.25mg/kg or 0.4mg/kg doses to alteplase for all acute ischaemic stroke. Several phase III clinical efficacy trials of tenecteplase compared to alteplase are ongoing (TASTE Anzctr.org.au registration: ACTRN12613000243718, ATTEST-2 Clinicaltrials.gov registration: NCT02814409, AcT Clinicaltrials.gov registration: NCT03889249, NOR-TEST2 NCT03854500). Tenecteplase is also being trialled in mild stroke in an extended time window (TEMPO-2 Clinicaltrials.gov registration: NCT02398656), in large vessel occlusion from 4.5-24 hours compared to standard therapy (ETERNAL-LVO Clinicaltrials.gov registration: NCT04454788), in patients with wake-up symptoms (TWIST Clinicaltrials.gov registration: NCT03181360) and in a mobile stroke unit compared to alteplase (TASTE-A Clinicaltrials.gov registration: NCT04071613).

No large observational study has ever investigated the use of tenecteplase in basilar artery occlusion and to date, this has been mostly described in case reports. (207, 208) No randomized controlled trial has ever investigated the effect of tenecteplase in a cohort of patients with basilar artery occlusion. The EXTEND-IA TNK (204, 209) trial was the only tenecteplase trial including patients with basilar artery occlusion. However, it is unclear whether its findings can be extrapolated to basilar artery occlusion as only 6 patients were included with no differences in primary outcome (1/3 in each treatment arm).

Intravenous thrombolysis in extended time window

The EPITHET trial was a phase II trial comparing alteplase versus placebo in the 3-6 hour time epoch in n=101 patients imaged using multimodal perfusion-diffusion MRI to assess the presence of ischaemic penumbra. (210) The primary outcome of reduced geometric mean growth with alteplase was neutral. However, reperfusion was more common with alteplase than with placebo and was associated with less infarct growth (p=0.001), better neurological outcome (p<0.0001), and better functional outcome (modified Rankin scale 0-2, 63% versus 32%, p=0.007) compared to absence of reperfusion. (210) These results concur with those from the earlier non-randomised DEFUSE study, (211) in which reperfusion was associated with significantly increased odds of achieving a favourable clinical response in patients with favourable MRI profiles treated with intravenous alteplase within 3–6 h of stroke onset.

Recently, the Australian-led EXTEND trial was completed (212) and paved the way for a change in clinical practice and guidelines recommendation for intravenous thrombolysis. The EXTEND trial enrolled n=225 patients from 4.5-9 hours of onset, or 9 hours from mid-point of sleep for wake-up strokes, using automated processing of CT perfusion or perfusion-diffusion MRI to select patients with perfusion mismatch. It showed improved excellent outcomes (modified Rankin Scale 0-1, adjusted risk ratio 1.44 [95% CI 1.01-2.06], p=0.04) for alteplase compared to placebo. However, there was an increase in symptomatic haemorrhagic transformation (6.2% vs 0.9%, p=0.053). (212) Another trial, ECASS-4 EXTEND, explored thrombolysis with alteplase in 4.5-9 hour time window using visually assessed MRI-perfusion selection but was stopped prematurely due to slow recruitment. In n=119 patients enrolled, they found a non-statistically significant trend towards better outcomes with alteplase (odds ratio 1.20 [95% CI 0.63-2.27, p=0.58]). (211) A subsequent meta-analysis of the EPITHET, EXTEND and ECASS-4 EXTEND trials confirmed that penumbral selection for patients >4.5 hours from onset is associated with higher rates of excellent outcome (modified Rankin Scale 0-1, adjusted odds ratio 1.86 [95% CI 1.15-2.99, p=0.011]) and overall improvement in 3-month outcomes (ordinal modified Rankin Scale analysis, adjusted common odds ratio 1.60 [95% 1.12-2.27, p=0.009]). (213) The subgroup of patients with wake-up symptoms selected by penumbral imaging appeared to benefit from alteplase as those with known onset between 4.5 and 9 hours. (214)

Other studies explored alternative imaging selection criteria to treat patients with alteplase beyond 4.5 hours. Using MRI diffusion-weighted imaging- T2 fluid-attenuated inversion recovery mismatch (including patients with ischaemic lesions seen on diffusion-weighted imaging but not yet on T2 fluid-attenuated inversion recovery), the WAKE-UP trial (215) showed an increase in excellent outcomes for alteplase-treated patients compared to placebo (modified Rankin Scale 0-1, 53.3% vs 41.8%, adjusted odds ratio 1.61 [95% CI 1.09-2.36, p=0.02]). Although prematurely terminated due to lack of funding, the trial enrolled n=503 patients and found no statistically significant increase in symptomatic haemorrhagic transformation (2.0% vs 0.4%, p=0.15). (215)

A Japanese-led trial (THAWS) (216), which was stopped prematurely due to the results from WAKE-UP, showed neutral results (modified Rankin Scale 0-1, 47.1% vs 48.3%, relative risk 0.97 [95% CI 0.68-1.41, p=0.892]) comparing a lower dose of alteplase of 0.6mg/kg versus standard of care, using the same MRI approach of the WAKE-UP trial. Finally, a recent meta-analysis of the extended time window alteplase trials (EXTEND, ECASS-4 EXTEND, WAKE-UP and THAWS) found overall improved excellent outcome compared to placebo (modified Rankin Scale 0-1, 47% vs 39%, adjusted odds ratio 1.49 [95% CI 1.10-2.03, p=0.011]). (217)

In summary, current evidence supports the use of intravenous thrombolysis for all patients within 4.5 hours of symptom onset (if they meet non-contrast CT brain and clinical eligibility criteria) and intravenous thrombolysis for ischaemic strokes 4.5-9 hours of symptom onset or with wake-up symptoms, with a favourable CT or MRI-perfusion profile (EPITHET, EXTEND and ECASS-4 EXTEND trials) or MRI diffusion weighted-fluid attenuated inversion recovery mismatch (WAKE-UP and THAWS trials). Patients with basilar artery occlusion were not included in the extended-time window intravenous thrombolysis trials.

Intravenous thrombolysis in basilar artery occlusion in extended time window

The time window for intravenous thrombolysis for posterior circulation strokes has not been established in randomized controlled trials. However, several observational studies have explored intravenous thrombolysis beyond 4.5 hours in basilar artery occlusion patients. In the Helsinki basilar artery occlusion cohort (n=116), treatment protocols for basilar artery occlusion (218) recommended thrombolysis with alteplase up to 12 hours in case of sudden onset of a severe syndrome and up to 48 hours from the onset of a monophasic course of progressing symptoms without resolution, thus excluding prodromes, provided that extensive ischemic changes have not yet occurred in the posterior circulation fossa on non-contrast CT brain.(173) According to the same treatment protocol, a full-dose of anticoagulation with either intravenous unfractionated heparin or low-molecular-weight heparin to prevent re-occlusion until the patient is mobilized was recommended. Anticoagulation treatment could be initiated either immediately after or before thrombolysis after exclusion of intracranial bleed on the baseline CT brain. (173) Although only 35% of these patients were treated within 6 hours of symptom onset, 65% of the cohort had partial or complete recanalization. Among patients who achieved recanalization, 25/59 (42%) were independent (modified Rankin scale 0-2) and 32/59 (54%) had slight disability (modified Rankin scale score 0-3) at 3 months. The overall rate of symptomatic haemorrhages in this study was 16%, according to ECASS II criteria, (155) likely due to the full dose of anticoagulation associated with intravenous thrombolysis. In a subsequent study from the Helsinki cohort including n=184 patients with basilar artery occlusion, Strbian et al. analysed the association between onset to treatment time and functional outcome and whether extensive ischemic changes on non-contrast CT brain (pc-ASPECTS <8) influenced this association. (219) The authors found that in 96% of patients presenting with extensive infarction (pc-ASPECTS < 8), the outcome was poor (modified Rankin scale score 3-6). Simalar results (94%) were found even if the artery was recanalized. In contrast, in the absence of extensive ischemic changes, successful recanalization led to a good outcome (modified Rankin Scale 2-6) in 50% of patients and moderate outcome (modified Rankin Scale 3-6) in 62% of patients, even when treated beyond 12 hours from symptom onset. Recanalization was achieved in 73% of patients without extensive baseline ischemia and was associated with good outcome, consistent with previous studies. (65, 220) Importantly, the likelihood of successful recanalization did not decrease across different onset to treatment time categories (0-6, 6-12, 12-24 hours), in the absence of extensive baseline infarction, being 82%, 70%, and 75%, respectively. (219) The rate of symptomatic haemorrhage was only 6%, (according to the SITS definition) (161) in patients without extensive baseline ischemia, despite the full dose of anticoagulation used in addition to intravenous thrombolysis in these patients. Importantly, this risk is comparable to the rate of symptomatic haemorrhage reported in the extended-time window thrombolysis randomized controlled trials in anterior circulation stroke. (212, 213) Furthermore, the rates of symptomatic haemorrhage did not differ across different onset to treatment time categories. (219)

In a more recent analysis of the BASICS registry, Vergouwen et al.(179) found that basilar artery occlusion patients with severe strokes at presentation treated beyond 9 hours all had poor clinical outcome. However, unlike pivotal randomized controlled trials in anterior circulation stroke, patients with extensive infarct at baseline were not excluded from the BASICS registry. In the Helsinki series (219), a similar decay of therapeutic efficacy was seen beyond 9 hours but disappeared when the results were adjusted for the extent of baseline ischemia. Thus, patients treated later than 9 hours were simply more likely to have extensive infarctions before treatment. It has been postulated that distinct features of the posterior circulation, such as a highly developed, persistent collateral arterial network and reverse filling from the distal basilar artery might sustain the patency of brainstem perforators for longer times. (23) Besides backflow from the anterior circulation through the posterior communicating arteries, blood supply can be provided caudally from anastomotic vascular networks such as the PICA-derived collaterals to both AICA and SCA systems. Anastomoses between the superficial brainstem arteries may become recruited by abnormal hemodynamic and blood pressure gradient circumstances.

Intra-arterial thrombolysis

Intra-arterial thrombolysis is a technique based on delivery of thrombolytic agents to the occluded vessel via catheter angiography. Intra-arterial delivery of thrombolytic agents has been used for decades and was trialled in the ProACT II randomized trial of pro-urokinase plus heparin versus heparin control group in n=180 patients with middle cerebral artery occlusion. (221) The rate of recanalization was higher in the pro-urokinase arm (66% vs 18%, p<0.001) with better clinical outcomes (modified Rankin Score 0-2, 40% vs 25%, p=0.04). However, there was a trend towards increased symptomatic intracerebral haemorrhage (10% vs 2%, p=0.06). No further trials were conducted with pro-urokinase and licensing for the drug was abandoned.

Endovascular therapy

Endovascular therapy (EVT) is an intra-arterial treatment that achieves recanalisation of occluded vessels through mechanical clot retrieval using a stent retriever or aspiration techniques.

<u>First and second-generation mechanical devices</u>

The first device for mechanical clot retrieval was the mechanical stent retriever device (MERCI), registered in the USA in 2004. In registry studies, this device was able to recanalise the artery in 46% of cases, with clinically significant procedural complications in 7.1% of patients and a 7.8% rate of symptomatic intracerebral haemorrhage. (222) Subsequent versions of the device improved recanalization to 57% and when combined with other mechanical and lytic strategies overall recanalization reached 70%, with a 5.5% rate of clinically significant procedural complications and symptomatic haemorrhage seen in 9.8% of cases. (223) A second-generation clot aspiration device (PENUMBRA) was registered in 2008. The Penumbra device acts as an intra-vascular suction device, with the theoretical advantage of working from the accessible clot face rather than requiring the interventionalist to traverse the clot blindly in order to deploy the device. Two single-arm trials showed complete or partial vessel recanalisation with the penumbra device in 100% and 82% respectively, with procedural and haemorrhagic complication rates lower or equivalent to the first-generation MERCI device. (224, 225)

In 2013 the first three randomised controlled trials comparing intravenous thrombolysis with intra-arterial approach using mechanical clot retrieval devices were published. All these trials failed to show a significant benefit of intra-arterial therapy against intravenous thrombolysis. However, the studies had major limitations. First and foremost, these trials had poor selection criteria, with patients often being randomized without the demonstration of large vessel occlusion. Other major limitations included the low rates of successful recanalization, non-consecutive patient recruitment, the heterogeneity of treatment methods used and the delay in endovascular treatment.

The first of these trial was an Italian-led study (SYNTHESIS) comparing intravenous alteplase to intra-arterial therapy (using catheter-directed alteplase with or without the use of any mechanical clot disruption or retrieval) within 4.5 hours of onset in n=362 patients. (226) In this trial, Ciccone et al. found that intra-arterial therapy did not improve 3-month excellent outcomes (modified Rankin Scale 0-1, 30.4% vs 34.8%, adjusted odds ratio 0.71 [95% CI 0.44-1.44, p=0.16]), with no difference in symptomatic haemorrhagic transformation (6% vs 6%). This pragmatic trial had several limitations including the enrolment based on a clinical uncertainty principle, (227) with no required demonstration of large vessel occlusion or baseline clinical severity, and patients in the active arm receiving treatment later than those in the control arm (3.75 hours vs 2.75 hours, p<0.001). (226)

The IMS-3 trial (228) was ceased prematurely due to futility after enrolment of n=656 patients within 3 hours of symptom onset. In this trial, a confirmation of large vessel occlusion was initially not required but patients needed to have a baseline National Institutes of Health Stroke Scale score of ≥10. Good outcomes were similar between arms (modified Rankin Scale 0-2, 40.8% vs 38.7%, absolute adjusted difference 1.5% [95% CI -6.1-9.1]) with no increased haemorrhagic complications in the active arm. Successful recanalisation was achieved in only 23-44% of cases.

The MR RESCUE trial (229) compared endovascular therapy with MERCI stent retriever or PENUMBRA aspiration device with rescue intraarterial thrombolysis to standard management including intravenous thrombolysis within 8 hours of onset in n=118 participants. In this study, 3-month outcomes did not differ between arms (mean modified Rankin Scale 3.9 vs 3.9, p=0.99) and patients with favourable perfusion imaging did not benefit in subgroup analysis (p=0.23). Successful recanalization was present in only 27% of patients.

Third generation mechanical devices

The latest generation of devices are the “stent-retrievers”. Neurointerventionalists serendipitously discovered during aneurysm coiling that the Solitaire retrievable stent was effective in removing clots and this paved the way for using other stents such as TREVO and

REVIVE for endovascular therapy. Compared to the first-generation MERCI stent retriever, initial trials showed partial or complete recanalisation to be superior for both the SOLITAIRE stent retriever (61% vs 24%, non-inferiority p<0.0001, superiority p=0.0001) (230) and TREVO stent retriever (86% vs 60%, superiority p<0.0001).(122)

The use of these new-generation devices led to several randomized controlled trials published in 2015, which finally demonstrated the benefit of endovascular therapy compared to standard therapy, including intravenous thrombolysis, in patients with large vessel occlusion stroke. The first of these trials was a Dutch-led study (MR CLEAN) including n=500 patients with proven anterior circulation large vessel occlusion within 6 hours of onset. (231) Participants were assigned to either endovascular treatment using predominantly third-generation devices mechanical devices (81.5% of cases) and/or intra-arterial thrombolysis in addition to standard care versus standard care alone (control). Intravenous thrombolysis could be given in both arms. This study showed a significant shift in functional outcomes in favour of the endovascular therapy arm (ordinal modified Rankin Scale analysis, adjusted common odds ratio 1.67 [95% CI 1.21-2.30]) with a rate of successful recanalization of 58.7% and no significant increase in symptomatic haemorrhage. (231)

Following this first positive trial, seven trials of predominantly anterior circulation stroke (232-238), including the Australian-led trial EXTEND-IA, were terminated early due to lack of equipoise, Table 3. All these trials except two reported a positive result. The five positive trials published in 2015 have led to guideline changes in the management of patients with large vessel occlusion worldwide. These trials differed from all previously published trials of endovascular therapy because their protocols emphasised fast treatment, had imaging criteria to include only patients with large vessel occlusions who are most likely to benefit from endovascular therapy and used new generation thrombectomy devices, which have better recanalisation rates and lower complication rates than first-generation devices.

A pooled meta-analysis of the first five positive EVT trials (239), including n=1287 patients, reported improved 3-month excellent functional outcomes (modified Rankin Scale 0-1, 26.9% vs 12.9%, adjusted odds ratio 2.72 [95% CI 1.99-3.71]), good functional outcomes (modified Rankin Scale 0-2, 46.0% vs 26.5%, adjusted odds ratio 2.71 [95% CI 2.07-3.55]) or any improvement in outcome (ordinal modified Rankin Scale analysis, adjusted odds ratio 2.49 [95% 1.76-3.53]), with a number needed to treat to achieve any improvement in 3-month modified Rankin Scale of 2.6 (common odds ratio 2.49 [95% 1.76-3.53, p<0.0001]). (239)

Similar to intravenous thrombolysis, the efficacy of endovascular therapy is dependent on time from symptom onset. However, endovascular therapy has a more powerful treatment effect compared to intravenous thrombolysis. (240) Based on the pooled analysis of the first five positive trials, (241) it has been estimated that every hour of delay to treatment commencement, a 3.4% absolute decrease (odds ratio 0.87 [95% CI 0.79-0.97]) in chances of achieving independence (modified Rankin Scale 0-2) occur and for every 4 minutes of delay from hospital arrival to reperfusion time, around 1 in 100 patients would have a poorer outcome. A subsequent analysis using an open-label treatment registry showed an absolute decrease of 5.3% for chances of achieving independence per hour of treatment delay, (242) indicating a greater negative impact of delayed reperfusion in a real-world setting. In a separate analysis of the pragmatic MR CLEAN trial, (231) every minute of earlier commencement of endovascular therapy was estimated to save an average of 4.2 days of extra healthy life (95% CI 2.3-5.4), with patients younger than 55 years with severe strokes gaining more than a week per each minute saved. In this study, every 20 minutes decrease in treatment delays led to a gain of average equivalent of 3 months of disability-free life. (243)

Patients with basilar artery occlusion were excluded from most of these trials. A French-led trial (THACE) was originally designed to include patients with occlusions of the superior third of the basilar artery. Patients were randomly assigned to receive either intravenous thrombolysis alone (control group) or intravenous thrombolysis plus mechanical thrombectomy (active group). They found that 85 (42%) of 202 patients in the intravenous thrombolysis group and 106 (53%) of 200 patients in the active group achieved functional independence at 3 months (odds ratio 1·55, 95% CI 1·05–2·30; p=0·028), with no increase in the rate of symptomatic intracranial haemorrhage (p=0.71). However, only 4 patients with basilar artery occlusion (2 in each arm) were enrolled among the n=414 patients recruited for the study. Thus, the findings of this trial only apply to patients with anterior circulation strokes.

Stent-retriever versus aspiration techniques

Most of the pivotal trials that showed the benefit of endovascular therapy used a stent retriever device in the treatment arm. A direct-aspiration first-pass technique (ADAPT) is a technique involving first-line aspiration to remove the thrombus through a large-bore aspiration catheter.(244) These large catheters are important tools for thrombectomy of large-vessel occlusion allowing high rates of reperfusion. A French-led trial (ASTER) of n=381 patients published in 2017, compared contact aspiration (with stent retriever as rescue therapy) to stent retriever technique in patients with anterior circulation large vessel occlusion stroke. (245) This study found that contact aspiration had a similar rate of successful recanalisation (85.4% vs 83.1%, p=0.53) and functional outcomes (modified Rankin Scale 0-2, 45.3% vs 50.0%, p=0.38), although there was a slightly higher rate of rescue therapy after first-line strategy in the aspiration arm (32.8% vs 23.8%, p=0.05). (245) These results suggest that contact aspiration is a valid alternative to stent-retriever thrombectomy.

Table 3. Summary of initial trials of endovascular therapy using third-generation devices.								
	MR CLEAN[175]	**EXTEND IA[176]**	**ESCAPE[177]**	**SWIFT PRIME[178]**	**REVASCAT[179]**	**THERAPY[180]**	**THRACE[181]**	**PISTE[182]**
Number of patients	500	70	316	196	206	108	414	65
Intra-arterial therapy in active arm	Retrievable stent retriever (81.5%) and/or intraarterial thrombolysis	SOLITAIRE stent retriever	Retrievable stent retriever	SOLITAIRE stent retriever	Retrievable stent retriever	PENUMBRA aspiration device	Stent retriever or aspiration device	Stent retriever or aspiration device
Vessel Occlusion	ICA, M1, M2, A1, A2, extracranial tandem	ICA, M1, M2, extracranial tandem*	ICA, M1, M2*, extracranial tandem	ICA, M1, M2*	ICA, M1, M2*, extracranial tandem	ICA, M1, M2 - ≥8mm clot length	ICA, M1, M2 **proximal basilar**	ICA, M1, M2*,
Time limit from onset to randomisation	6 hrs	6 hrs	12 hrs	6 hrs	8 hrs	4.5 hrs	4 hrs	4.5 hrs
NIHSS limit	≥2	Nil	≥6	8-29	≥6	≥8	10-25	≥6
Imaging Selection	NCCT – no large established infarction	CTP – salvageable penumbra and core <70mL	NCCT – ASPECTS >5 Multiphase CTA or CTP – moderate to good collaterals	NCCT – ASPECTS >5 First n=71 CTP or MRI with salvageable penumbra and small core	NCCT – ASPECTS >6	NCCT – no large established infarction	MRI or NCCT – no large established infarction	NCCT – no large established infarction
Age, mean or median (active/	66/66	69/70	71/70	66/65	66/67	67/70	62/62	67/64

control)								
NIHSS, median (active/ control)	17/18	17/13	16/17	17/17	17/17	17/18	17/17	18/14
Intravenous thrombolysis rates (active/ control)	87.1%/ 90.6%	100%/100%	72.7%/ 78.7%	100%/100%	68.0%/ 77.7%	100%/100%	100%/100%	100%/ 100%
Successful recanalisation (TICI 2b/3) in active arm	58.7%	86.2%	72.4%	88.0%	65.7%	69.8%	68.8%	87%
Modified Rankin Scale 0-2 at 3-months, active vs control [95% CI]	32.6% vs 19.1% (aOR 2.16 [1.39-3.38])	71% vs 40% (aOR 4.2 [1.4-12], p=0.01)	53% vs 29.3% (aRR 1.7 [1.3-2.2], p<0.001)	60% vs 35% (RR 1.70 [1.23-2.33], p<0.001)	44% vs 28% (aOR 2.1 [1.1-4.0])	38% vs 30% (OR 1.4 [0.60-3.3], p=0.44)	53% vs 42% (OR 1.55 [1.05-2.30], p=0.028)	51% vs 40% (aOR 2.12 [0.65-6.94], p=0.204
Symptomatic haemorrhagic transformation, active vs control [95%CI]	7.7% vs 6.4%	0% vs 5.7%	3.6% vs 2.7% (aRR 1.2 [0.3-4.6])	0% vs 3.1% (p=0.12)	1.9% vs 1.9% (RR 1.0 [0.1-7.0])	9.3% vs 9.7% (OR 1.0 [0.3-3.9], p=1.0)	2.2% vs 1.6% (OR 1.39 [0.31-6.31], p=0.71)	0% vs 0%

*Non-intentional inclusion. Abbreviations: A1 (first segment anterior cerebral artery); A2 (second segment anterior cerebral artery); aOR (adjusted odds ratio); aRR (adjusted relative risk); ASPECTS (Alberta stroke program early CT score); CTA (CT-angiogram); CTP (CTperfusion); ICA (internal carotid artery); M1 (first segment middle cerebral artery); M2 (second segment middle cerebral artery); NCCT (non-contrast CT brain); NIHSS (National Institutes of Health Stroke Scale); OR (odds ratio); RR (relative risk); TICI (Treatment In Cerebral Ischemia score).

Endovascular therapy in extended time window

A pooled analysis of the first five published trials (241) found that endovascular therapy was associated with improved outcomes up to 7.3 hours. Importantly, four of the 5 trials formally excluded patients with large ischemic cores evident on initial brain imaging from study participation. Building on this concept, in 2018 two late time window trials were published testing the hypothesis that strict imaging selection criteria may identify patients likely to benefit from endovascular therapy in extended time window. The first study (DAWN) (246) enrolled n=206 patients assigned to either EVT with the TREVO stent retriever or best medical care within 6-24 hours post-stroke onset (or wake-up symptoms). Eligibility criteria required internal carotid or first segment middle cerebral artery occlusion and fulfilling a clinical-radiological mismatch, including limits of estimated ischaemic core, age and clinical severity. The trial was terminated for efficacy at a pre-specified interim analysis and found a substantial benefit of EVT in this selected late window population, with return to independence strongly favouring the active arm (49% vs 13%, probability of superiority using Bayesian analysis >0.999) and no significant increase in symptomatic haemorrhagic transformation (6% vs 3%, p=0.50).

The second late window EVT trial (DEFUSE-3) (247) enrolled n=182 patients to EVT or best medical treatment between 6-16 hours after stroke onset (or wake-up symptoms), using CT or MR-perfusion parameters (core <70mL with penumbra mismatch ratio >1.8 and volume >15mL). This trial was terminated for efficacy at a pre-specified interim analysis. This trial found a strong beneficial effect of EVT treatment in imaging selected patients, with significant improvements in return to independence (45% vs 17%, relative risk 2.67 [1.60-4.48, p<0.001]). A pooled analysis of five late window EVT trials (AURORA, not yet published) (248) showed an improvement in good outcomes (modified Rankin Scale 0-2, 46.7% vs 16.7%, adjusted odds ratio 4.65 [95% CI 2.02-10.72, $p<0.001$] and any improvement in 3-month outcomes (ordinal modified Rankin Scale shift, adjusted odds ratio 2.77 [95% 1.95-3.94, $p<0.001$]), with an estimated number needed to treat for any shift in the modified Rankin Scale grade at 3-months of 2.5. This figure is almost identical to the effect of endovascular therapy within 6 hours. Given that post-stroke outcomes are generally expected to decline with delays in treatment, this phenomenon was termed the "late window paradox", (249) which may be explained by the use of penumbral selection picking out patients who were more likely "slow progressors" with very good collaterals and higher chances of benefitting from reperfusion therapies.

In summary, EVT is recommended for patients with anterior circulation large vessel occlusion stroke within 6 hours of onset with no large established ischaemic change on non-contrast CT-brain (evidence from multiple trials including MR CLEAN) or up to 24 hours of onset (or wake-up symptoms) if fulfilling imaging criteria used in the DAWN or DEFUSE-3 trials. Patients with basilar artery occlusion were excluded from most of the early and late window ETV trials.

Endovascular therapy in basilar artery occlusion

Given the dismal prognosis of basilar artery occlusion, in many centres there is a general agreement that basilar occlusion is an indication for EVT, despite being almost entirely excluded from the initial positive EVT trials. However, the current American Heart Association/ American Stroke Association guidelines, which recommend endovascular therapy within 6 hours in large vessel occlusion anterior circulation stroke and within 24 hours in selected patients with large vessel occlusion anterior circulation stroke (Class I, Level of Evidence A), state that there is uncertainty about the benefit of thrombectomy in basilar artery occlusion but that may be reasonable in carefully selected patients within the first 6 hours of stroke onset (Class IIb; Level of Evidence C). (250) This recommendation is based on evidence largely derived from retrospective studies, (251, 252) including the BASICS registry. (65)

Intra-arterial therapy in basilar artery occlusion

The first case of intra-arterial therapy for stroke was a patient treated with intra-arterial thrombolysis for basilar artery occlusion described in 1982. (253) Subsequently, Hacke et al. (254) published a series of n=43 patients with basilar artery occlusion who received intra-arterial thrombolysis with urokinase or streptokinase and n=22 who were treated conservatively (e.g. with anticoagulants or antiplatelets). They demonstrated that patients treated with intra-arterial thrombolysis who had recanalisation had lower mortality (p= 0.0005) and more favourable outcomes (p= 0.017) than those with persistent occlusions. The Australian Urokinase Stroke Trial was the first randomized trial comparing intra-arterial therapy with conservative management in patients with basilar artery occlusion. Among the sixteen patients randomized, a good outcome was observed in 4 of 8 patients who received intra-arterial urokinase compared with 1 of 8 patients in the control group. (255) In a systematic analysis comparing intravenous thrombolysis with alteplase and intra-arterial therapy, mostly using urokinase [n=76 patients in 3 studies of intravenous thrombolysis (within or beyond 4.5 hours) and 344 patients in 10 studies of intra-arterial thrombolysis], Linsberg et al. (251) reported that patients had equal odds of death or dependency in both groups: 78% after intravenous thrombolysis and 76% after intra-arterial thrombolysis (p=0.82). The rate of recanalization was slightly higher after intra-arterial thrombolysis compared with intravenous thrombolysis in this study, but this did not translate into better outcomes in the intra-arterial thrombolysis group. Therefore, the authors concluded that stroke centres that have an interventional neuroradiology service should pursue intra-arterial thrombolysis to treat their patients but there is no reason for stroke centres without this capacity to refrain from thrombolysis, even beyond 4.5hours. Although clinical factors such as a long duration from coma have a negative prognostic value, (251) the decision to administer thrombolysis should also depend on other characteristics such as the underlying vascular lesion, resource availability and the presence of salvageable tissue rather than time itself. The route of administration of thrombolysis (either intravenous or intra-arterial) does not appear to play a major role for clinical prognosis. (251)

The BASICS registry was the first large (n=592) prospective study comparing intra-arterial therapy versus intravenous thrombolysis in patients with basilar artery occlusion. (65) In this study, patients were divided into three groups according to the treatment they received: antithrombotic treatment or systemic anticoagulation; primary intravenous thrombolysis, including subsequent intra-arterial thrombolysis; or intraarterial therapy, which comprised thrombolysis, mechanical thrombectomy, stenting, or a combination of these approaches. Importantly, the estimated time of basilar artery occlusion was taken as the time of symptom onset to allow inclusion of patients who had severe neurological syndromes preceded by hours, days or weeks of prodromal symptoms. Moreover, intravenous thrombolysis was allowed beyond 4.5 hours. Among patients who received intravenous thrombolysis, 55% were treated within 3 hours, 26% between 3-6 hours, 6% between 7-9 hours and 12% beyond 9 hours.

Compared with antithrombotic treatment, both intravenous thrombolysis and intra-arterial therapy were associated with improved outcomes for patients with severe deficits. (65) However, patients with mild to moderate deficits had worse outcomes after intra-arterial therapy compared with intravenous thrombolysis (adjusted risk ratio 1.49 [95% CI 1.00–

2.23]), whereas outcomes for patients with severe deficits were similar in patients treated with intra-arterial or intravenous thrombolysis (adjusted risk ratio 1.06 [95% CI 0.91–1.22]). Of note, a third of patients analysed in the intravenous thrombolysis group received subsequent intra-arterial thrombolysis. The BASICS study provided evidence in support of treatment with intravenous thrombolysis, to be initiated as soon as possible (but potentially extending beyond 4.5 hours), in patients with mild-to-moderate deficits, whereas intra-arterial therapy should be considered in case of subsequent acute worsening. However, the lack of robust imaging selection criteria, as well as the use of intra-arterial thrombolysis and early mechanical thrombectomy generation devices, may have affected the BASICS registry results.

In a meta-analysis including 45 studies (n=2056), (256) recanalization of acute basilar artery occlusion was associated with a lower risk of death or dependency (pooled risk ratio 0.67; number needed to treat 3) and mortality (pooled risk ratio 0.49; number needed to treat 2.5). Although recanalization rates were higher in the intra-arterial (77%; n=1715) compared to the intravenous group (59%; n=341), functional outcomes between these two groups did not differ. (256) This may be explained by the use of intra-arterial thrombolysis or first-generation retrieval devices, which also failed to show a benefit of EVT compared to intravenous thrombolysis in anterior circulation stroke. (228, 229, 257)

Endovascular therapy with stent-retrievers in basilar artery occlusion

The ENDOSTROKE study (131) included n=148 patients treated with EVT, with 59% having received intravenous thrombolysis prior to EVT. They reported that 34% had good (modified Rankin scale 0-2) and 42% had moderate (modified Rankin Scale 0-3) clinical outcome; with a mortality rate of 35%. Successful recanalization was achieved by 79%, but in this study, was not significantly associated with better outcomes. Both old and new generation devices were used in this study, with the most frequent being the Solitaire device (n=77). (131) A subsequent meta-analysis (n=17 studies, including the ENDOSTROKE study) analysed outcomes and recanalization rates in patients with basilar artery occlusion treated with stent-retriever devices (77% treated with stent retriever devices and 21% treated with non-stent retrievers or intra-arterial thrombolysis). (258) The weighted pooled estimates of successful recanalization and good outcome (modified Rankin Scale ≤2) were 80.0% (95% CI 0.71- 0.88; p<0.001) and 42.8% (95% CI 0.34- 0.52; p=0.002), respectively. Pooled mortality was 29.4% (95% CI 0.24- 0.35; p=0.087), with a 10.0% (95% CI 0.37-0.18; p=0.017) of procedure-related complications and 6.8% (95% CI 0.35-0.11; p=0.08) of symptomatic haemorrhage. (258)

In a systematic analysis (259) including 15 studies (n=803 patients), good outcome was reported more frequently in patients treated with mechanical approaches compared to those treated with intravenous or intraarterial thrombolysis protocols (modified Rankin Scale 0-2, 35.5% versus 24.4%, $p < 0.001$), as well as higher recanalization rates (84.1% versus 70.9%, $p < 0.001$). The most significant predictor of outcome was extensive baseline ischemia, increasing the odds of futile recanalization by 20-fold (95%CI 4.39–92.29, $p < 0.001$). (259)

In a more recent Korean multicenter retrospective study, including 212 consecutive patients with basilar artery occlusion who underwent either stent-retriever or contact aspiration thrombectomy as the first-line approach, successful reperfusion was achieved in 91.5% of patients and 44.8% had good outcomes (modified Rankin scale 0-2) at 3 months, with a mortality rate of 16%, symptomatic haemorrhage rate of 1.9% and procedure-related complication rate of 4.2%. (260)

A Chinese-led non-randomised prospective cohort study (the BASILAR study, n=829 patients), published in 2020 (261), compared EVT in addition to standard medical therapy (n=647) to standard medical therapy alone (n=182) within 24 hours of symptom onset. This study represents the largest prospective cohort of patients with basilar artery occlusion to date. The standard medical therapy-alone group received intravenous thrombolysis with rt-PA within 4.5 hours of the estimated time of basilar artery occlusion, urokinase within 6 hours of estimated time of occlusion, antiplatelet drugs, anticoagulation, or combinations of these medical treatments. Patients in the EVT group underwent mechanical thrombectomy with stent retrievers and/or thromboaspiration, balloon angioplasty, stenting, intra-arterial thrombolysis, or the various combinations of these approaches. In the standard medical therapy group, 25.8% (15% with alteplase) were treated with intravenous thrombolysis versus 18.4% (15% with alteplase) in the EVT group. This study showed that 90-day functional outcomes were substantially improved by EVT (adjusted common odds ratio, 3.08 [95% CI 2.09-4.55]; p<0.001). However, the rate of favourable outcome (modified Rankin scale 0-3) in the intervention group was only 32% (261). This very low rate of favourable outcomes may be due to the high percentage of patients with extensive baseline ischemia (pc-ASPECTS <8, 39%) and poor collaterals [median PC-CS 4 (interquartile range 3-6)] in the intervention arm. Despite this, outcomes in the intervention arm of the BASILAR study were significantly better than those in the standard medical therapy (modified Rankin scale 0-3, 9.3%, adjusted odds ratio, 4.70 [95% CI, 2.53-8.75];p < 0.001). Furthermore, EVT was associated with a lower rate of 90-day mortality [adjusted odds ratio 2.93 (95% CI 1.95-4.40); p<0.001) despite an increase in symptomatic intracerebral haemorrhage (7.1% vs 0.5%; p<0.001). Nonetheless, considering the poor baseline pc-ASPECTS and PC-CS, the rate of 7% symptomatic hemorrhage after endovascular therapy within 24 hours is acceptable. The propensity score matching or multivariable analyses used for this study analyses can never adjust completely for unmeasured confounders, unlike a randomized controlled trial. However, this study showed that, in real-world practice, patients with basilar artery occlusion may benefit from EVT when administered within 24 hours of symptom onset. Recently, Sange et al. (334) showed that endovascular thrombectomy was associated with higher rates of favorable outcomes in the pc-ASPECTS 5 to 7 and 8 to 10 subgroups [modified Rankin Scale 0-3, adjusted relative risk 4.35 (95% CI 1.30–14.48) and 3.20 (95% CI 1.68–6.09); respectively] and lower mortality (60.8% versus 77.6%, p=0.005 and 35.0% versus 66.2%, p<0.001; respectively) than standard medical therapy in the BASILAR study. Furthermore, onset-to-puncture time was not significantly associated with functional outcomes adjustment for pc-ASPECTS (adjusted odds ratio, 0.98 [95% CI, 0.94–1.02]). (334)

Two randomized controlled trials in basilar artery occlusion were published in 2020. A Chinese-led trial (BEST) (262) assigned patients to either EVT or best standard care within 8 hours of onset. Of a planned enrolment of 288 patients, only n=131 were recruited due to poor recruitment and a high cross-over to intervention in the control arm (22%). Intravenous thrombolysis was given in 27% of the active arm compared to 32% of the control arm, whereas rates of successful recanalisation were 71% in the active arm and 64% in the control arm. There were no statistically significant differences in return to independence at 3 months (modified Rankin Scale 0-2, 33% vs 28%, adjusted odds ratio 1.40, 95% CI 0.64-3.10; p=0.48). However, patients who actually received the intervention were more likely to have favourable outcomes compared to those who received standard medical therapy alone in both per-protocol (44% vs 25%; adjusted odds ratio 2·90, 95% CI 1.20–7.03) and as-treated (47% vs 24% with standard therapy; 3·02, 1.31–7.0) populations. These results are substantially better than the 17.4% proportion of functional independence at 30 days observed with intra-arterial therapy in the BASICS registry. (65) Although there was also a trend towards increased symptomatic haemorrhagic complications in the active arm (8% vs 0%, p=0.06), the overall mortality was not different between the two arms (33% vs 38%, p=0.54).(262)

The BASICS trial (242) (results yet to be published) provides the highest-quality evidence on treatment for patients with basilar artery occlusion to date. This Dutch-led trial (263) enrolled n=300 patients assigned to either EVT or best medical care within 6 hours of onset. Intravenous alteplase was administered in 79.1% and 79.5% of the active and control arms respectively, which was a higher percentage in comparison with the BEST trial. This study showed a non-significant trend towards benefit in the active arm (modified Rankin Scale 0-2, 44.2% vs 37.7%, adjusted risk ratio 1.18 [95% CI 0.92-1.50]). There was no increased risk of symptomatic haemorrhagic complications or mortality in the active arm. Post-hoc analysis suggested that patients with higher baseline severity (National Institutes of Health Stroke Scale ≥10) may benefit more from EVT (interaction p=0.02). The results of the BASICS trial may therefore suggest the use of endovascular therapy for patients with National Institutes of Health Stroke Scale ≥10 and intravenous thrombolysis for patients with milder symptoms. These patients may have milder symptoms due to smaller basilar thrombi which may be more responsive to intravenous thrombolysis alone. (183) The first patient of the BASICS trial was recruited in December 2011 and recruitment was completed in December 2019. The slow recruitment over more than 8 years was likely due to concerns regarding randomisation of patients with a poor natural history in the control group without endovascular therapy. Although most of the patients were enrolled after the publication of the first five positive endovascular therapy trials and therefore were treated with stent-retriever devices, (239) the 8-year recruitment spanned improvement of endovascular therapy devices and learning curve of interventionalists during the trial. Despite this, the 44.2% rate of favourable outcomes (modified Rankin scale 0-3) in the BASICS trial in the intervention group is similar to the

44% in the per-protocol analysis, and 47% in the as-treated analysis of the BEST trial. (65, 262)

The two randomized controlled trials and the non-randomized BASILAR study have several differences (summarized in Table 4), including the different time windows used (6 hours for BASICS, 8 hours for BEST and 24 hours for the non-randomized BASILAR study). Moreover, there are specific limitations that may have affected the results of each study such as the slow recruitment for the BASICS trial, the high-cross over rate for the BEST study and the non-randomized design for the BASILAR study. Nonetheless, the most important difference between the three studies appears to be the rate of good outcomes reported in the standard medical therapy arm. This was 37.7% in the BASICS trial, 25% in the per-protocol, 24% in the as-treated populations for the BEST trial and 9.3% for the BASILAR study. Another noticeable difference is the rate of intravenous thrombolysis in the standard therapy arm which was 79.5% in the BASICS trial, 32% in the BEST trial 25.8% in the BASILAR study.

Putting this in perspective, the limited risk difference of 6.5% found in the BASICS trial may be due to a better than expected outcome after standard medical therapy because of the high rate of intravenous thrombolysis, rather than to a lack of benefit of endovascular therapy in the intervention group. The 37.7% rate of favourable outcomes in the BASICS standard therapy group was higher than the estimated 30% used for the sample size calculation of n=300, assuming an expected absolute risk difference of 16%. Therefore, the trial was underpowered to detect such treatment effect differences. Although subgroup analyses should be interpreted carefully in an underpowered trial, patients tended to have more favourable outcome after endovascular therapy when this was preceded by intravenous thrombolysis.

In contrast to the BEST trial, which used a 0-4.5h time window for intravenous thrombolysis, the BASICS trial opted to extend the intravenous thrombolysis window to 4.5 hours from the estimated time of basilar artery occlusion. This raises the possibility that the BASICS more inclusive criteria for treatment with intravenous thrombolysis might have led to better outcomes in patients in the control group compared with those in the control group of the BEST trial, which used the traditional and more conservative intravenous thrombolysis approach.(262)

Stent-retriever versus aspiration techniques

Two meta-analyses have shown that stent retrievers can achieve a high recanalization rate (>80%) and functional independence (>40%) in patients with basilar artery occlusion. (258, 264) Gory et al. (265) showed that ADAPT as the first-line strategy achieves higher rate of complete reperfusion (mTICI grade 3; unadjusted odds ratio 2.59, 95% CI 1.14–5.86, p= 0.021) with shorter procedure times (median 45 minutes, IQR 34 to 62 minutes vs 56 minutes, IQR 40 to 90 minutes; p= 0.05) and lower rates of periprocedural complications (4.3% vs 25.9%, p= 0.003) in comparison with the stent retriever thrombectomy arm. However, no significant difference was found in 3-month good functional outcome (modified Rankin Scale 0-2, odds ratio 1.29, 95% CI 0.56-2.98, p=0.55) and 3-month all-cause mortality (odds ratio 1.21, 95% CI 0.54 to 2.72, p= 0.65) between the two groups. (265) In a subsequent meta-analysis including 5 cohort studies (n=193 cases were treated with first-line ADAPT and n=283 cases received first-line stent-retriever), successful recanalization rate was significantly higher in the first-line ADAPT group (odds ratio 2.0, 95% CI 1.1 to 3.5) with shorter procedure time (mean difference=−27.6min, 95% CI −51.0 −4.3) and lower rate of new territory embolic event (odds ratio 0.2, 95% CI 0.05 to 0.83) in the first-line ADAPT group. However, no significant differences were detected in terms of hemorrhagic complications or 3-month functional outcomes. Large bore balloon guide catheters were routinely used in the stent-retriever group of the ASTER trial. A recent meta-analysis (266) has shown that endovascular therapy with large bore balloon guide catheters may achieve higher first-pass, successful and complete recanalization than treatment without balloon guide catheters. (267) However, posterior circulation stroke is a condition where balloon guide catheters may not be effective. As the basilar artery is supplied by bilateral vertebral arteries, the unilateral position of balloon guide catheters cannot effectively arrest proximal flow,

(266) which might partially explain the better performance of first-line ADAPT in posterior circulation strokes.

Time window for endovascular therapy in basilar artery occlusion

Although the current US guidelines recommend EVT only within 6 hours, (250) most centers apply endovascular therapy for basilar artery occlusion up to 12–24 hours after symptom onset, given its devastating prognosis if recanalization does not occur. (23) Although the BASICS study (65) reported poor outcomes in patients with severe stroke treated beyond 9 hours, several observational studies have demonstrated that recanalization in basilar artery occlusion can be achieved in extended time windows. In a meta-analysis of Kumar et al, (256) including n=2056 patients, recanalization rates were 81% in patients treated within 12 hours and 73% in those treated beyond 12 hours. In the ENDOSTROKE study, no significant relationship was found between onset-to-treatment time and clinical outcome, although there was a trend toward worse outcomes in the small group (n=8) treated beyond 9 hours after stroke onset. (131) In this study, a rate of 35% good outcomes in patients with an onset to treatment time > 6 hours (and 24% in patients with unknown symptom onset) was found. Furthermore, collateral status was strongly associated with functional outcome and recanalization.

In the BASILAR study, 28.5% were treated with EVT beyond 6 hours, including 13% treated beyond 9 hours. Good outcomes (modified Rankin Scale 0-2) were achieved in 29% of patients with an onset to imaging time within 6 hours and 17% of patients treated with an onset to imaging time beyond 6 hours. However, these percentages included patients with extensive ischemia on baseline imaging. Rather than onset to treatment time, more accurate outcome predictors in basilar artery occlusion appear to be recanalization, extent of infarction on initial brain imaging, and presence of collateral supply. (268-271) A highly developed and persistent collateral arterial network of the posterior circulation (i.e. reverse filling of the distal basilar artery from the posterior communicating arteries and second collateral pathways) might sustain the ischaemic penumbra for more than 6 hours and basilar artery occlusion patients with good collaterals may benefit from endovascular treatment even in delayed time windows. (23)

A Chinese-led trial testing EVT versus standard medical therapy in patients with basilar artery occlusion in the 6-24 hour time window is ongoing (BAOCHE, ClinicalTrials.gov Identifier: NCT02737189).

Bridging thrombolytic therapy

Although intravenous thrombolysis prior to EVT for eligible patients is the recommended practice in US and European guidelines, (272, 273) the use of bridging thrombolysis has been questioned given the low recanalisation rate of large vessel occlusion (167) with thrombolysis alone and the potentially higher risk of symptomatic haemorrhagic complications. Moreover, intravenous thrombolysis has additional costs and may cause distal migration of the clot, making it out of reach for endovascular therapy and converting a treatable into an untreatable lesion. (274) Patients with intracranial atherosclerotic disease or dissection may require antiplatelets or Gb IIb/IIIa inhibitors after stenting, which may significantly increase the risk of bleeding when combined with intravenous thrombolysis. These concerns are mainly for patients presenting directly to comprehensive stroke centres, where endovascular therapy can be performed without significant delays. In patients presenting to primary stroke centres, intravenous thrombolysis should be administered in eligible patients so that reperfusion can be started and not delayed by inter-hospital transfer between the primary stroke centre and the comprehensive stroke centre where EVT can be performed. (275)

Despite these disadvantages, intravenous thrombolysis prior to endovascular therapy can achieve early recanalisation, obviating the need for endovascular therapy and shortening brain ischemia time, or soften the thrombus facilitating the process of removing the clot with endovascular therapy. Moreover, intravenous thrombolysis may benefit patients in whom the endovascular procedure fails due to technical factors including poor vascular access. An analysis of 25 randomised and non-randomised studies found that bridging thrombolysis was associated with higher return to independence (relative risk 1.21 [95% CI 1.13-1.30]). (276) However, because the included studies did not have solely thrombolysis-eligible patients, there was a significant risk of bias by comparing EVT patients receiving bridging thrombolysis to those who received only EVT because they were ineligible for thrombolysis. However, recanalization was increased and the number of device passes required was reduced in patients who received thrombolysis. Another meta-analysis that examined only those who were thrombolysis-eligible found no difference in terms of return to independence (modified Rankin Scale 0-2, odds ratio 1.11 [95% CI 0.75-1.66]), (277) with higher reperfusion rates in the EVT-alone group (odds ratio 1.73 [95% CI 1.04-2.94]) and no differences in haemorrhagic complications between the two groups.

A Chinese-led non-inferiority trial (DIRECT-MT) (278) enrolled n=656 patients assigned to either EVT alone or bridging intravenous alteplase 0.9mg/kg. Results showed that EVT alone was non-inferior to bridging thrombolysis (adjusted common odds ratio 1.07 [95% CI 0.81-1.40], noninferiority p=0.04) but was associated with a slightly lower rate of overall reperfusion (79.4% vs 84.5%). However, this trial has been criticised for the wide 20% non-inferiority margin, the long hospital arrival to thrombolysis times (59 minutes), some cross-over of arms (9% did not receive full-dose thrombolysis in the bridging group) and the low recruitment of patients with intracranial atherosclerosis who may benefit more from withholding bridging therapy.

In the Japanese-led SKIP trial, n=204 thrombolysis-eligible patients who presented directly to an EVT centre were randomised to either EVT alone or bridging intravenous alteplase 0.6mg/kg. (279) The results showed that those who received EVT alone had similar rates of good outcomes (modified Rankin Scale 0-2, 59.4% vs 57.3%, p=0.78) but this did not fulfil the prespecified non-inferiority margin of 0.74. A short time interval, approximately 8 minutes, occurred between the lytic drug and EVT procedure start. Bridging thrombolysis showed a slightly higher rate of any haemorrhagic complications (50% vs 34%, p=0.02) but there was no difference in symptomatic haemorrhages, vessel recanalisation rates or mortality. The trial was therefore considered underpowered to provide a definitive answer. (280)

In a recently published Chinese-led trial (DEVT) (281), Zi and colleagues, enrolled n=234 patients to either EVT alone or bridging intravenous alteplase 0.9mg/kg. In this study, the proportion of patients achieving functional independence at 90 days (modified Rankin Scale 0-2) occurred in 54.3% of patients in the EVT alone group vs 46.6% of patients in the bridging therapy group (p =0 .003 for non-inferiority), and met the prespecified non-inferiority criteria (margin of −10%). Longer time interval, approximately 40 minutes, occurred between the lytic drug start and EVT procedure start. With its higher drug dose and longer interlude for drug action, the DEVT trial more strongly probed the ability of intravenous lytics to improve outcome by quickly dissolving the target occlusion before EVT can be performed. (275)

Taken together, the results from these studies suggest that an EVT alone strategy is broadly non-inferior to bridging therapy for patients with anterior circulation large vessel occlusion stroke presenting to EVT-capable stroke centres and may be considered for these patients.

(275) Additional trials are needed to determine whether these findings generalize to non-Asian patients and are ongoing (MR CLEAN-NO IV, Isrctn.com registration: ISRCTN80619088; SWIFT-DIRECT, Clinicaltrials.gov registration: NCT03192332; DIRECT-SAFE, Clinicaltrials.gov registration: NCT03494920).

Patients with basilar artery occlusion were not included in these trials, given that the benefit of EVT in addition to intravenous thrombolysis has not yet been ascertained by a definitive positive trial.

Neurosurgical treatments

Hemicraniectomy

Decompressive hemicraniectomy is an effective neurosurgical intervention for malignant middle cerebral artery infarction, typically caused by large vessel occlusion without reperfusion, which consists of a craniectomy of the ipsilateral hemisphere with dural incision to allows expansion of swollen brain tissue and reduce the risk of excessive intracranial pressure and brain herniation. The largest meta-analysis of seven hemicraniectomy trials comparing surgery to best medical therapy (n=338) showed a strong effect on reduced mortality (30% vs 69%, risk ratio 2.05 [95% CI 1.54-2.72, p<0.00001]) and severe disability (modified Rankin Scale 0-4, 27% vs 14%, risk ratio 1.58 [95% CI 1.02-2.46, p=0.04]). (282) The majority of trials were performed within 48 hours and in patients younger than 60 years of age, with a subsequent trial in patients older than 60 years showing reduced mortality but increasing severe long-term disability. (283)

Suboccipital decompressive craniectomy

Cerebellar infarctions can swell due to vasogenic oedema within the constraints of the non-yielding posterior fossa, and lead to brainstem compression or obstruction of the fourth ventricle, causing acute hydrocephalus and fatal tonsillar herniation. Despite advances in stroke therapy, it has been estimated that 20% of patients with massive cerebellar infarction deteriorate clinically as a result of mass effect of the infarct volume. (56) Patients should therefore be monitored for signs of increased intracranial pressure such as headache, vomiting, lethargy or neurologic deterioration, as well as hypertension, bradycardia, or irregular respiratory pattern. The neurosurgical treatment for malignant cerebellar infarctions is suboccipital decompressive craniectomy. Since the first reports of surgical treatment for massive cerebellar infarcts in 1956, (284, 285) several studies showed that suboccipital decompressive craniectomy is a life-saving procedure. (286) Current European (287) and US (60) guidelines recommend that suboccipital decompressive craniectomy with dural expansion, together with ventriculostomy to relieve obstructive hydrocephalus, should be performed in patients who deteriorate due to oedema after cerebellar infarction (Level 1, Class B evidence). Current evidence is based on observational studies, as there are no randomized controlled trials on this topic due to the lack of equipoise of withdrawing a life-saving treatment, which would raise major ethical concerns and likely lead to high crossover rates between the two treatment arms. A meta-analysis (288) of eleven retrospective studies (n=283 patients) showed that the pooled event rate for moderate-severe disability after suboccipital decompressive craniectomy was 28% (95% CI 0.2-0.37), with a mortality rate of 20% (95% CI 0.12-0.31) and an estimated rate of post-surgery complications of 23% (95% CI, 0.14-0.35). Timing of suboccipital decompressive craniectomy was variable, ranging from 24 hours to 4 days after the stroke. Sensitivity analyses found less mortality in patients younger than 60 years old and who had concomitant external ventricular drain insertion, and debridement of infarcted tissue. Improved functional outcomes were associated with a shorter time to surgery (modified Rankin Scale 3-5, 16% [95% CI 7-30] in patients treated <48 hours versus 30% [95% CI 21-42]) in patients treated >48 hours] and a higher pre-operative Glasgow Coma Scale (modified Rankin Scale 3-5, 22% [95% CI 16-28]) in patients with Glasgow Coma Scale 9-15 versus 37% [95% CI 7-81] in patients with Glasgow Coma Scale 0-8). Based on the current evidence, suboccipital decompressive craniectomy for cerebellar infarction appears to be safe and associated with substantially reduced mortality and improved long-term outcomes, (289) particularly when is performed in a timely fashion in non-comatose and younger than 60 years old patients. (288)

Neuroprotectant agents

Neuroprotection agents aim to either “freeze” the ischemic penumbra to allow extension of the time window for reperfusion therapies or to reduce secondary injury after reperfusion. Several negative phase III trials failed to translate successes in animal models to clinical practice, (290, 291) and neuroprotectants do not currently have a role in ischaemic stroke management. However, there are promising avenues that need further testing. For instance, neuroprotection may have a role prior to the commencement of reperfusion therapies (e.g. in the pre-hospital setting) or during secondary inter-hospital transfers for endovascular therapy. (292) The FAST- MAG trial tested prehospital intravenous magnesium sulfate administered by paramedics as a possible neuroprotectant in acute stroke in n=1700 participants. (293) This study found that pre-hospital use of magnesium sulfate as neuroprotective agent in acute stroke was safe and allowed the commencement of therapy within 2 hours after the onset of stroke symptoms (median symptom onset to drug administration time 45 minutes). However, there was no significant shift in the distribution of 90-day disability outcomes on the modified Rankin scale between patients in the magnesium group and those in the placebo group (p=0.28). (293)

A recently published human phase III trial (294) compared the inhibitor of neuronal excitotoxicity nerinetide to placebo in patients undergoing endovascular therapy. The trial failed to demonstrate the benefit of nerinetide compared to placebo (modified Rankin Scale 0-2, adjusted relative risk 1.04 [95% CI 0.96-1.14, p=0.35]). However, pre-specified subgroup analysis of patients who did not receive alteplase demonstrated a significant benefit of the drug. A further trial of nerinetide in patients ineligible for thrombolysis is ongoing (ClinicalTrials.gov registration: NCT04462536). Alternative approaches such as collateral circulation enhancement, (e.g. head positioning) (295), or induced hypothermia have also failed to show significant benefit in ischaemic stroke. (296, 297)

Thesis aims

The aim of this thesis was to investigate and determine clinical and imaging prognostic factors of outcome and treatment response in patients with posterior circulation ischaemic stroke.

The specific aims of this thesis were:

1) to assess the prognostic value of pc-ASPECTS on CT perfusion in patients with vertebrobasilar artery occlusion in comparison with CTA-SI.

2) to evaluate whether collaterals and thrombus burden influence the associations between revascularization, time-to-treatment, and outcome patients with basilar artery occlusion treated with endovascular therapy.

3) to develop and validate a modified version of the NIHSS, the Posterior NIHSS (POST-NIHSS), to improve the prognostic accuracy of NIHSS for posterior circulation stroke patients with mild-moderate symptoms.

4) to push boundaries for treatment in patients with basilar artery occlusion by determining whether tenecteplase is associated with better reperfusion rates than alteplase prior to endovascular therapy in basilar artery occlusion.

We created the Basilar Artery Treatment and MANagement (BATMAN) collaboration, an international multicentre prospective registry involving recruiting sites in Australia, New Zealand, Europe and the USA aiming to answer clinical questions regarding this devastating and under-researched form of stroke. The BATMAN registry has a retrospective and prospective arm, with 12 recruiting sites across the world [Royal Melbourne Hospital

(Melbourne, Australia); Austin Hospital (Melbourne, Australia); John Hunter Hospital, (Newcastle, Australia); Royal Adelaide Hospital (Adelaide, Australia); Princess Alexandra Hospital (Brisbane, Australia); Christchurch Hospital (Christchurch, New Zealand); University Hospital of Tor Vergata (Rome, Italy); Careggi University Hospital (Florence, Italy); IRCCS Neurological Institute C. Mondino and Policlinico S. Matteo (Pavia, Italy); University Hospital Motol (Prague, Czech Republic); Sainte Anne Hospital Center (Paris, France); Mount Sinai Hospital (New York, USA). Additional retrospective data from the BASICS registry was provided and used for the work presented in Chapter 2.

CHAPTER 1. Prognostic value of pc-ASPECTS on CT perfusion in patients with vertebra-basilar artery occlusion.

Research

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Cerebral blood volume lesion extent predicts functional outcome in patients with vertebral and basilar artery occlusion

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Abstract

Background: CT perfusion may improve diagnostic accuracy in posterior circulation stroke. The posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS) on Computed Tomography Angiography source images (CTA-SI) predicts functional outcome in patients with basilar artery occlusion.

Aims: We assessed the prognostic value of pc-ASPECTS on CT perfusion in patients with vertebral and basilar artery occlusion (VBAO) in comparison with CTA-SI.

Methods: Whole-brain CT perfusion from consecutive stroke patients with VBAO at four stroke centers was retrospectively analyzed. pc-ASPECTS – a 10-point score assessing hypoattenuation on CTA-SI – was calculated from CT perfusion parameters as focally reduced cerebral blood flow or cerebral blood volume, focally increased time to peak of the deconvolved tissue residue function (Tmax) or mean transit time. Two investigators independently reviewed the images. Reliability was assessed with intraclass correlation coefficient. Good outcome was defined as modified Rankin scale ≤ 3 at three months.

Results: We included 60 patients with VBAO. After assessment of four CT perfusion maps simultaneously, area-under-ROC curve (AROC) was 0.83 (95%CI 0.72–0.93) for cerebral blood volume, 0.76 (95%CI 0.64–0.89) for cerebral blood flow, 0.77 (95%CI 0.64–0.89) for Tmax, 0.70 (95%CI 0.56–0.84) for mean transit time versus area-under-ROC curve 0.64 (95%CI 0.50–0.79) for CTA-SI. Cerebral blood volume had greater accuracy compared with CTA-SI for poor outcome ($p = 0.04$). In logistic regression analysis, cerebral blood volume pc-ASPECTS ≤ 8 was independently associated with poor outcome (OR 9.3 95%CI 2.2–41; $p = 0.003$, adjusted for age and clinical severity). Inter-rater agreement was substantial for cerebral blood volume pc-ASPECTS (intraclass correlation coefficient 0.82 95%CI 0.71–0.90 versus 0.67 for CTA-SI 95%CI 0.43–0.81).

Conclusions: Cerebral blood volume pc-ASPECTS may identify VBAO patients at higher risk of disability.

Keywords
Cerebral blood volume, lesion, perfusion imaging, vertebrobasilar disease, prognosis, ASPECTS, reperfusion, stroke, vertebral artery occlusion, basilar artery occlusion

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Introduction

CT perfusion (CTP) increases diagnostic confidence in ischemic stroke by delineating the ischemic core and penumbra and identifying patients who may benefit from recanalization therapies. (101, 102) The Alberta Stroke Program Early CT score (ASPECTS) applied to CTP has been shown to be more accurate than non-contrast CT (NCCT) ASPECTS in identifying the extent of reversible and irreversible ischemia and predicting clinical outcome. (298, 299) Although CTP diagnostic accuracy in anterior circulation stroke is well established, (104) until recently its application remained challenging in posterior circulation stroke due to limited spatial coverage and the presence of beam hardening artifact. (105) The introduction of whole-brain coverage (97) has enabled the assessment of infratentorial structures and CTP has been shown to improve diagnostic sensitivity compared to NCCT. (106) In recent studies, a protocol including NCCT, Computed Tomography Angiography source images (CTA-SI) and CTP predicted a posterior circulation infarct with higher accuracy in comparison with NCCT and combined NCCT and CTA-SI. (107, 108) Approximately one-fifth of all stroke occurs in the posterior circulation arteries with 1% due to basilar artery occlusion (BAO), which is associated with high morbidity and mortality. (63) BAO patients were excluded from the recent randomized controlled trials (239) and the largest prospective observational study reported outcomes in patients treated with thrombectomy that were not significantly better than those treated with thrombolysis. (65) Guidelines recommend that the use of endovascular therapy is reasonable for patients with acute ischemic stroke due to vertebral and basilar artery occlusion (VBAO). (250) However, the identification of predictors of outcome and treatment response is useful in this uncertain scenario. The posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS) on CTA-SI predicts poor outcome in patients with BAO (119, 121) but does not discriminate between the ischemic core and penumbra and it has not been routinely adopted in treatment decision-making. Diffusion-weighted imaging (DWI) MRI is widely recognized as the reference standard for detection of posterior ischemic strokes and the prognostic value of pc-ASPECTS on DWI has been reported. (125) However, CTP is more readily available than MRI in the acute setting with advantages in speed of imaging and fewer contraindications. (101) We assessed the prognostic value of pc-ASPECTS on CTP maps in patients with posterior circulation stroke due to VBAO.

Methods

Clinical and radiological data were retrospectively collected from prospective databases of consecutive stroke patients treated at the Royal Melbourne Hospital (Melbourne, Australia), the John Hunter Hospital, University of Newcastle (New South Wales, Australia), the Royal Adelaide Hospital (Adelaide, Australia) and the University Hospital of Tor Vergata (Rome, Italy) between January 2013 and April 2017. Inclusion criteria were the presence of acute neurological deficits due to VBAO confirmed on CTA and whole-brain CTP performed within 24 h from symptoms onset. Reasons for exclusion were poor image quality and incomplete coverage of all pc-ASPECTS regions. Baseline demographic and clinical characteristics were recorded. Eligible patients received intravenous thrombolysis followed by endovascular treatment (EVT) or proceeded directly to EVT, in accordance with current guidelines. Successful reperfusion was assessed by the modified treatment in cerebral infarction (mTICI) scale and defined as TICI 2b-3. (300) Favorable outcome was defined as modified Rankin scale 3 at three months, consistent with the definition used in previous studies of BAO. (65) The Melbourne Health Human Research Ethics Committee approved this study under a waiver of consent. Imaging protocol NCCT, CTP and CTA were performed using a multidetector CT scanner 128-slice Definition FLASH (Siemens Healthcare, Forchheim, Germany) at Royal Melbourne Hospital, (Melbourne, Australia), a

CT Somatom Definition AS (Siemens Healthcare, Forchheim, Germany) at the Royal Adelaide Hospital (Adelaide Australia), a 64-slice Brilliance (Philips, Cleveland, USA) or 320-slice Aquilion One (Toshiba Medical Systems, Otawara, Japan) scanners at the John Hunter Hospital, University of Newcastle, (New South Wales, Australia) and a LightSpeed VCT 64-slice multidetector CT scanner (GE Healthcare, Waukesha) at the University Hospital of Tor Vergata, (Rome, Italy). Images were obtained every 1.5–3 s for 60 s after an initial 4 s delay with 40 mL contrast (Omnipaque 350, GE Healthcare, Princeton, NJ, USA) injected at 8 mL/s. CTP maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to maximum of the deconvolved tissue-concentration curve (Tmax) were produced using RAPID software (Stanford University, CA, USA) or GE Healthcare CT Perfusion 4D (Milwaukee, WI, USA). The neuroimaging data were reviewed using the institutional Picture and Archiving System.

Imaging analysis

The pc-ASPECTS was calculated based on hypoattenuation on CTA-SI and on perfusion abnormalities for each CTP map type. Beginning with 10 points for a normal CT scan, regional abnormalities were scored, and one point subtracted for involvement of each of the left or right thalamus, cerebellum or posterior cerebral artery (PCA) territory, and two points subtracted for involvement of each of the midbrain or pons. pc-ASPECTS was assessed as evident hypoattenuation on CTA-SI after window and level adjustment to allow maximum contrast differentiation on 0.75-mm to 5.0-mm slice thickness. (119, 121) We rated focally reduced CBF or CBV, focally increased time to peak of the residue function (Tmax) or MTT on CTP maps as abnormal in comparison with nonaffected regions (i.e. contralateral side, different vascular territories). Quantitative thresholds were not used. Two investigators experienced in stroke imaging (FA and DGS) independently scored pc-ASPECTS on CTA-

SI, blinded to CTP data and clinical outcome. After two weeks, pc-ASPECTS was assessed on each CTP map in isolation, blinded to other CTP maps, CTA-SI and clinical outcome. Subsequently, all four CTP maps (Tmax, MTT, CBF, CBV) were visualized simultaneously (as one would do in clinical practice) and pc-ASPECTS was determined for each map, blinded to CTA-SI and clinical outcome. Intraclass correlation coefficient (ICC) was then calculated. In case of disagreement, the final score was reached by consensus between the two investigators. CTP pc-ASPECTS mismatch was then considered as CBV pc-ASPECTS minus Tmax > 6 s pc-ASPECTS. Statistical analysis Statistical analyses were performed using IBM SPSS version 23 software (IBM SPSS Statistics, Armonk, NY). Univariate data analysis was performed using Fisher Exact test for categorical variables and the Mann–Whitney U test for continuous data. Multivariable binary logistic regression was performed including covariates with $p < 0.1$ [age and National Institutes of Health Stroke Scale (NIHSS)] in univariate analysis, separately for each CTP and CTA-SI parameter. Bayesian information criterion (BIC) was used as a scalar measure to compare the overall goodness of fit for regression models. Lower BIC with differences >10 indicates a very strong evidence of model superiority. (301) Receiver operating characteristic (ROC) analysis was used and compared (302) to assess prognostic performance. Optimal thresholds were determined (Youden index). ICC was used to assess inter-rater agreement.

Results

Overall, 60 patients with VBAO were included during the study period after 13 were excluded due to incomplete brain coverage or poor image quality and 2 for missing follow-up. Among them, 33 patients had a BAO, 16 a BAO combined with a vertebral artery occlusion and 11 an isolated vertebral artery occlusion. In 51 patients (85%), CTP was performed within 6 h from stroke onset and in 9 patients (15%) between 6 and 12 h. In 40 patients, MRI was performed within seven days from onset. Good outcome occurred in 28 (47%) patients. In univariate analysis, higher NIHSS and coma were significantly associated with poor outcome (Table 1). Prognostic accuracy of pc-ASPECTS on CTP versus CTA-SI. Whole-brain coverage CTP allowed assessment of all pc-ASPECTS regions in all included patients. MTT maps were not assessed in three patients because of artifacts. pc-ASPECTS median values in all imaging modalities and regions of interest are summarized in Tables 1 and 2. Figure 1 shows an illustrative case.

In univariate analysis, pc-ASPECTS on all imaging parameters was significantly associated with poor outcome (Table 1). In ROC analysis for poor outcome, the area-under-ROC curve (AROC) did not differ significantly between map types: 0.72 (95%CI 0.58–0.85) for CBV, 0.70 (95% CI 0.56–0.83) for CBF, 0.72 (95% CI 0.58–0.82) for Tmax, 0.69 (95% CI 0.55–0.82) for MTT compared to AROC 0.64 (95% CI 0.50–0.79) for CTA-SI. After assessment of all four maps simultaneously, the general performance of CTP pc-ASPECTS tended to improve for each of the map types with an AROC of 0.83 (95% CI 0.72–0.93) for CBV, 0.76 (95%CI 0.64– 0.89) for CBF, 0.77 (95% CI 0.64–0.89) for Tmax, 0.70 (95% CI 0.56–0.84) for MTT. CBV was the only modality which showed significantly higher accuracy in comparison with CTA-SI AUC for poor outcome (p=0.04). In our sample, the optimal dichotomy of CBV pc-ASPECTS to predict poor outcome was 8 (sensitivity 59.5% and specificity 89%; positive predictive value 86.4%, negative predictive value 66%). The previously validated dichotomy of pc-ASPECTS < 8 (119, 125) was associated with poor outcome with a sensitivity of 25% and a specificity of 100% (positive predictive value 100%, negative predictive value 54%). Among patients with pc-ASPECTS < 8, five (62.5%) died and three had severe disability at three months. The distribution of mRS according to CBV pc-ASPECTS groups is shown in Figure 2.

In logistic regression analysis adjusted for age and clinical severity, unfavorable CBV pc-ASPECTS (defined as pc-ASPECTS 0-8), was independently associated with poor outcome (OR 9.3 95%CI 2.2–41; p=0.003, online Supplement Table I). Although CTA-SI pc-ASPECTS was associated with poor outcome after adjustment for age (OR 5.7, 95%CI 1.1–30; p=0.04), this association was less robust following adjustment for NIHSS (OR 4.3 95%CI 0.8–24, p=0.09, online Supplement Table II).

Moreover, the model including CBV pc-ASPECTS, age and NIHSS performed better (BIC 63) than the model including age and NIHSS (BIC 76) or age, NIHSS and CTA-SI (BIC 75). In logistic regression analysis adjusted for the presence of coma and age, CBV pc-ASPECTS remained significantly associated with poor outcome (OR 11, 95%CI 2.4–51; p=0.002). Mismatch pc-ASPECTS (defined as CBV pc-ASPECTS minus Tmax pc-ASPECTS) was not associated with outcome (p=0.3). CBV pc-ASPECTS was moderately correlated with DWI pc-ASPECTS (r=0.423; p=0.007) and CTA-SI pc-ASPECTS (r=0.497; p<0.001). ICC demonstrated good interrater reliability for single CTP maps which improved after assessment of all four maps (Tmax 0.85 95%CI 0.74–0.91; MTT=0.84, 95%CI 0.73–0.91; CBV 0.82 95%CI 0.71–0.90; CBF 0.76 95%CI 0.61–0.86) versus 0.67 for CTA-SI 95%CI 0.43–0.81 (Table 2).

CBV pc-ASPECTS in patients with BAO

After exclusion of 11 patients with isolated vertebral artery occlusion, there were 49 BAO patients (mean age 69 ± 16, median NIHSS 15 (interquartile range, IQR 5–28). Good outcome occurred in 21 patients (43%). Median pc-ASPECTS was 9.5 (IQR 9–10) on CTA-SI, 8 (IQR 7–9) on Tmax, 8 (IQR 8–9) on MTT, 9 (IQR 8–10) on CBF, 9 (IQR 8–10) on CBV. In logistic regression analysis adjusted for age and NIHSS, unfavorable CBV pc-

ASPECTS was significantly associated with poor outcome (OR 10.5, 95%CI 2.4–48, p = 0.002, online Supplement Table I) but CTA-SI was not (OR 5.3 95%CI 0.9–30, p = 0.06, online Supplement Table II). Twenty-five patients underwent endovascular therapy: 24 mechanical thrombectomy and 1 intra-arterial therapy with urokinase. In logistic regression analysis adjusted for age and NIHSS, lower CBV pc-ASPECTS was significantly associated with poor outcome (OR 0.1, 95%CI 0.007–0.65; p= 0.02). This association remained after adjustment for age, NIHSS and recanalization status (OR 0.04, 95% CI 0.003–0.6, p=0.02). Successful recanalization occurred in 10/14 (71.5%) patients with favorable CBV pc-ASPECTS and in 9/11 (82%) with unfavorable pc-ASPECTS (p=0.7).

Discussion

CBV pc-ASPECTS was more strongly associated with functional outcome than CTA-SI in VBAO patients. This is in agreement with several studies that have shown that CBV ASPECTS is more strongly associated with functional outcome compared with baseline CT and CTA-SI ASPECTS in anterior circulation strokes (298, 299, 303) and extends previous work that demonstrated improved diagnostic accuracy with CTP in posterior circulation stroke.(107, 108) In a recent study from the BASICS collaboration, Pallesen et al. (123) explored the prognostic value of pc-ASPECTS on CTP but were limited by a small sample size (n=27) and incomplete CTP coverage (the pons was imaged in only 19% of patients). Despite this, they found that an extensive lesion on CBV maps (pc-ASPECTS < 8) was associated with high case fatality. These results are consistent with our findings. In our sample, mismatch was not associated with functional outcome. Although these findings should be carefully interpreted given the small sample of our population and the visual assessment of the ischemic changes, it is likely that a relatively high rate of revascularization has led to the extent of the ischemic core being more strongly related to outcome than the extent of penumbra. (298) Recent studies have shown a very good inter-rater agreement for CBV ASPECTS in the anterior circulation. (299, 304) In our study, we assessed pc-ASPECTS reliability on CTP maps. Reliability improved when each map was assessed in the context of the other maps, likely due to better recognition of artifacts. The inter-rater agreement for pc-ASPECTS on all CTP maps was higher than CTA-SI in our analysis and higher than the inter-rater agreement reported in the original study of Puetz et al. (119) Most of the ischemic changes in our patients were detected in the cerebellum and in the occipital regions with low detection rate of ischemic changes in brainstem and thalami. Indeed, assessment of ischemic changes in the brainstem remains challenging due to beam hardening artifact in both CTP and CTA-SI imaging modalities and this may have affected our results and explained the higher cut-off value in comparison with previous studies. (119, 121) However, these cut-offs were identified in BAO cases presenting with higher NIHSS (median 22 and 25) in comparison with ours. Moreover, to our knowledge, the optimal CBV pc-ASPECTS cut-off has not yet been ascertained. CBV pc-ASPECTS can be assessed without the need for volumetric software and may be a useful prognostic marker with potential implications for treatment decision-making and a possible role in future trials investigating the benefit of endovascular therapy in VBAO, although an external validation is needed. Our study emphasizes the potential value of including whole-brain CTP in the diagnostic evaluation of patients with VBAO. The main limitation of this study is its retrospective nature and the small number of patients. Beam hardening artifact may have reduced the accuracy of assessment of brainstem ischemic lesions. Different treatment protocols, scanners and software were used between the four centers for the acquisition of CTP images with variable number of slices and thickness. However, these differences increase the generalizability of our results.

Conclusions

This study showed that visual assessment of CTP pc-ASPECTS may represent a useful tool in the acute setting to recognize VBAO patients at higher risk of disability and mortality. Careful patient selection is likely to improve outcomes in VBAO patients treated with endovascular therapies. Further studies with CTP maps used as a parameter for treatment decision-making are warranted.

Table 1. Comparison of patient characteristics between those with good and poor outcomes.

	All patients (n = 60)	Good outcome (n = 28)	Poor outcome (n = 32)	P
Age (years), mean	68±16	64±17	71±14	0.07
NIHSS, median (IQR)	11 (3–22)	4.5 (2–15)	14 (11–30)	0.002
Coma, n(%)	14 (23)	2 (7)	12 (37.5)	0.006
Male sex, n(%)	41 (68)	19 (68)	22 (69)	0.9
Risk factors, n(%)				
Hypertension	40 (67)	19 (68)	21 (66)	0.9
Hypercholesterolemia	20 (33)	9 (32)	11 (34)	0.9
Diabetes mellitus	13 (22)	6 (21)	7 (22)	0.9
Atrial fibrillation	18 (30)	7 (25)	11 (34)	0.4
Smoking	9 (15)	4 (14)	5 (16)	0.9
Coronary artery disease	14 (23)	5 (18)	9 (28)	0.3
Previous TIA/stroke	14 (23)	8 (29)	6 (19)	0.5
Site of vessel occlusion, n(%)				
Basilar artery				
Proximal	24 (40)	9 (32)	15 (47)	0.4
Middle	15 (25)	5 (18)	10 (31)	0.4
Distal	30 (50)	12 (43)	15 (47)	0.6
Posterior cerebral artery	20 (33)	6 (21)	14 (44)	0.1
Vertebral artery	27 (45)	11 (39)	16 (50)	0.6
Stroke cause, n(%)				
Cardioembolic	20 (33)	6 (21)	14 (44)	0.1
Atherosclerotic	17 (28)	8 (29)	9 (28)	
Other	5 (8)	5 (18)	0	
Undetermined	18 (30)	9 (32)	9 (28)	
Intravenous thrombolysis, n(%)	28 (47)	12 (43)	16 (50)	0.6
Endovascular treatment, n(%)	25 (42)	9 (32)	16 (50)	0.2
Onset time to imaging, min(IQR)	134.5 (67–251)	105 (68–180)	180 (64–283)	0.4
Onset time to treatment, min(IQR)	295 (177–428)	224 (120–352)	347 (268–430)	0.2
pc-ASPECTS CTA-SI, median(IQR)	10 (9–10)	10 (10–10)	9 (9–10)	0.009
pc-ASPECTS Tmax, median(IQR)	8 (7–9)	9 (8–10)	7.5 (5–9)	0.001
pc-ASPECTS MTT, median(IQR)	9 (8–10)	9 (8–10)	8 (7.5–9)	0.007
pc-ASPECTS CBF, median(IQR)	9 (8–10)	9 (9–10)	8 (7–9)	0.001
pc-ASPECTS CBV, median(IQR)	9 (8–10)	10 (9–10)	8 (7–9)	<0.001
pc-ASPECTS MRI, median(IQR)	8 (7–9)	8 (8–9)	7.5 (6–8)	0.03

CBF: cerebral blood flow; CBV: cerebral blood volume; CTA-SI: CT angiography source images; MTT: mean transit time; NIHSS: National Institutes of Health Stroke Scale; pc-ASPECTS: posterior circulation Acute Stroke Prognosis Early CT score; TIA: transient ischemic attack; Tmax: time to maximum of the deconvolved tissue-concentration curve; TOAST: Trial of Org 10172 in Acute Stroke Treatment classification; IQR: interquartile range. Good outcome mRS 0–3, poor outcome mRS 4–6 at three months. Three patients did not receive treatment because of extensive early ischemic changes on admission non-contrast computed tomography.

Table 2. Localization of the ischemic changes and inter-rater agreement for CTP pc-ASPECTS.

	CTA-SI	Tmax	MTT	CBF	CBV
Localization, n(%)					
Cerebellum	11 (18)	44 (73)	32 (56)	28 (47)	25 (42)
Pons	3 (5)	7 (12)	4 (7)	5 (8)	4 (7)
Midbrain	2 (3)	6 (10)	3 (5)	6 (10)	4 (7)
PCA territory	4 (7)	18 (30)	13 (23)	7 (12)	7 (12)
Thalamus	3 (5)	9 (15)	5 (9)	5 (8)	4 (7)
Inter-rater agreement single map (95%CI)	0.67 (0.43–0.81)	0.80 (0.67–0.89)	0.78 (0.64–0.87)	0.72 (0.54–0.84)	0.73 (0.57–0.84)
Inter-rater agreement 4 maps (95%CI)		0.85 (0.74–0.91)	0.84 (0.73–0.91)	0.76 (0.61–0.86)	0.82 (0.71–0.90)

CBF: cerebral blood flow; CBV: cerebral blood volume; CI: confidence interval; CTA-SI: CT angiography source images; MTT: mean transit time; Tmax: time to maximum of the deconvolved tissue-concentration curve. In three cases MTT was not assessed for artifacts.

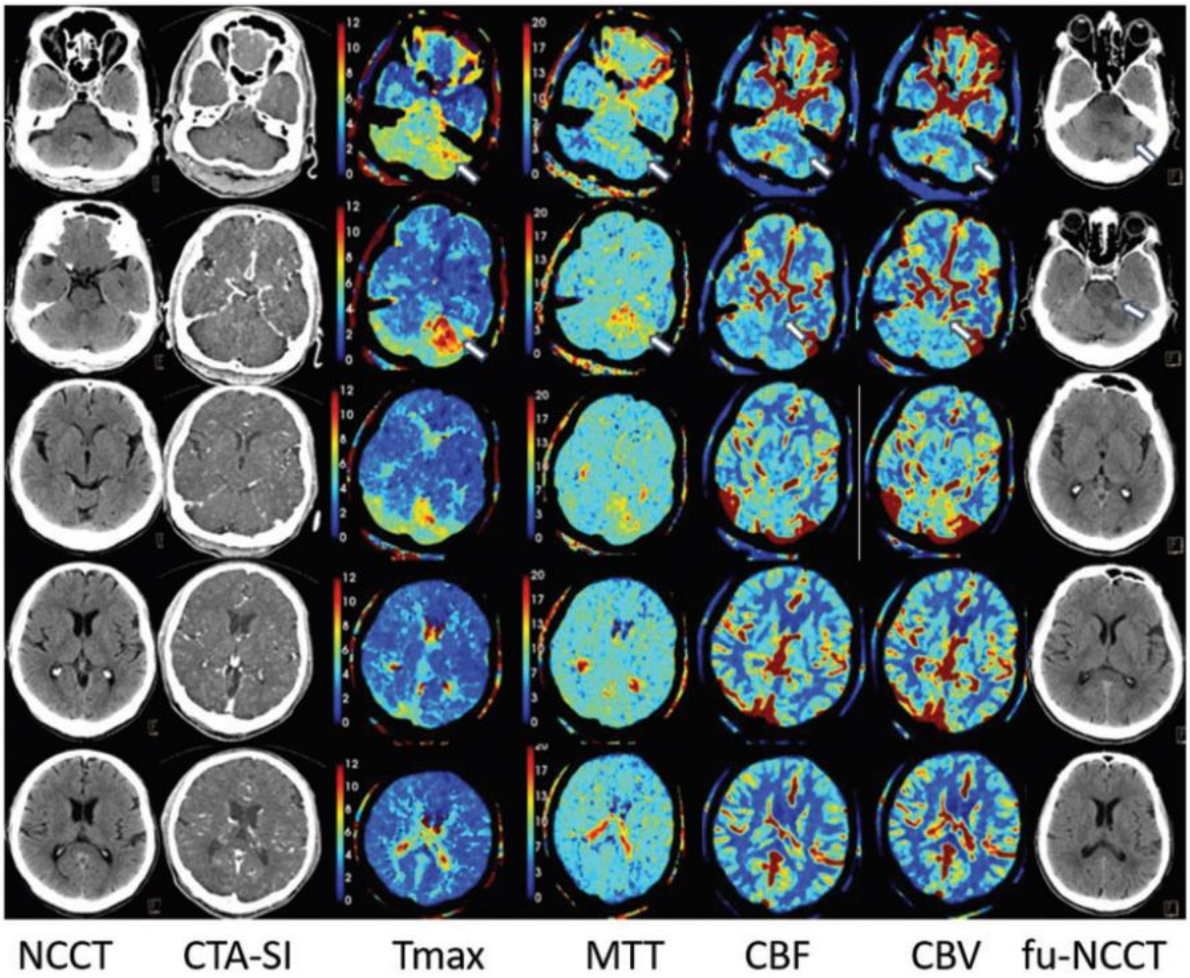

Figure 1. CBV pc-ASPECTS = 7 in patients with ischemic changes in the left cerebellum and brainstem on CTP maps. CBF: cerebral blood flow; CBV: cerebral blood volume; CTA-SI: CTangiography source images; fu-NCCT: follow-up NCCT; MTT: mean transit time; NCCT: non-contrast CT; Tmax: time to maximum of the deconvolved tissue-concentration curve.

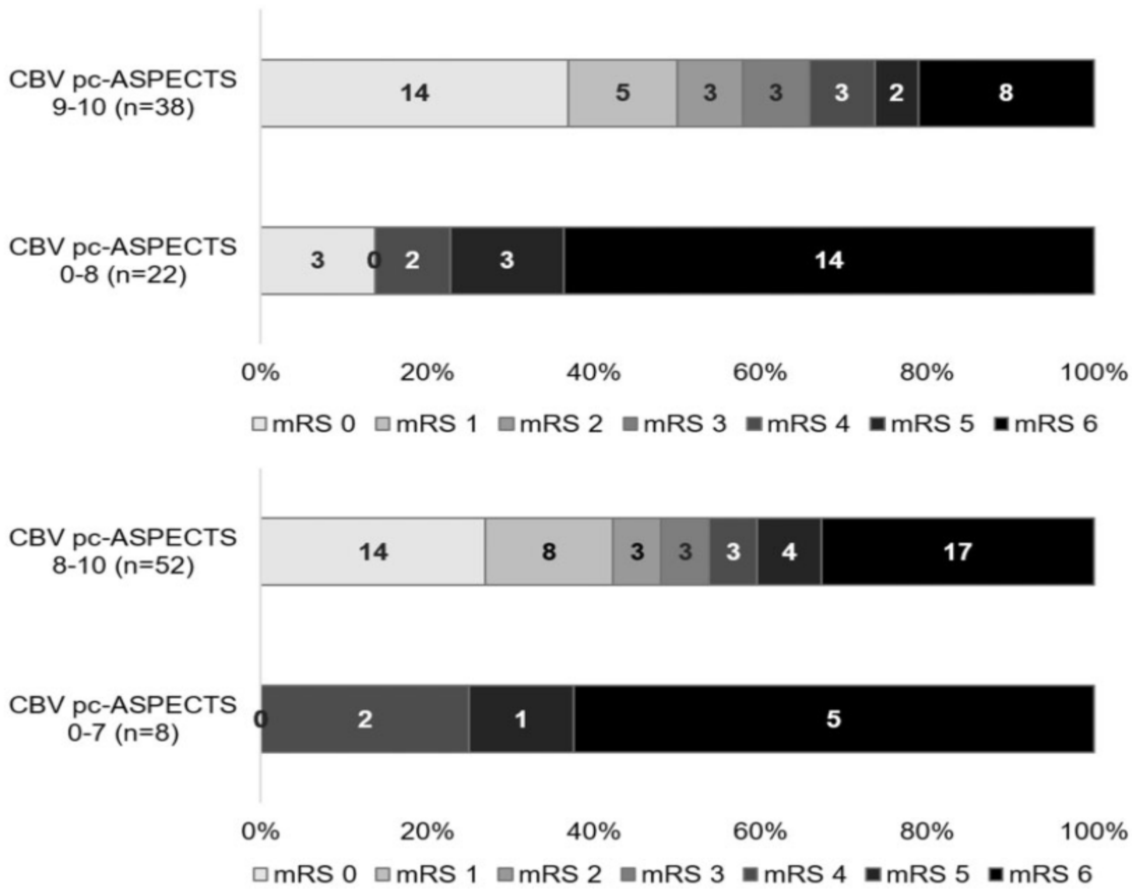

Figure 2. Distribution of modified Rankin scale (mRS) at three months according to dichotomized CBV pc-ASPECTS groups.CBV: cerebral blood volume; pc-ASPECTS: posterior circulation Acute Stroke Prognosis Early CT score.

Table I. Multivariable logistic regression analysis including CBV pc-ASPECTS in all vertebrobasilar occlusion patients and the subgroup with basilar artery occlusion.

	VBAO* patients (n=60)			BAO† patients (n=49)		
	OR‡	95% CI§	P	OR	95% CI	P
Age	1.0	0.9-1.1	0.2	1.0	0.9-1.1	0.6
NIHSS‖	1.0	0.9-1.1	0.1	1.0	0.9-1.1	0.2
CBV# pc-ASPECTS**	9.3	2.2-41	0.003	10.5	2.4-48	0.002

*VBAO vertebrobasilar artery occlusion, †BAO basilar artery occlusion, ‡OR Odds Ratio, §CI Confidence Interval, ‖NIHSS National Institutes of Health Stroke Scale, #CBV cerebral blood volume, **pc-ASPECTS posterior circulation Acute Stroke Prognosis Early CT score.

Table II. Multivariable logistic regression analysis including CTA-SI pc-ASPECTS in all vertebrobasilar occlusion patients and the subgroup with basilar artery occlusion.

	VBAO* patients (n=60)			BAO† patients (n=49)		
	OR‡	95% CI§	P	OR‡	95% CI§	P
Age	1.0	0.9-1.1	0.2	1.0	0.9-1.1	0.5
NIHSS‖	1.0	0.9-.1.1	0.06	1.0	0.9-1.1	0.1
CTA-SI# pc-ASPECTS**	4.3	0.8-24	0.09	5.3	0.9-30	0.06

*VBAO vertebrobasilar artery occlusion, †BAO basilar artery occlusion, ‡OR Odds Ratio, §CI Confidence Interval, ||NIHSS National Institutes of Health Stroke Scale,#CTA-SI CT Angiography source images, **pc-ASPECTS posterior circulation Acute Stroke Prognosis Early CT score.

CHAPTER 2. Effect of collaterals and thrombus burden on the associations between revascularization, time-to-treatment, and outcome in patients with basilar artery occlusion.

Original Contribution

Response to Late-Window Endovascular Revascularization Is Associated With Collateral Status in Basilar Artery Occlusion

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Background and Purpose**—**The benefit of endovascular therapy in extended time windows has been demonstrated in patients with anterior circulation large vessel occlusion ischemic stroke and favorable imaging profile. We evaluated whether collaterals and thrombus burden influence the associations between revascularization, time-to-treatment, and outcome in endovascular therapy-treated patients with basilar artery occlusion.

Methods**—**We retrospectively analyzed clinical and imaging data of consecutive endovascular therapy-treated patients with basilar artery occlusion included in the multicenter Basilar Artery Treatment and Management Collaboration. The BATMAN (Basilar Artery on Computed Tomography Angiography score, which evaluates thrombus burden and collaterals) and the PC-CS (Posterior Circulation Collateral score, which evaluates collaterals) were assessed on computed tomography angiography, blinded to clinical outcome. Good outcome was defined as modified Rankin Scale score of ≤3 within 3 months; revascularization (successful reperfusion) as modified Thrombolysis in Cerebral Infarction 2b–3 (or TIMI [Thrombolysis In Myocardial Infarction] 2–3 in the BASICS [Basilar Artery International Cooperation Study] registry).

Results**—**We included 172 patients with basilar artery occlusion treated with endovascular therapy (124 with mechanical thrombectomy): mean (SD) age 65 (13) years, median National Institutes of Health Stroke Scale 22 (interquartile range 12–30), 64 (37%) treated >6 hours. Revascularization (achieved in 79% of patients) was associated with good outcome (*P*=0.003). The use of new generation thrombectomy devices was associated with good outcome (*P*=0.03). In patients who achieved revascularization, 29/46 (63%) of patients with a favorable BATMAN score and 26/51 (51%) with favorable PC-CS had good outcomes. In logistic regression analysis (adjusted for age, National Institutes of Health Stroke Scale, and time-to-treatment ≤6/>6 hours), revascularization was associated with good outcome in patients with favorable BATMAN score (odds ratio, 15.8; 95% CI, 1.4–175; *P*=0.02) or PC-CS (odds ratio, 9.4; 95% CI, 1.4–64; *P*=0.02). In patients who achieved revascularization, early (time-to-treatment ≤6 hours) but not late treatment was associated with improved outcome in patients with unfavorable BATMAN score (18/52 [35%]; odds ratio, 15; 95% CI, 1.9–124; *P*=0.01) or PC-CS (16/44 [36%]; odds ratio, 5.5; 95% CI, 1.4–21; *P*=0.01).

Conclusions**—**Revascularization is associated with good outcome in patients with basilar artery occlusion with good collaterals and less extensive occlusion, even >6 hours after onset. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.118.023361.)**

Key Words: basilar artery ■ computed tomography angiography ■ reperfusion ■ stroke ■ thrombectomy ■ time-to-treatment

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*A list of all Basilar Artery Treatment and Management (BATMAN) Collaboration participants is given in the Appendix.

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Introduction

The benefit of endovascular therapy (EVT) for large vessel occlusion (LVO) anterior circulation ischemic stroke decreases as time-to-treatment (TTT) increases. (239, 241) However, the benefit of EVT in extended time windows has been shown in patients with anterior circulation LVO ischemic stroke and favorable imaging profiles, (246, 247) and the association of TTT with outcome can be modified by collateral status. (305) Good collateral circulation protects cortical areas and maintains ischemic penumbra, leading to improved outcome after EVT. (306, 307) Moreover, the benefit of revascularization is associated with TTT in patients with poor collaterals, but this association is weaker in patients with good collaterals (305-307) who seem to tolerate ischemia for longer times. Basilar artery occlusion (BAO) remains a devastating subtype of stroke with high rates of mortality and disability. (23, 62, 63) Patients with BAO were excluded from the randomized controlled trials which showed the benefit of EVT within 6 hours and in extended time windows. (239, 246, 247) The BASICS (Basilar Artery International Cooperation Study) registry, the largest prospective observational study in BAO, showed similar outcomes in patients treated with intravenous thrombolysis (IVT) and EVT. (65) However, the lack of robust imaging selection criteria, as well as the use of early generation devices, may have affected these results. Better outcomes were observed in 4 out of 8 patients who received intraarterial urokinase compared with 1 of 8 controls in the small Australian Urokinase Stroke Trial. (255) Although the recent BEST trial (Basilar Artery Occlusion Endovascular Intervention versus Standard Medical Treatment) was terminated prematurely and declared negative because of a high cross-over rate and non-significant differences in the intention to treat analysis, patients with BAO who were actually treated with EVT within 8 hours achieved better outcomes than patients treated with standard medical therapy. (262) Pending the results from the BASICS trial (URL: www.clinicaltrials.gov. Unique identifier: NCT01717755), the American Heart

Association/American Stroke Association guidelines which recommend EVT within 24 hours in selected LVO anterior circulation stroke patients (Class I, Level of Evidence A), still state that thrombectomy in BAO may be reasonable only in carefully selected patients within 6 hours of stroke onset (Class IIb, Level of Evidence C). (250) Revascularization of BAO has been shown to be associated with favorable outcome in observational data, (256, 308) but several studies did not establish an association between TTT and outcome. (173, 219) However, the BASICS study reported poor outcomes in patients with severe stroke treated beyond 9 hours. (179) In the recent ENDOSTROKE study (Endovascular Stroke Treatment), no association was found between TTT and clinical outcome, although there was a trend toward worse outcomes after 9 hours from stroke onset. In this study, collateral status was associated with functional outcome and revascularization. (131) Whether collaterals and thrombus burden influence the effect of revascularization on outcome in BAO treated with EVT in extended time windows is uncertain. A highly developed and persistent collateral network (ie, reverse filling of the distal basilar artery from the posterior communicating arteries [PComs] and secondary collateral pathways) may sustain the ischemic penumbra for >6 hours, and patients with good collaterals may benefit from EVT even in delayed time windows. The Basilar Artery on Computed Tomography Angiography (BATMAN) score (128) and the Posterior Circulation Collateral score (PC-CS) (127) are 2 recently described computed tomography angiography (CTA)-based vascular scores which have been shown to be associated with outcome in BAO. The aim of our study was to evaluate the effect of favorable imaging characteristics (low thrombus burden and good collaterals using the PC-CS and BATMAN score) on the associations between revascularization, TTT, and functional outcome.

Methods

Patients

We retrospectively analyzed clinical and imaging data from patients with BAO in the multicentre Basilar Artery Treatment and Management (BATMAN) collaboration which pooled consecutive patient databases from the Royal Melbourne Hospital and Royal Adelaide Hospital (Australia), University Hospital of Tor Vergata and Careggi University Hospital (Italy) (2009–2017), and from the international BASICS registry (2002–2007). EVT-treated patients with BAO between August 2002 and December 2017 who had sufficient quality of CTA images and available follow-up outcome data were included in the analysis. In BASICS, patients with acutely symptomatic and radiologically confirmed BAO were included. Treatment with IVT, EVT, or antithrombotic was at the clinician's discretion. The protocol has been detailed previously. (65) In the non-BASICS cohort, EVT (preceded by IVT in eligible patients) was performed within 24 hours from symptoms onset in patients with a symptomatic BAO demonstrated on CTA, in the absence of early extensive ischemic changes on baseline noncontrast CT brain. Treatment with old (Merci retriever in the BASICS registry) or new generation devices (Solitaire, Revive, Trevo, Penumbra, or Sophia aspiration catheters) was performed. Time of onset of symptoms was recorded as described by the patient or witness. If unknown, onset was considered to be the last time the patient was seen well. In patients presenting with mild symptoms followed by sudden onset of decrease in conscious state, the time of deterioration in clinical state was taken as estimated time of BAO. TTT was defined as the time from symptom onset (or in case of secondary worsening the estimated time of BAO) to arterial puncture and categorized into TTT of 0 to 6 hours and beyond 6 hours. The Melbourne Health Human Research Ethics Committee approved this study under a waiver of consent. There was no industry funding of the registries. The data that support the findings of this study are available from the corresponding author on request.

Imaging Analysis Neuroimaging data were collected in Digital Imaging and Communications in Medicine format and reviewed using the institutional Picture and Archiving System. The BATMAN score and the PC-CS were assessed on CTA images (Figure 1).

The PC-CS allocates collaterals a maximum of 10 points; 1 point for each patent posterior inferior cerebellar artery, anterior inferior cerebellar artery, and superior cerebellar artery, 1 point for each patent PCom smaller than the ipsilateral P1 segment of the posterior cerebral artery, and 2 points for each PCom with a caliber equal or larger than the ipsilateral P1 segment. The BATMAN score evaluates both the extent of BAO and the presence of collateral circulation from PComs. It allocates 1 point for each patent intracranial vertebral artery, 1 point for each patent segment of the basilar artery (the proximal segment [from the vertebrobasilar junction to the anterior inferior cerebellar arteries], the middle segment [from the anterior inferior cerebellar arteries to the superior cerebellar arteries], the rostral segment [from the superior cerebellar arteries to its rostral end]), 1 point for each patent P1 segment, 2 points for each non-fetal PCom, 1 point for a hypoplastic PCom (defined as diameter PCom, <1 mm8) or 3 points for each fetal PCom (to incorporate the point otherwise attributed to a patent P1 segment). Arterial patency is a surrogate for clot burden. (309) Two investigators experienced in stroke imaging (F. Alemseged, D. Shah, or F. Di Giuliano) independently reviewed the CTA images, blinded to clinical outcome and other imaging parameters. In case of disagreement, the final score was reached by consensus. Previously, validated dichotomies for favorable BATMAN score (≥7) and PC-CS (≥6) were used.

Outcome Measures

The primary objective of our study was to evaluate the effect of favorable imaging characteristics (low thrombus burden and good collaterals using the PC-CS and BATMAN score) on the associations between revascularization, TTT, and functional outcome. Good outcome was defined as modified Rankin Scale (mRS) score of 0–3 within 3 months (at 1 month in the BASICS registry11 and 3 months at the other sites), assessed by the site investigator. Revascularization (successful reperfusion) was assessed by the site investigator using the modified Thrombolysis in Cerebral Infarction scale and defined as Thrombolysis in Cerebral Infarction 2b–320 or the TIMI (Thrombolysis In Myocardial Infarction) scale and defined as TIMI 2–3 in the BASICS registry.(65)

Statistical Analysis

Statistical analyses were performed using SPSS (v.24, IBM, Armonk NY). Analysis of univariable data was performed using the Mann-Whitney U test for continuous data and Fisher Exact test for categorical variables. Multivariable binary logistic regression was performed with covariates included if $P<0.1$ in univariable analysis. The association between TTT and the distribution of outcomes on the mRS (shift analysis) was assessed using ordinal logistic regression analysis. All p values were 2 sided, and $p<0.05$ was considered significant.

<u>Results</u>

In the 592 patients of the BASICS registry, 304 patients were treated with antithrombotic treatment or IVT only and 288 patients with EVT. Among these, we included patients with available CTA images of sufficient quality (71/288). In the non-BASICS cohort, 30/131 patients with BAO were not treated with EVT because of mild symptoms or extensive early ischemic changes on baseline non-contrast CT brain. Overall, 172 patients were included during the study period (71 from the BASICS registry and 101 from the other sites); 124 patients were treated with mechanical thrombectomy and 48 with intraarterial urokinase. Data on final reperfusion status were available in 156/172 (91%) patients. Mean age was 65±13 and median National Institutes of Health Stroke Scale 22 (interquartile range 12–30). Sixty-four patients (37%) had TTT >6 hours. Favorable BATMAN score was present in 35/108 (32%) patients with TTT≤6 hours and 22/64 (34%) patients with TTT>6 hours. Revascularization was achieved in 123/156 (79%). Overall, 55/172 (32%) of patients achieved good outcomes within 3 months (41 [38%] treated ≤6 hours and 14 [22%] treated >6 hours [p=0.04]). Sixteen patients (9%) were treated >12 hours. In univariable analysis, younger age, lower National Institutes of Health Stroke Scale, IVT, TTT ≤6 hours, posterior circulation Alberta Stroke Program Early CT Score on CTA source images, revascularization, and mechanical thrombectomy using new generation devices were associated with good outcome. Higher BATMAN score and PC-CS were associated with good outcome (p≤0.01), even when considered as dichotomous variables, (p=0.001 for BATMAN score ≥7; p=0.02 for PC-CS ≥6). Baseline characteristics and findings of univariable analysis in patients with poor and good outcome are summarized in Table 1. Baseline characteristics were well matched between the early and late treatment groups with the exception of IVT group, Table 2. In patients who achieved revascularization (n=123), 29/46 (63%) patients with favorable BATMAN score and 26/51 (51%) with favorable PC-CS had good outcomes. In patients who did not achieve revascularization, 2/7 (29%) patients with favorable BATMAN score and 2/11 (18%) patients with favorable PC-CS had good outcomes. The rate of revascularization did not differ between patients with TTT ≤6 hours versus>6 hours (81% versus 76%; P=0.5) nor between patients with and without favorable BATMAN score (87% versus 75%; P=0.1) or PC-CS (82% versus 77%; P=0.4). In logistic regression analysis adjusted for age, National Institutes of Health Stroke Scale, and TTT dichotomized as ≤6 or >6 hours, revascularization was associated with good outcome among all patients (odds ratio [OR] 6.5; 95% CI, 1.8–24; P=0.004) and in those with favorable BATMAN score (adjusted OR, 15.8; 95% CI, 1.4–175;

P=0.02) or PC-CS (OR, 9.4; 95% CI, 1.4–64; P=0.02). No significant association was found between revascularization and good outcome in patients with unfavorable BATMAN score (OR, 3.9; 95% CI, 0.7–20; P=0.1) or PC-CS (OR, 4.8; 95% CI, 0.8–29; P=0.08). In patients who achieved revascularization, early (TTT≤6 hours) but not late treatment was associated with improved outcome only in patients with unfavorable BATMAN score (18/52 [35%]; OR, 15; 95% CI, 1.9–124; P=0.01) or PC-CS (16/44 [36%]; OR, 5.5; 95% CI, 1.4–21; P=0.01). The same findings were confirmed after adjustment for recruiting site ([BASICS versus non-BASICS, Table I in the online-only Data Supplement]), for type of EVT (intraarterial urokinase, mechanical thrombectomy with old versus new generation devices, Table 3) and in sensitivity analyses excluding patients treated with intraarterial urokinase and old generation devices (Tables II and III in the online-only Data Supplement).

The association of revascularization with good outcome remained when TTT was considered as continuous variable only in those with favorable BATMAN score (OR, 18.7; 95% CI, 1.3–261; P=0.03) or PC-CS (OR, 11.4; 95% CI, 1.0–132; P=0.05). Revascularization remained associated with good outcome (OR, 10; 95% CI, 1.0–98; P=0.04) in patients with favorable BATMAN score, whereas TTT (P=0.9) and the interaction between revascularization and TTT (P=0.9) were not. In patients with favorable PC-CS, revascularization was again associated with good outcome (OR, 9.3; 95% CI, 1.0–85; P=0.04), whereas TTT (P=0.4) and the interaction between revascularization and TTT (P=0.2) were not. In a univariable analysis in patients who achieved revascularization, favorable BATMAN score was associated with good outcome in both patients treated ≤6 hours (P=0.009) and beyond 6 hours (P<0.001), but this association was stronger beyond 6 hours (Figure I in the online-only Data Supplement).

Rates of a good outcome were similar in patients with revascularization and favorable imaging who were treated ≤6 versus>6 hours (67% versus 58%, P=0.7 for BATMAN score; 57% versus 38%, P=0.2 for PC-CS). In ordinal logistic regression analysis, TTT≤6 hours was not associated with good outcome in patients with favorable BATMAN score (unadjusted OR, 1.4; 95% CI, 0.5–3.7; P=0.6; adjusted [for age and National Institutes of Health Stroke Scale] OR, 2.0; 95% CI, 0.6–6.7; P=0.3). In contrast, TTT≤6 hours was significantly associated with good outcome in patients with unfavorable BATMAN score (unadjusted OR, 2.7; 95% CI, 1.0–6.7; P=0.046 and adjusted OR, 3.2; 95% CI, 1.1–9.5; P=0.03; Figures 2 and 3). In patients with favorable PC-CS, TTT was not significant in unadjusted analysis (OR, 2.4; 95% CI, 0.8–6.7; P=0.1) but did become significant in adjusted regression analysis (OR, 4.0; 95% CI, 1.0–14.9; P=0.04). Additional receiver operating characteristic analyses are detailed in Figure II in the online-only Data Supplement.

Discussion

This study showed a robust association between revascularization and good outcome in patients with BAO with low thrombus burden and good collaterals on baseline CTA. This association seems to extend well beyond the recommended 6-hour time window for EVT. Although there was a consistent trend towards better outcomes within 6 hours, patients with BAO with good collaterals and less extensive occlusion showed significant benefit from revascularization, even beyond 6 hours. Conversely, in patients with poor collaterals and extensive occlusion good outcome was highly dependent on achieving early revascularization. In our analysis, 59% of patients with favorable BATMAN score and 40% of patients with favorable PC-CS treated beyond 6 hours had good outcomes (mRS score of 0–3). Half of the patients with favorable BATMAN score achieved good outcomes when considered as mRS score of 0–2. Such favorable outcomes are comparable with those reported in the recent randomized controlled trials in patients with anterior circulation LVO strokes and favorable clinical-radiological mismatch or CT/magnetic resonance imaging perfusion profiles. (246, 247) Importantly, approximately one-third of patients had favorable

BATMAN score, even in those with TTT>6 hours. In a recent retrospective analysis of endovascular patients with vertebrobasilar occlusion, no association was found between TTT and functional outcomes. (310) Conversely, Mokin et al. (311) demonstrated that TTT≤6 hours was strongly associated with a good outcome. Variability in collateral status might explain these conflicting findings. Lindsberg et al. (23) hypothesized that, when present, a highly developed persistent collateral network and reverse filling of the basilar artery from the anterior circulation might sustain patency of brainstem perforators, preserve penumbral tissue and slow tissue necrosis, allowing reperfusion to be beneficial for a longer period of time. (23) Therefore, the collateral assessment may have a role in the acute setting as a selection criterion for reperfusion therapies in delayed time windows. Although several studies have shown the diagnostic and prognostic value of whole-brain CTP in posterior circulation stroke, (108, 312) routine application remains challenging because of the presence of beam hardening artifact. The PC-CS and BATMAN scores can be assessed on CTA without the need for additional imaging, providing significant advantages in speed of pre-treatment workup. Analogous to collateral scores for anterior circulation stroke, (307) the PC-CS takes into account the main collaterals involved in the vertebrobasilar system. (127, 309) The BATMAN score considers collaterals not in isolation but as a modifying factor that could limit or worsen the ischemic damage secondary to the BAO extent (and thus the likely number of obstructed perforating arteries, posterior inferior cerebellar arteries, anterior inferior cerebellar arteries, and superior cerebellar arteries). Similarly, it has been suggested that collaterals may affect the association between thrombus burden and outcomes in anterior circulation strokes.(313) The BATMAN score has been externally validated in BAO endovascular patients (129) and seems to have good prognostic accuracy and substantial reliability when evaluated on catheter angiography. (314) Interestingly, the benefit of revascularization in patients with favorable BATMAN score seems to be greater in delayed time windows. Previous studies demonstrated that patients with LVO anterior circulation stroke and poor collaterals develop large diffusion magnetic resonance imaging lesions within a few hours, whereas patients with good collaterals have minimal diffusion lesion growth for 12 hours or longer (up to 3 days).(249) This might explain the better outcomes in patients with favorable BATMAN score versus unfavorable BATMAN score in delayed time windows and that TTT seems to have an effect on outcome in patients with unfavorable BATMAN score. Importantly, our study showed better outcomes in patients treated with new generation devices. These findings reflect the improvement in endovascular techniques since the BASICS registry was performed and support the hypothesis that randomized controlled trials using modern devices may be able to show the benefit of EVT in BAO (in keeping with the recent BEST trial results). Although we could not exclude selection bias, IVT was associated with good outcomes in our analysis. There is an ongoing debate about the relevance of IVT in LVO stroke that focuses on hemorrhagic transformation risk and limited reperfusion efficacy. This retrospective analysis highlights the potential relevance of IVT even in the EVT era. (308) Our study has several limitations. First, its retrospective nature and the relatively small number of patients treated beyond 6 hours may have affected the results. Adjudication of revascularization and outcomes was not done centrally. Less than one-third (52/172) of the patients in this study were included in the BATMAN score derivation cohort, although the aim of this analysis differed. Treatment protocols included intraarterial therapy with urokinase and mechanical thrombectomy with first generation devices in the BASICS registry. The primary outcome was considered as mRS within 3 months (to incorporate the outcome at 1 month of the BASICS registry), although 1 and 3 months mRS are strongly correlated. (315) Furthermore, our results were confirmed after adjustment for recruiting site (which accounts for the majority of variation in recruitment period including changes in thrombectomy devices, learning curve of interventionalists, the world-wide establishment of Stroke Unit cares and neuro ICU) and type of EVT technique. Patient selection, treatment protocols, and CT scanners differed between participating centers. However, these differences increase the generalizability of our results. Further studies in larger and prospective series are needed to confirm these findings and better define the time window to treat patients with favorable imaging characteristics. Randomized controlled trials using mechanical thrombectomy with recent devices and imaging selection criteria may finally be able to show the benefit of patients with EVT in BAO, even beyond 6 hours from symptoms onset.

Conclusions

Revascularization was associated with good outcome in patients with BAO with good collaterals and less extensive occlusion, regardless of TTT. Although treatment should be performed as soon as possible in all patients with BAO, selected patients with favorable imaging characteristics may achieve a good outcome, even in delayed time windows. Conversely, patients with poor collaterals and more extensive thrombus are highly dependent on early revascularization to achieve good outcomes. BATMAN score and PC-CS may be useful prognostic markers to identify eligible patients for EVT beyond 6 hours. Although not recommended in the current guidelines, clinicians should consider providing EVT beyond 6 hours in BAO patients with favorable imaging profile.

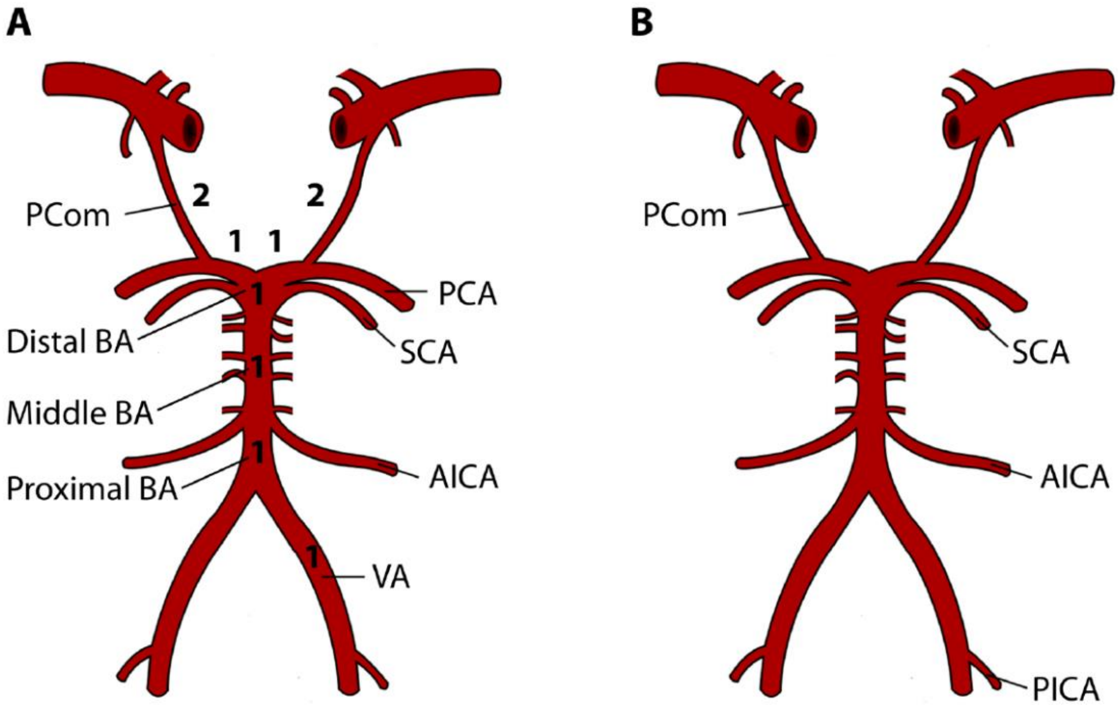

Figure 1. Computed Tomography Angiography-based vascular scores. (A) BATMAN (Basilar Artery on Computed Tomography Angiography) score; (B) PC-CS (Posterior Circulation Collateral Score). AICA indicates anterior inferior cerebellar artery; BA, basilar artery; PCA, posterior cerebral artery; PCom, posterior communicating artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; and VA, vertebral artery.

Table 1. Baseline characteristics in patients with poor and good outcome.

	All patients (n=172)	Good outcome (n= 55)	Poor outcome (n=117)	p
Age (years), mean	65±13	61±12.5	67±13.5	0.02
NIHSS*, median (IQR)	22 (12-30)	15 (9-25)	24 (15-30)	0.001
Coma, n(%)	73 (42.5)	16 (29)	57 (49)	0.02
Male sex, n(%)	118 (69)	38 (69)	80 (68)	0.99
Risk factors, n(%)				
Hypertension	98 (57)	29 (53)	69 (59)	0.19
Hypercholesterolemia	44 (26)	14 (25.5)	30 (26)	0.95
Diabetes Mellitus	38 (22)	7 (13)	31 (26.5)	0.03
Atrial fibrillation	39 (23)	12 (22)	27 (23)	0.20
Smoking	39 (23)	16 (29)	23 (20)	0.17
Coronary artery disease	30 (17.5)	10 (18)	20 (17)	0.93
Stroke etiology†, n(%)				
Cardioembolic	52 (30)	20 (36)	32 (27)	0.58
Atherosclerotic	53 (31)	12 (22)	41 (35)	
Other	12 (7)	1 (2)	11 (9.5)	
Undetermined	41 (24)	18 (33)	23 (20)	
Intravenous thrombolysis, n(%)	48 (28)	23 (42)	25 (21)	0.007
Mechanical thrombectomy, n(%)	124 (72)	43 (78)	81 (69)	0.27
Intra-arterial urokinase, n(%)	48 (28)	11 (20)	37 (32)	0.03
Old generation devices, n(%)	32 (19)	7 (13)	25 (21)	
New generation devices, n(%)	90 (52)	37 (67)	53 (45)	
Non BASICS‡ patients, n(%)	101 (59)	42 (76)	59 (50)	0.002
Time to treatment, median (min)	347 (255-480)	340 (220-385)	360 (270-527)	0.03
Time to treatment ≤6/>6 hours				
0-6 hours	108 (63)	41 (74.5)	67 (57)	0.04
>6 hours	64 (37)	14 (25.5)	50 (43)	

mTICI 2b-3§	123 (79)	48 (92)	75 (72)	0.003
BATMAN‖ score, median (IQR)	5 (4-7)	7 (5-8)	5 (3-6)	<0.001
PC-CS#, median (IQR)	5 (4-7)	6 (4-7)	5 (4-6)	0.01
pc-ASPECTS**, median (IQR)	9 (8-10)	10 (9-10)	9 (8-10)	0.01

*NIHSS National Institutes of Health Stroke Scale;†Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification;‡BASICS Basilar Artery International Cooperation Study;§mTICI modified thrombolysis in cerebral infarction (NB data on final reperfusion status were available in 156/172 patients);‖BATMAN Basilar Artery on Tomography Angiography score;#PC-CS Posterior Circulation Collateral Score;**pc-ASPECTS posterior circulation Alberta Stroke Program Early CT Score.

Table 2. Baseline characteristics in patients treated ≤6 and >6 hours.

	Time to treatment ≤6 hours (n= 108)	Time to treatment >6 hours (n=64)	p
Age (years), mean	66±12	64±15	0.21
NIHSS*, median (IQR)	22 (11-30)	21(12.5-29.5)	0.72
Coma, n(%)	51 (47)	22 (34)	0.14
Male sex, n(%)	80 (74)	38 (59)	0.06
Risk factors, n(%)			
Hypertension	61 (56.5)	37 (58)	0.39
Hypercholesterolemia	26 (24)	18 (28)	0.69
Diabetes Mellitus	23 (21)	15 (23)	0.39
Atrial fibrillation	24 (22)	15 (23)	0.29
Smoking	26 (24)	13 (20)	0.19
Coronary artery disease	21 (19.5)	9 (14)	0.46
Stroke etiology†, n(%)			
Cardioembolic	36 (33)	16 (25)	0.54
Atherosclerotic	30 (28)	23 (36)	
Other	7 (6.5)	5 (8)	
Undetermined	25 (23)	16 (25)	
Intravenous thrombolysis, n(%)	37 (34)	11 (17)	0.01
Mechanical thrombectomy n(%)	77 (71)	47 (73.5)	0.86
Non-BASICS‡ patients, n(%)	63 (58)	38 (59)	0.99
mTICI 2b-3§	79 (81)	44 (76)	0.54
BATMAN¦ score, median (IQR)	5 (4-7)	5 (4-7)	0.48
PC-CS#, median (IQR)	5 (4-7)	4.5 (4-7)	0.26
pc-ASPECTS* *, median (IQR)	9 (8-10)	9 (8-10)	0.30

*NIHSS National Institutes of Health Stroke Scale;†Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification;‡BASICS Basilar

Artery International Cooperation Study; [§]mTICI modified thrombolysis in cerebral infarction (NB data on final reperfusion status were available in 156/172 patients);[||]BATMAN score Basilar Artery on Tomography Angiography score;[#]PC-CS Posterior Circulation Collateral Score;* *pc-ASPECTS posterior circulation Alberta Stroke Program Early CT Score.

Table 3. Logistic regression analysis for good outcome adjusted for age and NIHSS.

	All patients (n=172)			Favorable BATMAN† score (n=57)			Favorable PC-CS§ (n=65)			Unfavorable BATMAN score (n=115)			Unfavorable PC-CS (n=107)		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Revascularization	7.1	1.9-27	0.004	21	1.6-263	0.02	14	1.6-112	0.01	3.3	0.6-18	0.23	4.5	0.8-27	0.97
TTT*≤6hrs	4.6	1.7-12	0.002	2.1	0.4-11	0.43	2.6	0.5-13	0.34	18	2.2-153	0.007	5.6	1.4-21	0.01
New generation devices	1.7	0.9-2.9	0.07	1.4	0.5-3.8	0.49	2.2	0.9-5.2	0.06	2.0	0.8-4.8	0.99	1.3	0.6-2.8	0.51

*TTT Time to treatment; †BATMAN Basilar Artery on Computed Tomography Angiography; §PC-CS Posterior Circulation Collateral Score.

Table I. Logistic regression analysis for good outcome adjusted for age and NIHSS.

	All patients (n=172)			Favorable BATMAN[†] score (n=57)			Favorable PC-CS[§] (n=65)			Unfavorable BATMAN score (n=115)			Unfavorable PC-CS (n=107)		
	OR	95%CI	p	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P	OR	95%CI	p
Revascularization	8.2	2-32	0.002	24	1.9-311	0.01	16.7	1.9-145	0.01	3.7	0.7-21	0.13	5.2	0.8-12	0.08
TTT*≤6hrs	4.9	1.8-13	0.002	2.2	0.4-12	0.36	2.8	0.5-15	0.22	18.5	2-157	0.007	5.6	1.4-22	0.01
Non-BASICS patients	4.0	1.5-11	0.005	2.9	0.5-17	0.25	6.1	1.3-29	0.02	5.0	1.2-21	0.02	3.1	0.8-12	0.08

*TTT Time to treatment. [†]BATMAN Basilar Artery on Computed Tomography Angiography. [§]PC-CS Posterior Circulation Collateral Score.

Table II. Sensitivity analysis for good outcome in patients with favorable and unfavorable BATMAN score treated ≤6hrs and >6hrs after excluding patients treated with old generation devices or intra-arterial urokinase.

	Patients with favorable BATMAN score treated ≤6hours	Patients with favorable BATMAN score treated >6hours	p	Patients with unfavorable BATMAN score treated ≤6hours	Patients with unfavorable BATMAN score treated >6hours	p
*mRS 0-3, n (%)	18/31 (58)	11/18 (61)	0.99	17/55 (31)	1/31 (3)	0.002
†mRS 0-3	16/27 (59)	10/16 (62)	0.99	16/50 (32)	1/31 (3)	0.002

*Sensitivity analysis for good outcome after excluding patients treated with old generation devices.†Sensitivity analysis for good outcome after excluding patients treated with intra-arterial urokinase.

Table III. Sensitivity analysis for good outcome in patients with favorable and unfavorable PC-CS treated ≤6hrs and >6hrs after excluding patients treated with old generation devices or intra-arterial urokinase.

	Patients with favorable PC-CS treated ≤6hours	Patients with favorable PC-CS treated >6hours	p	Patients with unfavorable PC-CS treated ≤6hours	Patients with unfavorable PC-CS treated >6hours	p
*mRS 0-3	21/38 (55)	7/16 (44)	0.55	14/34 (41)	5/33 (15)	0.18
†mRS 0-3	18/32 (56)	6/15 (40)	0.36	14/45 (31)	5/32 (16)	0.18

*Sensitivity analysis for good outcome after excluding patients treated with old generation devices.

†Sensitivity analysis for good outcome after excluding patients treated with intra-arterial urokinase

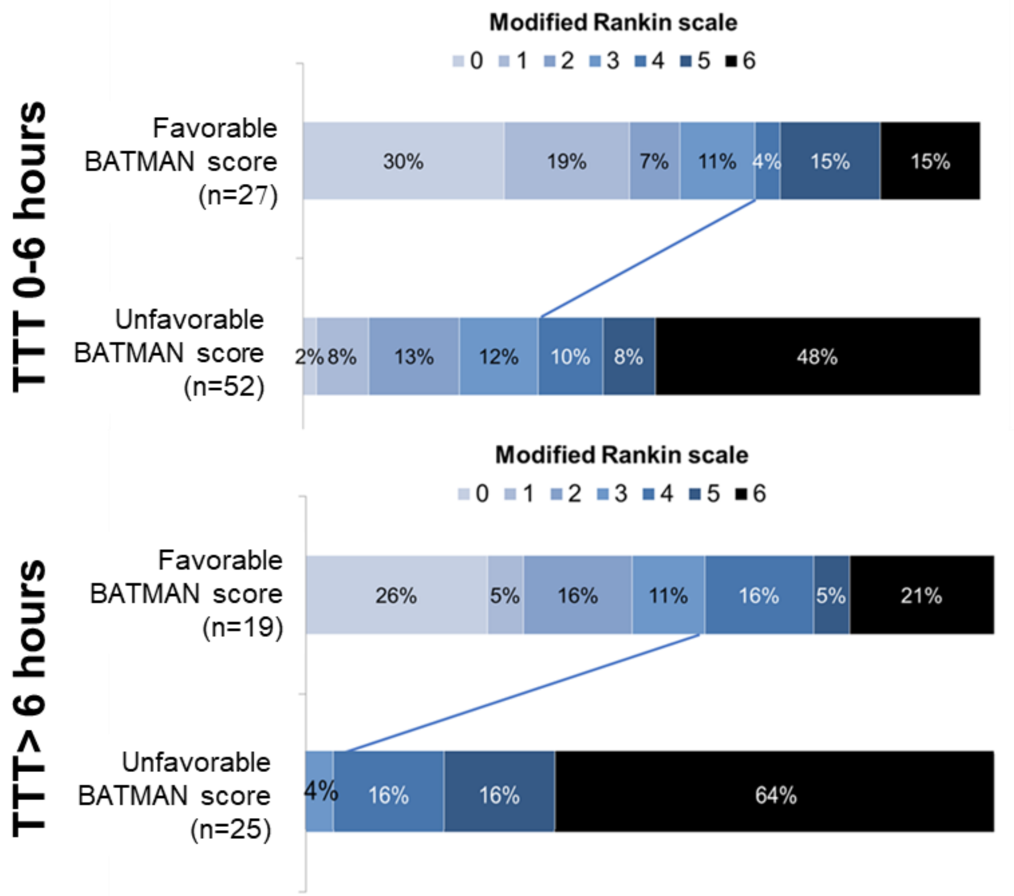

Figure I. Distribution of mRS within 3 months according to BATMAN score groups in patients with revascularization ≤6 and >6 hours. TTT time to treatment.

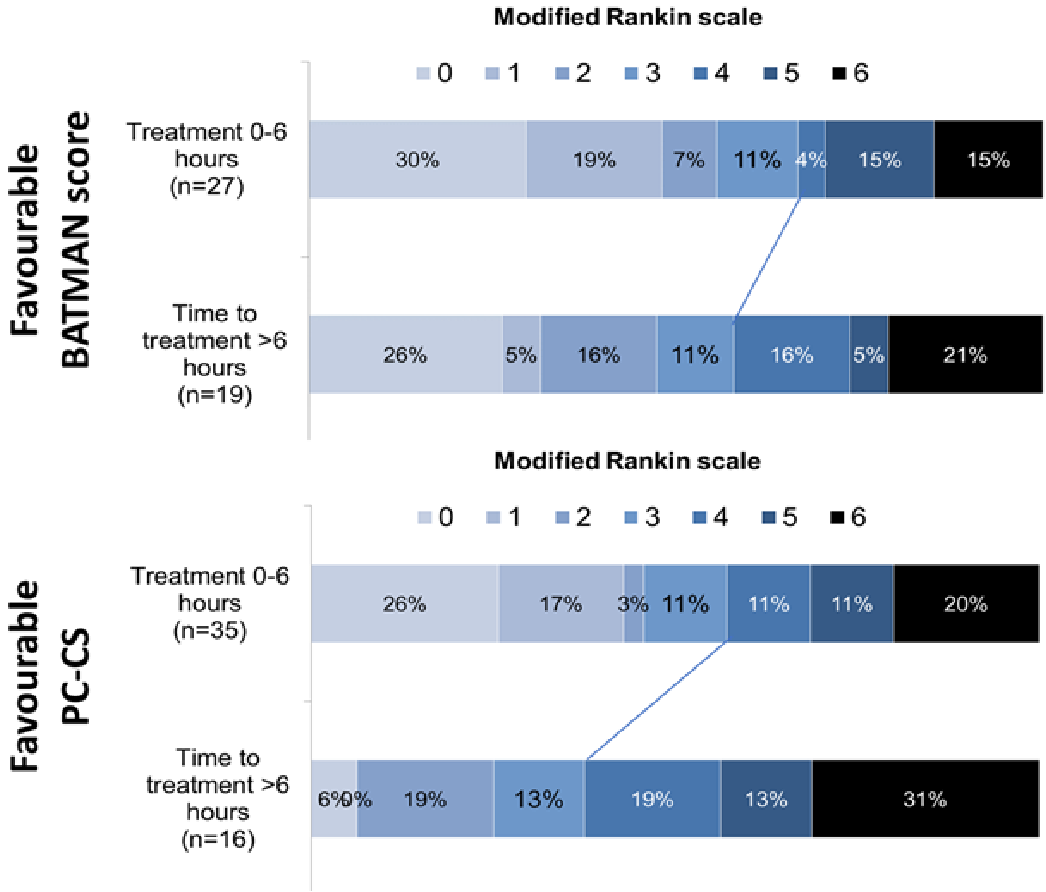

Figure 2. Distribution of modified Rankin Scale within 3 mo according to dichotomized time-to treatment (TTT) in patients with revascularization and favorable BATMAN (Basilar Artery on Computed Tomography Angiography) score and PC-CS (Posterior Circulation Collateral Score).

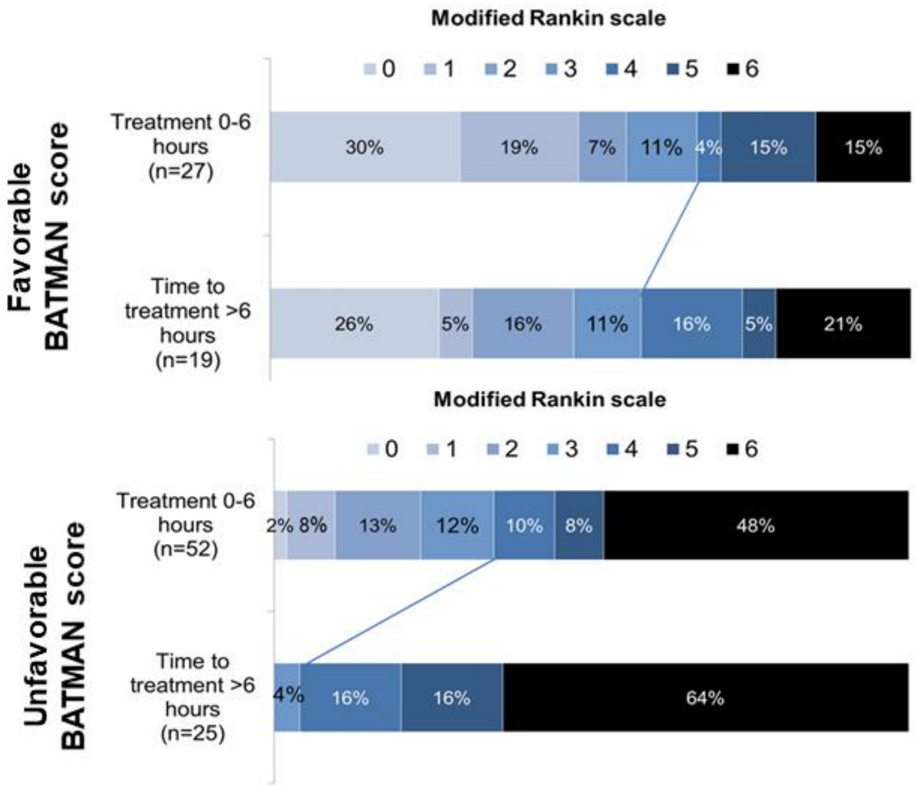

Figure 3. Distribution of modified Rankin Scale within 3 mo according to dichotomized timeto-treatment (TTT) in patients with revascularization and favorable or unfavorable BATMAN (Basilar Artery on Computed Tomography Angiography) score.

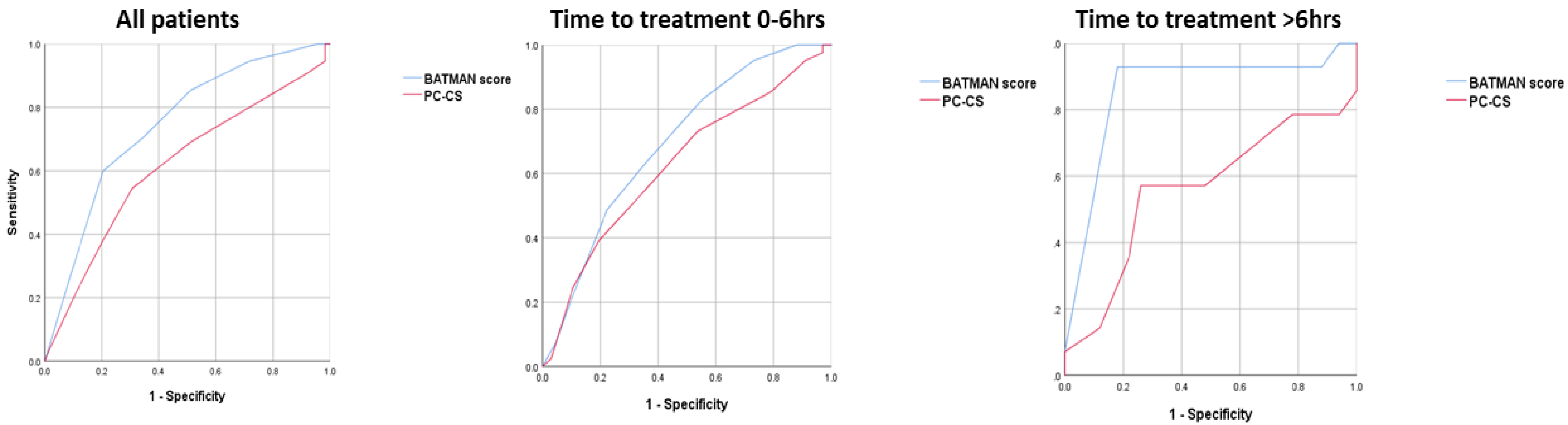

Figure II. Receiver Operating Characteristic area-under-curve (AROC) was 0.74 (95% CI 0.67-0.82) for BATMAN score and 0.62 (95% CI 0.52-0.71) for PC-CS score in all patients. In the early time-window group, ROC curve was 0.69 (95% CI 0.59-0.79) for BATMAN score and 0.62 (95% CI 0.59-0.79) for PC-CS. The optimal threshold to differentiate between good and poor outcome was 5 for both scores in the early treatment group. In the late treatment group, BATMAN score (AROC, 0.86; 95%CI 0.73-0.98) showed significantly higher accuracy in comparison with PC-CS (AROC, 0.56 95%CI 0.36-0.76; p=0.01). The optimal threshold to differentiate between good and poor outcome was 8 for the BATMAN score and 6 for the PC-CS.

CHAPTER 3. Improving NIHSS prognostic accuracy in patients with posterior circulation stroke.

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Group Authorship: Basilar Artery Treatment and Management (BATMAN) collaboration

Abstract

Background and purpose: The National Institutes of Health Stroke Scale (NIHSS) underestimates clinical severity in posterior circulation stroke and patients presenting with low NIHSS may be considered ineligible for reperfusion therapies. This study aimed to develop a modified version of the NIHSS, the Posterior NIHSS (POST-NIHSS), to improve NIHSS prognostic accuracy for posterior circulation stroke patients with mild-moderate symptoms. *Methods:* Clinical data of consecutive posterior circulation stroke patients with mild-moderate symptoms (NIHSS <10), who were conservatively managed, were retrospectively analyzed from the BATMAN registry. Clinical features were assessed within 24 hours of symptom onset; dysphagia was assessed by a speech therapist within 48 hours of symptom onset. Random forest classification algorithm and constrained optimization were used to develop the POST-NIHSS in the derivation cohort. The POST-NIHSS was then validated in a prospective cohort. Poor outcome was defined as modified Rankin Scale mRS ≥3 at 3 months. *Results:* We included 202 patients [mean (SD) age 63 (14) years, median NIHSS 3 (IQR 1-5)] in the derivation cohort and 65 patients [mean (SD) age 63 (16) years, median NIHSS 2 (IQR 1-4)] in the validation cohort. In the derivation cohort, age, NIHSS, abnormal cough, dysphagia and gait/truncal ataxia were ranked as the most important predictors of functional outcome. POST-NIHSS was calculated by adding 5 points for abnormal cough, 4 points for dysphagia, and 3 points for gait/truncal ataxia to the baseline NIHSS. In Receiver operating characteristic (ROC) analysis adjusted for age, POST-NIHSS area-under-ROC-curve (AUC) was 0.80, 95%CI 0.73-0.87 versus NIHSS AUC 0.73, 95%CI 0.64-0.83, p=0.03. In the validation cohort, POST-NIHSS AUC was 0.82, 95%CI 0.69-0.94 versus NIHSS AUC 0.73, 95%CI 0.58-0.87, p=0.04. *Conclusions:* POST-NIHSS showed higher prognostic accuracy than NIHSS and may be useful to identify posterior circulation stroke patients with NIHSS <10 at higher risk of poor outcome.

Introduction

One in five ischemic strokes affect the posterior circulation. (14) This subtype of stroke is associated with a high risk of recurrence, disability and mortality. (268) The National Institutes of Health Stroke Scale (NIHSS) is a widely-used scoring system to assess neurologic deficits in acute stroke patients.(133) It is an indispensable tool in treatment-decision-making and stroke research, and is strongly associated with outcomes after stroke. Advantages include simplicity, rapidity of administration, and agreement between clinicians. (316-318) However, the NIHSS is strongly weighted towards deficits caused by anterior circulation lesions (such as motor function and cortical signs, especially language).(138, 139) Clinical features of posterior circulation stroke such as gait/truncal ataxia, vertical gaze palsy, nystagmus and bulbar signs are not measured, hence NIHSS scores are often lower in patients with posterior circulation stroke compared to patients with anterior circulation stroke. The NIHSS cut-off for favorable outcomes is lower in patients with posterior circulation stroke compared to patients with anterior circulation stroke, suggesting that the NIHSS underestimates clinical severity in posterior circulation stroke.(138)

Previous studies have reported that more than 75% of patients with posterior circulation stroke present with a baseline NIHSS 0-5. (138, 139) Posterior circulation stroke patients presenting with low NIHSS have 23% increased odds of disability at 3 months than anterior circulation stroke patients. (319) The recent BASilar artery International Cooperation Study (BASICS) trial assessed the efficacy of endovascular therapy versus best medical management in patients with basilar artery occlusion and was neutral overall. However, endovascular therapy benefitted patients with NIHSS $\geq$10. (263) In patients presenting with mild-moderate clinical deficits (NIHSS <10) the benefit of reperfusion therapies is less certain and decision-making may be enhanced by an improved tool to identify those at higher risk of poor outcome, who may therefore require more aggressive treatment with reperfusion therapies. We assessed the prognostic value of additional clinical features in consevatively managed patients with posterior circulation stroke and mild-moderate symptoms (NIHSS <10), and used this information to derive and validate a modified version of the NIHSS, the Posterior NIHSS (POST-NIHSS).

Methods

The data that support this analysis are available from the corresponding author on reasonable request.

Patients

Clinical data of consecutive posterior circulation stroke patients with NIHSS <10 were retrospectively analyzed from the Basilar Artery Treatment and Management (BATMAN) registry. The BATMAN registry is an international, multicenter registry of patients with posterior circulation stroke including recruiting sites in Australia, Europe and USA. (320) Patients with a clinical and radiological diagnosis of posterior circulation stroke who were conservatively managed (not treated with intravenous thrombolysis or endovascular therapy) were included in this study. Patients treated with reperfusion therapies were excluded from this study as we were interested in investigating the natural history of posterior circulation stroke presenting with mild-moderate symptoms. The derivation cohort included patients recruited between January 2006 and May 2017. The validation cohort included patients prospectively recruited between June 2017 and December 2019. The Melbourne Health Human Research Ethics Committee approved the BATMAN registry under a waiver of consent.

Additional clinical features

NIHSS and posterior circulation stroke signs were assessed by a stroke physician/neurologist in the emergency department in all patients with suspected posterior circulation stroke presenting within 24 hours of symptom onset. Posterior circulation stroke signs included were gait/truncal ataxia, diplopia, ptosis, nystagmus, internuclear ophthalmoplegia, vertical gaze palsy, Horner's syndrome, palatal paralysis/hypomotility, tongue deviation, and abnormal voluntary cough. Dysphagia was assessed by a speech therapist within 48 hours of symptom onset.

Outcome measures

The primary objective of our study was to assess the prognostic value of additional clinical features in posterior circulation strokes with NIHSS <10 and derive a revised version of the NIHSS, the POST-NIHSS. Poor outcome was defined as modified Rankin Scale (mRS) 3-6 at 3 months. Disability/death was defined as mRS 2-6 at 3 months.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 26 software (IBM SPSS Statistics, Armonk, NY) and Stata (v.15 IC, StataCorp, College Station, TX). Random forest classification and constrained optimization were conducted in Python (library: scikit-learn, version 0.23.2). Analysis of univariate data was performed using the Mann–Whitney U test for continuous data and Fisher exact test for categorical variables.

A random forest classification algorithm, which consists of multiple decision trees (100 trees, maximum depth 5) comprising multiple true or false conditions using input variables, was used to identify the most important predictors of 90-day functional outcome in the derivation cohort. Variables with larger Gini index were considered more important. (321) Constrained optimization was used to identify the specific numbers of extra points to be attributed to the most important predictors of 90-day functional outcome, while maintaining the rank order from random forest classification algorithm, to maximise the area-under the receiver operating characteristic (AUC) curve. These points were added to the baseline NIHSS to calculate the POST-NIHSS. Logistic regression models for POST-NIHSS adjusted for age were then performed to generate individual patients' predicted probabilities for poor outcome in the derivation and validation cohort. Receiver operating characteristic (ROC) curves for the predicted probability were subsequently calculated to assess prognostic performance in the derivation cohort and validation cohort. ROCs were compared using a chi-square test. Bayesian information criterion (BIC) was used as a scalar measure to compare the overall goodness of fit for regression models incorporating different prognostic scores. Lower BIC indicates a more informative model with differences >10 regarded as very strong evidence of model superiority. (301) All p-values were 2-sided, and p <0.05 was considered significant.

Results

Overall, 450 consecutive patients with posterior circulation stroke with complete data on NIHSS, 90-day functional outcome and additional posterior circulation stroke clinical features were analyzed from the BATMAN registry. Of these, 378 had NIHSS <10 and were considered for this study. Among these, 111 patients were excluded because of treatment with endovascular therapy or intravenous thrombolysis. Of the 267 remaining patients, 202 were in the derivation cohort and 65 in the prospective validation cohort. The flow diagram of included patients is shown in Supplementary Figure I, Online-only Data Supplement. The two cohorts did not differ in their baseline characteristics, except for NIHSS which tended to be lower in the validation cohort, and history of hypertension (Table 1).

Derivation of the Posterior NIHSS

In the derivation cohort, we included 202 posterior circulation stroke patients, mean age 63 (SD 14), median NIHSS 3 (IQR 1-5). Among these, 31/202 (15%) patients had poor outcome and 70/202 (35%) had disability/death at 3 months. In univariate analysis, older age, higher NIHSS, female sex, coronary artery disease and previous stroke/TIA were significantly associated with poor outcome at 3 months (Table 2). Gait/truncal ataxia (p=0.02), abnormal (absent or weak) voluntary cough (p=0.01) and dysphagia (p=0.004) were the additional clinical features strongly associated with poor outcome (Table 3). In logistic regression analysis adjusted for age, gait/truncal ataxia (OR 3.14, 95%CI 1.24-7.92, p=0.02), dysphagia (OR 5.22, 95% CI 1.63-16.7, p=0.005) and abnormal voluntary cough (OR 8.17, 95% CI 1.49-44.8, p=0.02) were significantly associated with poor outcome. Gait ataxia outperformed limb ataxia in logistic regression analysis for poor outcome adjusted for age (gait ataxia OR 3.14, 95% CI 1.24-7.92, p=0.02 BIC 127 versus limb ataxia OR 2.36, 95%CI 1.04-5.38, p=0.04 BIC 159). Age, NIHSS, abnormal voluntary cough, dysphagia, and gait/truncal ataxia were ranked as the five most important predictors of 90-day functional outcome in the random forest classification algorithm (Figure 1). After constrained optimization, 5 points for abnormal cough, 4 points for dysphagia, and 3 points for gait/truncal ataxia were identified as the optimal weighting of additional points to maximise the POST-NIHSS ROC curve. The POST-NIHSS was therefore calculated by adding 3 points for gait/truncal ataxia, 4 points for dysphagia, and 5 points for abnormal cough to the baseline NIHSS. In logistic regression analysis for poor outcome adjusted for age, the POST-NIHSS performed well against the NIHSS (POST-NIHSS OR 1.21 95%CI 1.09-1.34, p=0.001 BIC 150 versus NIHSS OR 1.20 95%CI 1.02-1.42, p=0.03 BIC 158). In ROC analysis for poor outcome adjusted for age, the POST-NIHSS outperformed NIHSS (POST-NIHSS AUC was 0.80, 95%CI 0.73-0.87 versus NIHSS AUC 0.73, 95%CI 0.64-0.83, p=0.03). In the derivation cohort, 156/202 (77%) patients presented with NIHSS 0-5. In a sensitivity analysis in this subgroup of patients, POST-NIHSS remained significantly associated with poor outcome in logistic regression analysis adjusted for age (OR 1.40, 95%CI 1.14-1.70, p=0.01), whereas NIHSS did not (OR 1.12, 95%CI 0.82-1.56, p=0.46).

Validation of the Posterior NIHSS

In the validation cohort, 65 posterior circulation stroke patients [mean age 63 (SD 16), median NIHSS 2 (IQR 1-4)] were prospectively recruited. Among these, 17/65 (26%) had poor outcome and 26/65 (40%) had disability at 3 months. Results of univariate analysis in the validation cohort are shown in Supplementary Table I. In logistic regression analysis for poor outcome adjusted for age, POST-NIHSS outperformed NIHSS (POST-NIHSS 1.43, 95% CI 1.16-1.77, p=0.001 BIC 56 versus NIHSS OR 1.34, 95% 1.05-1.69). In ROC analysis adjusted for age, POST-NIHSS showed significantly higher accuracy than NIHSS (POST-NIHSS AUC 0.82, 95%CI 0.69-0.94 versus NIHSS AUC 0.73, 95%CI 0.58-0.87, p=0.04). In the validation cohort, 57/65 (88%) patients presented with NIHSS 0-5. In a sensitivity analysis in this subgroup of patients, POST-NIHSS remained significantly associated with poor outcome in logistic regression analysis adjusted for age (OR 1.41, 95%CI 1.11-1.78, p=0.005), whereas NIHSS did not (OR 1.33, 95%CI 0.88-2.03, p=0.18).

We therefore propose the POST-NIHSS: a modified version of the NIHSS including testing of gait/truncal ataxia, voluntary cough, and swallowing, where 3 points are given for gait/truncal ataxia in item 7 (gait/truncal and limb ataxia, Figure 2) and an algorithm to assess bulbar signs is performed in an additional item 12 (Figure 3). If there is both limb ataxia as well as gait/truncal ataxia, 3 points should be given. The algorithm to assess bulbar signs is based on the preliminary investigation/indirect swallowing test and the Swallow Liquid attempt of the Gugging Swallowing Screen (GUSS) (322) which has been well-validated and used by clinicians from multidisciplinary backgrounds. (323)

Discussion

We developed the POST-NIHSS, a modified version of the NIHSS including assessment of gait/truncal ataxia and bulbar signs, which appears to improve NIHSS prognostic accuracy in patients with posterior circulation stroke presenting with mild-moderate symptoms. The incorporation of gait ataxia and bulbar signs assessment in a structured tool may help with early prognostication for posterior circulation stroke patients presenting with NIHSS <10 by identifying those at higher risk of poor outcome. Although patients with NIHSS <10 were included in our study, the median NIHSS in our derivation and validation cohort was 3 and 2 respectively, a group in whom thrombolysis or endovascular therapy may not routinely be used. Therefore, POST-NIHSS may assist clinicians in treatment-decision making in selected patients (e.g. patients presenting with NIHSS 0-5 or having relative contraindications to reperfusion therapies in whom the risks and benefits of treatment should be carefully weighed). Moreover, a structured examination approach may standardise and simplify neurological assessments in the hyperacute phase. The additional items can be readily performed at the bedside. Trunk ataxia can be tested when gait ataxia is not testable, voluntary cough and dysphagia should be assessed with the patient upright. Cough is examined first and if normal the examiner proceeds to a preliminary oral examination to exclude obvious anatomical abnormalities (palatal paralysis/asymmetry or tongue deviation) which would suggest the presence of bulbar signs and likely dysphagia. Water swallow test is only performed if preceding steps are normal.

Dysphagia occurs in up to two-thirds of stroke patients and can lead to serious complications such as aspiration pneumonia and malnutrition.(54) It has been associated with prolonged hospital stays, higher admission rates to residential care facilities and increased mortality.(55) Poor cough is a particularly strong predictor of aspiration pneumonia and was strongly associated with poor outcome in our data. (41, 324) Impaired gait and trunk control are common in stroke patients, even if limb ataxia is not present. In our study, more than a third of posterior circulation stroke patients presented with gait/truncal ataxia, consistent with previous studies.(41) Gait ataxia increases the risk of falls, and impairs independence of activities of daily living. Balance status is associated with longer hospitalization periods and post-stroke disability. (325)

Current stroke guidelines recommend that intravenous thrombolysis may be reasonable for patients with mild disabling stroke symptoms within 4.5 hours of symptom onset. (250) Our data provide greater clarity on what constitutes potentially disabling symptoms in posterior circulation strokes and therefore may support increased utilisation of intravenous thrombolysis in this patient group. Furthermore, the potential risk of hemorrhagic transformation appears to be lower in posterior circulation stroke in comparison with anterior circulation stroke. (175, 326) In our study, up to 26% of patients with NIHSS <10 had poor outcome and up to 40% had disability at 3 months. These findings are consistent with previous studies. (139, 319) To date, there is no validated alternative scale to the NIHSS for posterior circulation stroke patients. The Israeli Vertebrobasilar Stroke Scale is a 44-point scoring system which was developed in a cohort of 43 patients with vertebrobasilar stroke, containing 11 items (including dysphagia and gait ataxia) and using an arbitrary weighting system based on clinical experience. (140) Dysphagia was tested by instructing patients to swallow three consecutive teaspoons of water followed by half a glass of water and recording any swallowing difficulties (coughing or wet voice) which appeared feasible. In this study, inter-rater agreement between two examiners was excellent for both dysphagia and gait ataxia. More recently, Olivato et al. (141) developed an extended version of the NIHSS (the expanded NIHSS) in 22 patients with posterior circulation stroke and 25 with anterior circulation stroke, to improve the NIHSS diagnostic accuracy in posterior circulation stroke. This scale included additional items such as trunk ataxia, nystagmus, Horner's syndrome, IX and XII cranial nerve deficits, which were weighted using an arbitrary scoring system. Both the expanded NIHSS and the Israeli Vertebrobasilar Stroke Scale score were developed in small cohorts, used arbitrary scoring systems, and did not demonstrate a higher prognostic accuracy in comparison with the NIHSS. We developed a simple, pragmatic, and rapid tool that may assist clinicians in treatment-decision making. POST-NIHSS is easy to perform as it includes clinical features that should be assessed after NIHSS whenever a posterior circulation stroke is suspected. A de novo scoring system alternative to the NIHSS, would add more complexity to the neurological assessment, given diagnosing posterior circulation stroke can be challenging and clinicians may be unsure on which scale to use. Although model performance usually tends to worsen in validation datasets, the POST-NIHSS prognostic accuracy improved, likely due to the lower NIHSS (median NIHSS 2) in the validation cohort compared to the derivation cohort.

Our study has several limitations. Dysphagia assessment was performed by a speech therapist within 48 hours and not by the physician, concurrently with the NIHSS. Moreover, it was not assessed using the same screening tool in all patients. We have suggested a practical and well-validated approach for the rapid bedside assessment of dysphagia to allow this to be performed concurrently with the NIHSS. Although the score was derived using machine learning algorithms, which have been proven to have high accuracy in predicting stroke outcomes, (327) and was prospectively validated, the POST-NIHSS requires further validation in larger prospective datasets. The score inter-rater reliability must be evaluated. However, similar gait and dysphagia assessments showed excellent reliability in previous studies. (140, 322) Furthermore, the GUSS had a sensitivity of 100%, a specificity of 69% in predicting dysphagia (confirmed by fiberoptic endoscopic evaluation), and a robust interrater reliability (k=0.835) (140) when conducted by stroke nurses within 24 hours of onset. We do not anticipate inter-rater agreement to be significantly worse when performed by stroke physicians. Given dysphagia and gait/truncal ataxia can be present in patients with anterior circulation strokes (frontal lobe, basal ganglia, corona radiata lesions), a validation of the POST-NIHSS in patients with low NIHSS regardless of the stroke topography is also warranted.

Conclusions

The POST-NIHSS has higher prognostic accuracy than NIHSS in patients with posterior circulation stroke presenting with mild-moderate symptoms (NIHSS <10). POST-NIHSS, which includes assessment of gait/truncal ataxia and bulbar signs, may be useful to identify posterior circulation stroke patients presenting with low NIHSS who may be at higher risk of poor outcome and might benefit from reperfusion therapies.

Table 1. Baseline characteristics of conservatively managed posterior circulation stroke patients in the derivation cohort and validation cohort.

	Derivation cohort (n=202)	Validation cohort (n=65)	p
Age (years), mean	63±14	63±16	0.9
NIHSS*, median (IQR)	3 (1-5)	2 (1-4)	0.05
Male sex, n(%)	138 (68)	41 (63)	0.5
Risk factors, n(%)			
Hypertension	128 (63)	28 (43)	0.01
Hypercholesterolemia	67 (33)	17 (26)	0.2
Diabetes Mellitus	58 (29)	12 (18)	0.08
Atrial fibrillation	29 (14)	9 (14)	0.9
Smoking	56 (28)	25 (38)	0.2
Coronary artery disease	23 (11)	10 (15)	0.5
Previous stroke or TIA	37 (18)	7 (11)	0.1
Stroke etiology†, n(%)			
Cardioembolic	39 (19)	12 (18)	0.9
Atherosclerotic	38 (19)	11 (17)	
Small vessel disease	28 (14)	11 (17)	
Other	13 (6)	10 (15)	
Undetermined	74 (37)	21 (32)	
Vertebro-basilar artery occlusion, n(%)	11 (5)	6 (9)	0.4

*NIHSS National Institutes of Health Stroke Scale; †Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Table 2. Outcomes in the derivation cohort.

	Good outcome (n=171)	Poor outcome (n=31)	p
Age (years), mean	62±14	72±13	0.001
NIHSS*, median (IQR)	3 (1-5)	5 (3-6)	0.001
Female sex, n(%)	49 (29)	15 (48)	0.04
Risk factors, n(%)			
Hypertension	106 (62)	22 (71)	0.4
Hypercholesterolemia	53 (31)	14 (45)	0.2
Diabetes Mellitus	48 (28)	10 (32)	0.7
Atrial fibrillation	21 (12)	8 (26)	0.09
Smoking	59 (35)	9 (29)	0.6
Coronary artery disease	15 (9)	8 (26)	0.01
Previous stroke or TIA	26 (15)	11 (35)	0.01
Stroke etiology†, n(%)			
Cardioembolic	46 (27)	10 (32)	0.5
Atherosclerotic	43 (25)	10 (32)	
Small vessel disease	24 (14)	8 (26)	
Other	15 (9)	1 (3)	
Undetermined	72 (42)	10 (32)	
Basilar artery occlusion, n(%)	9 (5)	2 (6)	0.7

*NIHSS National Institutes of Health Stroke Scale; †Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Table 3. Clinical features associated with poor outcome in the derivation cohort.

	All patients (n=202)	Good outcome (n=171)	Poor outcome (n=31)	p
Gait/truncal ataxia, n(%)	68 (34)	54 (32)	14 (45)	0.02
Diplopia, n(%)	31 (15)	27 (16)	4 (13)	0.8
Ptosis, n(%)	10 (5)	6 (4)	4 (13)	0.05
Nystagmus, n(%)	44 (22)	35 (21)	9 (29)	0.3
Internuclear ophthalmoplegia, n(%)	7 (4)	5 (3)	2 (7)	0.3
Vertical gaze palsy, n(%)	7 (4)	4 (2)	3 (10)	0.8
Horner's syndrome, n(%)	3 (2)	2 (1)	1 (3)	0.4
Palatal paralysis/hypomotility	16 (8)	12 (7)	4 (13)	0.3
Tongue deviation, n(%)	10 (5)	7 (4)	3 (10)	0.2
Dysphagia, n(%)	16 (8)	9 (5)	7 (23)	0.004
Abnormal cough, n(%)	7 (4)	3 (2)	4 (13)	0.01

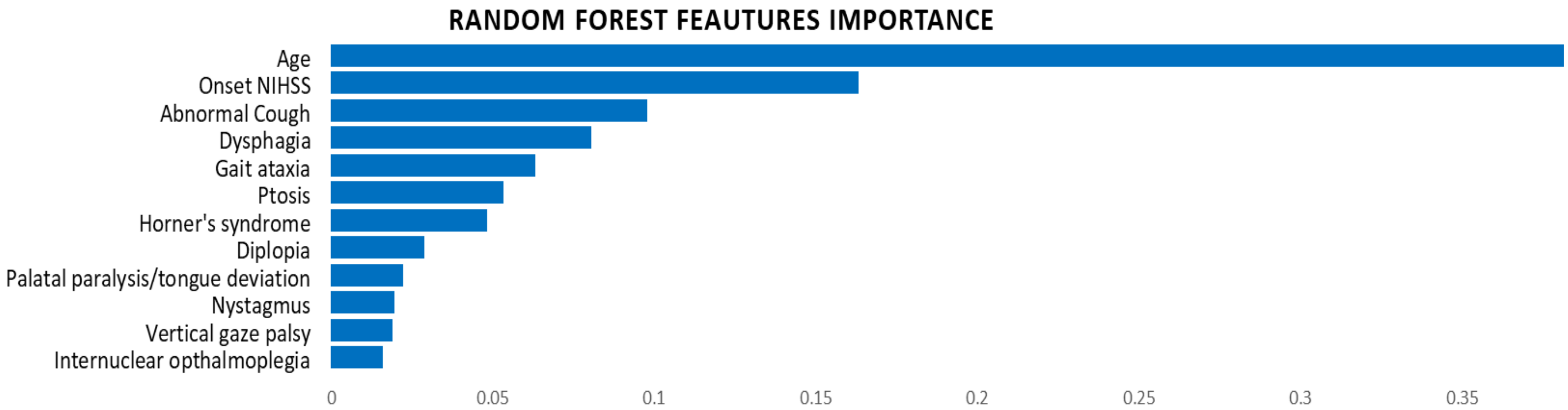


Figure 1. Random Forest features importance.

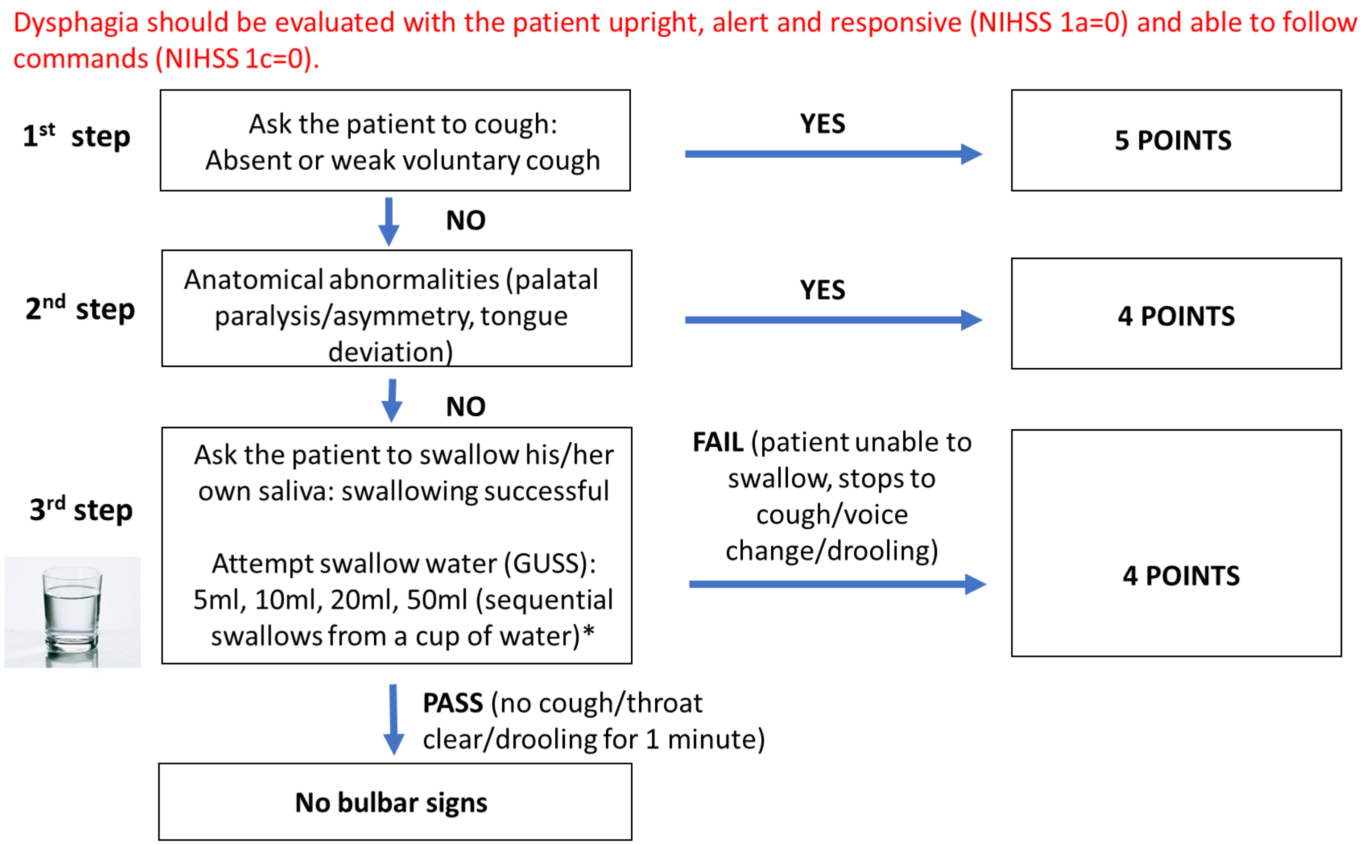
Gait/trunk and limb ataxia

This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field.

• The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.
• The examiner instructs the patient to stand with feet together with eyes open for a few seconds and subsequently to walk naturally. If this test is normal, ask the patient to walk in tandem. In stroke patients who are unable to walk due to limb weakness, truncal ataxia should be evaluated in sitting position by assessing trunk control.

0 Absent.
1 Present in one limb.
2 Present in two limbs.
3. Patients cannot walk or maintain a sitting position without assistance. Retro and/or lateropulsion can be present. Broad-based gait and increased sway of the body can be present.
UN Amputation or joint fusion, explain:

Figure 2. Posterior NIHSS Item 7: Gait/truncal and limb ataxia.



*Materials required for step 3: a glass filled with approximately 100 ml of water, a 20 ml syringe, a second cup/glass where to pour 5ml, 10ml and 20ml of water drawn up with the syringe. If no cough/voice change/drooling after each of the three swallows, ask the patient to drink the remaining water from the first glass.

Figure 3. Posterior NIHSS Item 12: Bulbar signs.

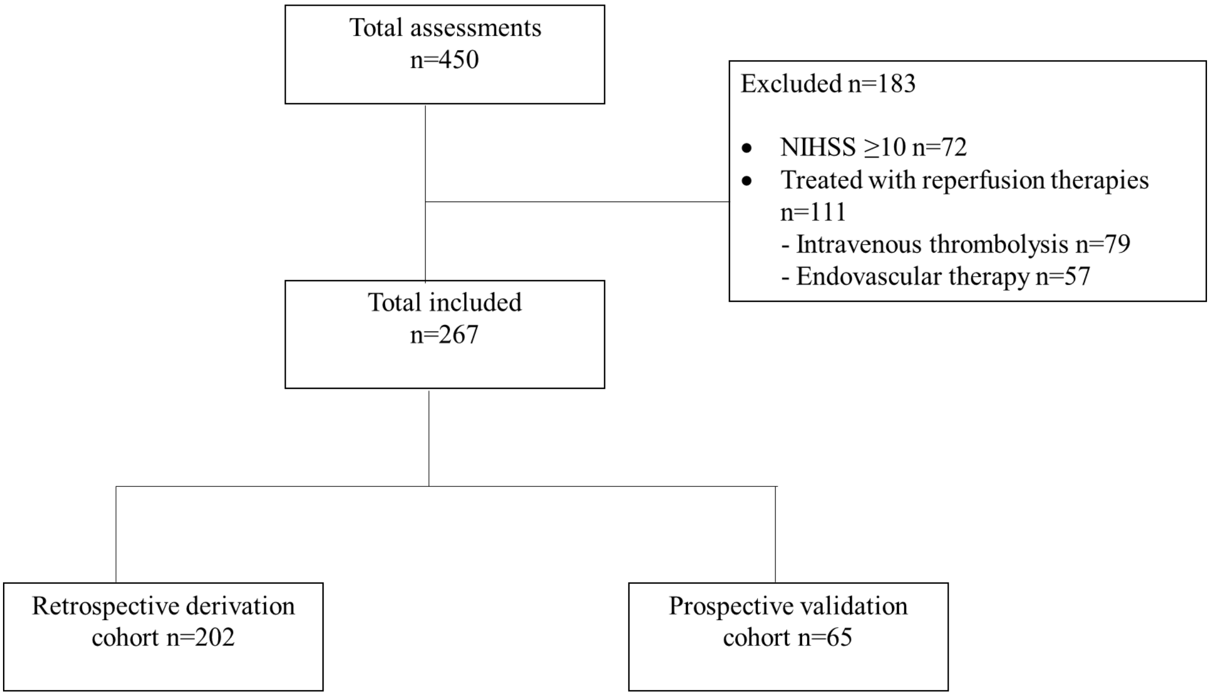


Figure I. Summary flow diagram of included study patients.

Table I. Outcomes in the validation cohort.

	Good outcome (n=48)	Poor outcome (n=17)	P
Age (years), mean	61±15	70±16	0.04
NIHSS*, median (IQR)	2 (1-4)	4 (2-7)	0.004
Male sex, n(%)	31 (65)	10 (59)	0.8
Risk factors, n(%)			
Hypertension	19 (40)	9 (53)	0.4
Hypercholesterolemia	13 (27)	4 (24)	0.9
Diabetes Mellitus	6 (13)	6 (35)	0.07
Atrial fibrillation	7 (15)	2 (12)	0.9
Smoking	19 (40)	6 (35)	0.9
Coronary artery disease	5 (10)	5 (29)	0.1
Previous stroke/TIA	3 (6)	4 (24)	0.07
Stroke etiology†, n(%)			
Cardioembolic	9 (19)	3 (18)	0.4
Atherosclerotic	5 (10)	6 (35)	
Small vessel disease	10 (21)	1 (6)	
Other	8 (17)	2 (12)	
Undetermined	16 (33)	5 (29)	
Basilar artery occlusion, n(%)	2 (4)	4 (24)	0.04

*NIHSS National Institutes of Health Stroke Scale; †Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

CHAPTER 4. Pushing boundaries for treatment in patients with basilar artery occlusion.

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Tenecteplase Versus Alteplase Before Endovascular Therapy in Basilar Artery Occlusion

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Article Info & Disclosures

Abstract

Objective: To investigate the efficacy of tenecteplase (TNK), a genetically modified variant of alteplase with greater fibrin specificity and longer half-life than alteplase, prior to endovascular thrombectomy (EVT) in patients with basilar artery occlusion (BAO).

Methods: To determine whether tenecteplase is associated with better reperfusion rates than alteplase prior to EVT in BAO, clinical and procedural data of consecutive BAO patients from the Basilar Artery Treatment and MANagement (BATMAN) registry and the Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial were retrospectively analyzed. Reperfusion >50% or absence of retrievable thrombus at the time of the initial angiogram was evaluated.

Results: We included 110 BAO patients treated with intravenous thrombolysis prior to EVT [mean age 69(SD 14); median NIHSS 16(IQR 7-32)]. Nineteen patients were thrombolysed with TNK (0.25mg/kg or 0.40mg/kg) and 91 with alteplase (0.9mg/kg). Reperfusion>50% occurred in 26% (n=5/19) of patients thrombolysed with TNK vs 7% (n=6/91) thrombolysed with alteplase (RR 4.0 95%CI 1.3-12; p=0.02), despite shorter thrombolysis-to-arterial-puncture time in the TNK-treated patients (48[IQR 40-71]mins) vs alteplase-treated patients (110[IQR 51-185]mins, p=0.004). No difference in symptomatic intracranial hemorrhage was observed (0/19(0%) TNK, 1/91(1%) alteplase, p=0.9).

Conclusions: Tenecteplase may be associated with an increased rate of reperfusion in comparison with alteplase before EVT in BAO. Randomized controlled trials to compare tenecteplase with alteplase in BAO patients are warranted.

Classification of evidence: This study provides Class III evidence that tenecteplase leads to higher reperfusion rates in comparison with alteplase prior to EVT in BAO patients.

Introduction

Basilar artery occlusion (BAO) is a large vessel occlusion (LVO) ischemic stroke subtype associated with high disability and mortality. (320) Despite its proven efficacy, alteplase only achieves rapid reperfusion in ~4% of BAO patients. (167) Tenecteplase (TNK) is a genetically modified variant of alteplase with greater fibrin specificity and longer half-life permitting bolus administration, cheaper than alteplase in most countries. The Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial (203) demonstrated TNK led to higher reperfusion rates prior to endovascular therapy (EVT) and improved clinical outcomes compared with alteplase in LVO ischemic strokes. Reperfusion at the initial angiogram occurred in 22% of TNK versus 10% of alteplase patients. It is unclear whether this finding can be extrapolated to BAO as only 6 patients were included with no differences in primary outcome (1/3 in each treatment arm).

Methods

The primary research question is whether tenecteplase is associated with better reperfusion rates than alteplase prior to EVT in BAO (Class IV evidence). Individual patient level data of consecutive BAO were pooled from the EXTEND-IA TNK (65) (alteplase 0.9mg/kg vs TNK 0.25mg/kg), EXTEND-IA TNK part 2 (204) (TNK 0.25mg/kg vs TNK 0.4mg/kg) trials and Basilar Artery Treatment and MANagement(BATMAN) registry. (320) The EXTEND-IA TNK trial (March 2015-July 2019) was a multicenter, prospective, randomized, open-label, blinded outcome trial in ischemic stroke patients within 4.5h after onset, who had internal carotid, middle cerebral, or basilar artery occlusion, eligible for intravenous thrombolysis (IVT) and EVT. The BATMAN registry (October 2009-July 2019) is a multicenter registry of prospectively collected consecutive BAO patients. Patients within 4.5h after onset, eligible for IVT and EVT were considered for this study.

A neurointerventionalist (P.J.M.) or neurointerventional fellow (C.W.) assessed reperfusion using the modified Treatment in Cerebral Ischemia (mTICI) classification. (131) If no retrievable thrombus was found on initial angiogram, the endovascular procedure was terminated. If intracranial angiography could not be performed, reperfusion ≥50% of the involved territory was assessed on multimodal imaging (CT perfusion/CT Angiography) around the time angiography would otherwise have been performed. (204, 209)

The primary objective was to evaluate substantial reperfusion defined as mTICI 2b-3 on initial angiogram (before EVT was performed), or reperfusion≥50% of the involved territory on multimodal imaging. Parenchymal hematoma (PH) was defined as blood clot with mass effect, deemed symptomatic (sICH) if it occupied >30% of the infarcted territory and was associated with ≥4 point increase in NIHSS. (149) Functional outcome was assessed at 3 months using modified Rankin Scale score (mRS) dichotomized as ≤2 and ≤1.

Statistical analyses were performed using Stata (v.16 SE, StataCorp). Analysis of univariable data was performed using Mann-Whitney U-test for continuous data and Fisher Exact test for categorical variables. Multivariable analyses were performed using Poisson regression models with robust standard error. All p-values were 2-sided, $p<0.05$ was considered significant.

Standard protocol approvals, registrations, and patient consents

The Melbourne Health Human Research Ethics Committee approved the BATMAN registry under a waiver of consent. The EXTEND-IA TNK (ClinicalTrials.gov NCT02388061) and EXTEND-IA TNK part 2 (ClinicalTrials.gov NCT03340493) trials were approved by institutional ethics committees at each site. Written informed consent was obtained from each participant or legal representative. (204, 209)

Data availability

Deidentified data can be made available upon reasonable request to corresponding author from other researchers if ethical approval is granted.

Results

We included 110 BAO patients treated with IVT prior to EVT; mean age 69 (SD 14), median NIHSS 16 (IQR 7-32). Nineteen patients were treated with TNK and 91 with alteplase (Table 1). Baseline characteristics were well-matched between treatment groups with exception of age, with TNK-treated patients being older [77yrs (SD 14) vs 67yrs (SD 14); p=0.01)]. Onset-to-thrombolysis time did not differ between groups [181(93-203) mins in TNK-treated patients vs 160(130-200) mins, p=0.9]. Thrombolysis-to-arterial-puncture was shorter in TNK-treated patients [48(IQR 40-71) mins vs 110(IQR 51-185) mins, p=0.004]. A higher proportion of alteplase-treated patients [40/91(44%) vs 3/19(16%) TNK, p=0.04] received thrombolysis at primary stroke centers and subsequently transferred for EVT ("drip and ship"), Table 2. One patient did not have intracranial angiography and outcome was assessed using multimodal imaging.

Substantial reperfusion occurred in 26%(n=5/19) of patients treated with TNK vs 7%(n=6/91) treated with alteplase (RR 4.0, 95%CI 1.3-12; p=0.02), obviating the need for EVT, Table 3. This was confirmed in regression analyses adjusted for needle-to-arterial-puncture-time (RR 4.0, 95%CI 1.2-13, p=0.02), Table 3; four [2/19(11%) TNK vs 2/91(2%) alteplase, p=0.1] patients had no occlusion (mTICI 3) on initial angiogram or repeat multimodal imaging. No differences were observed in PH(p=0.9) or sICH [0/19(0%) TNK, 1/91(1%) alteplase, p=0.9].

Functional outcomes (after thrombolysis or bridging therapy) were not significantly different between treatment groups (Table 3).

Discussion

Unlike anterior circulation LVO stroke, current guidelines state that there is uncertainty about the benefit of thrombectomy in BAO (Class IIb; Level of Evidence C). (320) The recent BASilar artery International Cooperation Study (BASICS) trial, assessing the efficacy of EVT vs best medical management in 300 BAO subjects, demonstrated EVT benefit only in patients with NIHSS≥10 and suggested thrombolysis might be the optimal treatment in those with milder deficits". (263) Given this uncertainty, thrombolytic agents that may obviate the need for EVT or have beneficial effect during transfer to endovascular centers are warranted. The use of TNK in stroke is novel, not yet approved by regulatory agencies in most countries. Its supporting evidence largely comes from randomized controlled trials (RCTs) designed for anterior circulation LVO stroke. (203, 204) This study represents the largest series of TNK-treated BAO patients and the first to report TNK versus alteplase reperfusion rates before EVT in BAO. TNK led to higher reperfusion rates than alteplase, similarly to the 22% with TNK and 10% with alteplase reported in EXTEND-IA TNK trial. Functional outcomes were similar between treatment groups, although our study was underpowered to detect such differences. Larger studies are needed to detect treatment effect differences between thrombolytic agents prior to EVT, given the potentially EVT large effect. However, the strong relationship between earlier reperfusion and functional improvement, (159, 203) suggests TNK could improve outcomes and be beneficial during transfer to endovascular centers.

Our study has several limitations. The retrospective design and relatively small number of

TNK-treated patients reduces the precision of the results. Higher number of “drip and ship” patients in the alteplase group led to longer needle-to-arterial-puncture-times, likely due to transfer times between primary stroke centers administering thrombolysis (located in metropolitan and rural areas) and EVT centers. However, this imbalance should have favored reperfusion after alteplase, as it had additional time to act on the occlusion. More than 80% of TNK patients were treated in a RCT setting whereas 97% of alteplase data were from observational data with slower workflow (which further explains the needle-to-arterial-puncture-time imbalance). Although RCTs are considered more reliable than observational studies, previous studies comparing interventions effect size in both types of studies did not show systematic differences. (328) TNK were older than alteplase patients, likely due to more recent broader age selection criteria for reperfusion therapies, which would favor improved functional outcomes in the alteplase group. Therefore, our results may represent a conservative estimate of TNK benefits. No worse functional outcome or hemorrhagic complications were found in TNK patients despite being older, in accordance with previous studies. (159) Although age and clinical severity may influence clinical outcomes associated with reperfusion, recent evidence suggested time from thrombolysis to reperfusion assessment, thrombus location and permeability to be independently associated with reperfusion. (329) The dose of TNK varied. However, no differences were demonstrated between TNK 0.25mg/kg and 0.4mg/kg in the EXTEND-IA TNK study. (204)

Conclusions

Tenecteplase may be associated with increased reperfusion rates in comparison with alteplase before EVT in BAO. Given BAO dismal prognosis, RCTs to compare tenecteplase with alteplase in BAO patients are warranted.

Table 1. Number of patients recruited in the EXTEND IA TNK trials and the BATMAN registry.

	All patients (n=110)	Alteplase 0.9mg/kg (n=91)	TNK 0.25mg/kg (n=12)	TNK 0.4 mg/kg (n=7)
EXTEND IA TNK part I, n(%)	6 (5)	3 (3)	3 (25)	0 (0)
EXTEND IA TNK part II, n(%)	13 (12)	0 (0)	6 (50)	7 (100)
BATMAN registry, n(%)	91 (83)	88 (97)	3 (25)	0 (0)

Abbreviations: TNK=Tenecteplase.

Table 2. Baseline characteristics.

	All patients (n=110)	Alteplase (n=91)	Tenecteplase (n=19)	p
Age(years), mean	69±14	67±14	77±14	0.01
NIHSS, median(IQR)	16 (7-32)	15 (7-32)	20 (5-32)	0.9
Male sex, n(%)	70 (64)	60 (66)	10 (53)	0.3
Risk factors, n(%)				
Hypertension	64 (58)	53 (58)	11 (58)	0.9
Hypercholesterolemia	32 (29)	25 (27)	7 (37)	0.6
Diabetes Mellitus	28 (25)	26 (29)	2 (11)	0.1
Atrial fibrillation	28 (25)	23 (25)	5 (26)	0.9
Smoking	18 (16)	17 (19)	1 (5)	0.1
Coronary artery disease	24 (22)	20 (22)	4 (21)	0.9
Stroke etiology, n(%)				
Cardioembolic	44 (40)	35 (38)	9 (47)	0.9
Atherosclerotic	30 (27)	27 (30)	3 (16)	
Undetermined or other	36 (33)	28 (31)	7 (37)	
Onset-to-needle time, median(IQR), (min)	165 (126-200)	160 (130-200)	181 (93-203)	0.9
Needle-to-arterial-puncture time, median (IQR), (min)	84.5 (46-163)	110 (51-185)	48 (40-71)	0.004
"Drip and ship" patients, n (%)	43 (39)	40 (44)	3 (16)	0.04
mTICI 2b-3, n(%)	90 (82)	76 (84)	14 (74)	0.3

"Drip and ship" patients: patients thrombolysed at primary stroke centers and subsequently transferred to a comprehensive stroke center for endovascular therapy. Abbreviations:

NIHSS=National Institutes of Health Stroke Scale; TOAST=Trial of Org10172 in Acute Stroke Treatment classification; mTICI=modified thrombolysis in cerebral infarction; IQR= interquartile range.

Table 3. Outcomes.

	All patients (n=110)	Alteplase (n=91)	Tenecteplase (n=19)	RR	95%CI	p	Hosmer-Lemeshow goodness of fit p-value
Substantial reperfusion, n (%)	11 (10)	6 (7)	5 (26)	4.0[a]	1.3-12	0.02	0.7
Substantial reperfusion	-	-	-	4.0[b]	1.2-13	0.02	0.7
Substantial reperfusion	-		-	3.5[c]	1.1-11	0.03	0.9
mRS≤1, n(%)	45 (41)	34 (37)	9 (47)	1.6[d]	0.9-2.7	0.1	0.9
mRS≤2, n(%)	52 (47)	43 (47)	9 (47)	1.2[d]	0.7-2.0	0.5	1.0
Parenchymal hematoma, n(%)	3 (3)	3 (3)	0 (0)	0	N/A[e]	0.99	N/A[d]
Symptomatic intracerebral hemorrhage, n(%)	1 (1)	1 (1)	0 (0)	0	N/A[e]	0.99	N/A[d]

Substantial reperfusion: Reperfusion >50% or absence of retrievable thrombus. Hosmer-Lemeshow test: statistical test for goodness of fit for regression models. [a]Unadjusted Risk Ratio for substantial reperfusion (Risk Ratio for substantial reperfusion adjusted for age and NIHSS is RR

3.9, 95%CI 1.5-10; p=0.006, Hosmer-Lemeshow goodness of fit p-value: 0.8). Abbreviations: mRS=modified Rankin Scale score; RR=Risk ratio; [b]Risk ratio adjusted for needle-to-arterial-puncture time. [c]Risk ratio adjusted for cardioembolic aetiology. [d]Risk ratio adjusted for age and NIHSS. N/A Not applicable – [e]results not meaningful due to very low counts including zero.

Thesis conclusions and future directions

This thesis has explored and proposed novel approaches and solutions for the treatment and management of patients with posterior circulation stroke. These include:

1) the development of two novel imaging prognostic scores that can be used to predict functional outcome in patients with basilar artery occlusion and to select patients who are more likely to benefit from reperfusion therapies in extended time windows.

2) The development and validation of a modified version of the most widely used scale to assess clinical severity in stroke patients, the National Institutes of Health Stroke Scale. Our POST-NIHSS aims to improve prognostic accuracy in posterior circulation stroke patients and may help to identify patients with mild symptoms at high risk of poor outcome.
3) The use of the novel thrombolytic agent in stroke tenecteplase, which appears to be associated with higher recanalization rates compared to alteplase in patients with basilar artery occlusion.

Imaging prognostic scores in with basilar artery occlusion

We developed two novel imaging prognostic factors that appear to be strongly associated with functional outcome in patients with basilar artery occlusion.

In our work, CBV pc-ASPECTS was more strongly associated with functional outcomes than CTA-SI in patients with basilar artery occlusion, consistent with previous work that demonstrated improved diagnostic accuracy with CT Perfusion in posterior circulation stroke. (107, 108) This is analogous to anterior circulation stroke, where previous studies have shown that CBV ASPECTS is more strongly associated with functional outcome compared with baseline CT and CTA-SI ASPECTS in anterior circulation strokes. (298, 299, 303) CBV pc-ASPECTS can be assessed without the need for volumetric software and may have potential implications for treatment decision-making and a possible role in future trials in basilar artery occlusion. Moreover, our study emphasized the value of including whole-brain CT Perfusion in the diagnostic evaluation of patients with basilar artery occlusion. In another study, the value of pc-ASPECTS on CT Perfusion maps was evaluated as a predictor of malignant cerebellar oedema in n=51 patients with cerebellar ischemic deficits on whole-brain CT Perfusion and follow-up–confirmed cerebellar infarction. (330) Patients who developed malignant cerebellar oedema showed significantly lower median pc-ASPECTS in all CT Perfusion maps ($p<0.001$) compared with patients who did not develop malignant cerebellar oedema. In contrast, median pc-ASPECTS on non-contrast CT and CTA was not significantly different. Receiver operating characteristics area-under-the-curve values for the prediction of malignant cerebellar oedema development were 0.935 (95% CI 0.869–1.000) for pc-ASPECTS on CBF and 0.898 (95%CI 0.812–0.984) for pc-ASPECTS on CBV, whereas pc-ASPECTS on non-contrast CT (0.648, 95% CI 0.448–0.848) and CTA-SI (0.684, 95% CI 0.473–0.895) had less diagnostic value. In a subsequent study from the same group, including n=60 patients with cerebellar whole-brain CT Perfusion deficits and cerebellar infarction confirmed on follow-up imaging, pc-ASPECTS on CBF was significantly associated with final infarction volume (odds ratio 0.89; 95% CI, 0.68-1.09; p<0.001). (331) In a more recent study, assessment of pc-ASPECTS on qualitative analysis of colour-coded maps was more accurate in the detection of ischaemic changes compared to automatic quantitative analysis, whereas software-generated mismatch maps tended to underestimate the extent of the ischaemic core. (332)

Importantly, in the BASILAR study, patients with pc-ASPECTS ≥8 were more likely to have favourable outcomes in both the endovascular therapy (43.8% vs 14.3%) and standard medical therapy (16.7% vs 4%) arms compared to those with pc-ASPECTS<8. Although the prognostic accuracy of pc-ASPECTS has been well-validated in several studies and different imaging modalities, its use in the acute setting has not been implemented yet as the detection of ischaemic lesions in the posterior fossa remains challenging, particularly in the brainstem. In our study, most of the CBV abnormalities were detected in the cerebellum (42%) and the occipital regions (12%) with low detection rates of ischemic changes in brainstem and thalami (7%). Although improved on CT Perfusion in comparison with CTA-SI or non-contrast CT brain alone, this is not yet comparable to the accuracy of MRI diffusion-weighted imaging sequences.

Dual-energy CT has been explored as an alternative approach to improve the diagnostic accuracy of non-contrast CT brain in the posterior fossa. (333) In a small retrospective study of n=30 patients with suspected posterior circulation stroke, monoenergetic 80keV and 100keV reconstructions provided artifact reduction and maximization of image quality, significantly better than standard non-contrast CT brain (p<0.001). Sensitivity, specificity, positive predictive value, and negative predictive values were non-inferior compared to non-contrast CT brain. (333) Further larger studies would be required to confirm these findings and justify the routine use of dual-energy CT to improve diagnostic accuracy in the posterior fossa.

Recently, artificial intelligence approaches and machine learning models have been adopted more successfully to improve stroke imaging interpretation and the prognostic accuracy of imaging scores. ASPECTS was the first score to be validated using artificial intelligence algorithms for anterior circulation strokes. In several studies, automated assessment of ASPECTS showed similar performance to that of neuroradiologists and stroke experts. (334-337) This led to commercially available tools that aid decision-making of stroke physicians for anterior circulation strokes. A similar approach has been attempted in the posterior circulation. Recently, Kniep et al. (338) analysed 552 pc-ASPECTS regions extracted from non-contrast CT brain scans of n=69 patients with basilar artery occlusion who were subsequently treated with reperfusion therapies and achieved successful recanalization. Random forest algorithms with five-fold cross-validation were used to detect early ischemic changes and evaluate their association with infarction on follow-up imaging. Receiver operating characteristic areas-under the-curve for detection of early ischemic changes were 0.70 (95% CI [0.64; 0.75]) for cerebellum to 0.82 (95% CI [0.77; 0.86]) for thalamus. Importantly, the predictive performance of the artificial intelligence-based algorithm was significantly higher compared to the visual readings performed by two experienced neuroradiologists for the thalamus, midbrain, and pons ($p<0.05$). (338) Although this approach needs further validation in larger datasets, the implementation of machine-learning models that aid detection of ischemic changes in regions where visual assessment is more challenging (e.g. in the brainstem due to the beam hardening artifact) may improve both the diagnostic and prognostic accuracy of previously validated scores in the posterior circulation such as pc-ASPECTS and the pons-midbrain index. Similar to the automated ASPECTS, artificial intelligence-improved posterior circulation prognostic scores could be implemented as commercially available tools that may be used either in randomized controlled trial settings to select patients more likely to benefit from reperfusion therapies or to assist clinicians in treatment-decision making. An artificial intelligence-based approach has also been proposed for CT Perfusion maps in anterior circulation stroke. Robben et al. developed a deep neural network that can predict the final infarct volume from CT Perfusion images and additional treatment parameters. (339) Similar approaches could be used to predict functional outcomes at 3 months and potentially be applied to our CT Perfusion pc-ASPECTS to improve the detection rate of ischaemic changes in the brainstem, the score inter-rater reliability and prognostic accuracy.

The BATMAN score (128-130, 340-342) and the PC-CS (127, 128, 261, 343) are well-validated vascular scores in basilar artery occlusion. In the work presented in this thesis, done in collaboration with the BASICS group, (65) we demonstrated a robust association between revascularization and good outcome in patients with basilar artery occlusion with low thrombus burden and good collaterals (favourable BATMAN and PC-CS scores) which extends beyond the recommended 6-hour time window for endovascular therapy. Therefore, collateral assessment on CTA using these two scores may have a role in the acute setting to select patients for reperfusion therapies in delayed time windows. Interestingly, in our work, we found an effect similar to the "late paradox" described in anterior circulation strokes treated with endovascular therapy in late time windows, with the greater benefit of endovascular therapy for patients with favourable collateral scores (which would correlate with favourable CT perfusion profiles) seen in delayed time windows. A recent editorial published in Stroke, (344) highlighted that our study has important implications for future guidelines and research. Indeed, our study results offer a potential pathophysiological explanation for the conflicting findings regarding the effect of onset-to-treatment time in basilar artery occlusion. (310, 311) Revascularization is associated with good outcome in patients with basilar artery occlusion undergoing endovascular treatment in the setting of good collaterals and less extensive occlusion, even when treated >6 hours from onset. Importantly, in our study endovascular reperfusion was associated with improved outcomes within 6 hours of onset, even in patients with unfavourable BATMAN and PC-CS scores. The editorial also emphasises the value of our international collaboration in pooling real-world data for uncommon causes of stroke, providing an important contribution to the literature supporting the use of endovascular treatment for basilar artery occlusion. In light of the growing observational evidence, including the recent BASILAR study results supporting the benefit of EVT up to 24 hours, a modification of the current guidelines to recommend endovascular therapy within 24 hours in carefully selected patients with basilar artery occlusion might be considered.

More recently, Kwak et al. (270) investigated clinical and imaging prognostic factors of outcome in patients with acute basilar artery occlusion treated with mechanical thrombectomy. In n=81 patients, they found that higher BATMAN score [median 6 (interquartile range 4–7) versus 5 (4–5); p<0.001] and PC-CS [median 6 (interquartile range 4–7) versus 5 (4–6); p<0.001] were associated with good outcomes (modified Rankin scale 0-2). The area-under-the-curve was 0.701 (95% CI, 0.575–0.827; p=0.003) for the BATMAN score and 0.706 (95% CI, 0.583–0.829; p=0.002) for the PC-CS. The optimal cut-off to discriminate between good and poor outcomes for both scores was 6 (BATMAN score sensitivity 60%, specificity 78.4%; PC-CS sensitivity 60%, specificity 74.5%). In multivariable analyses, PC-CS ≥6 (p=0.04), baseline National Institutes of Health Stroke Scale <15 (p=0.004) and occlusion of the distal basilar artery (p=0.035) remained associated with good outcomes. In contrast to our study, other factors such as a favourable BATMAN score (categorized as ≥6) did not remain associated with better outcomes. Other factors such as age, successful recanalization and time from symptom onset to recanalization (categorized as 0-6 hours, 6-12 hours and >12 hours) were not significantly associated with functional outcomes in the univariate analysis.

Nonetheless, this study corroborates our findings that CTA collateral scores are strongly associated with functional outcomes in basilar artery occlusion, whereas onset time to reperfusion might not have the same strong association. Importantly, in this study, all five patients who achieved a favourable outcome without achieving successful recanalization had high baseline collateral scores (BATMAN score and PC-CS ≥6). Moreover, the group of patients with a distal basilar artery occlusion had higher BATMAN score (6.0±1.5 versus 4.5±1.3, p<0.001) and PC-CS (6.0±1.5 versus 4.7±1.2; p<0.001) compared with the group of patients with proximal basilar artery occlusion. (270)

The PC-CS and BATMAN scores allow assessment of collaterals and thrombus burden without the need for additional imaging, providing significant advantages in speed of pre-treatment workup. The implementation of artificial-intelligence-based versions of these scores (automated BATMAN or automated PC-CS) may provide significant benefits in terms of prognostication and assist clinicians in treatment-decision making to select patients who are more likely to benefit from reperfusion therapies, even in delayed time windows.

Posterior NIHSS

We developed a modified version of the NIHSS including assessment of gait/truncal ataxia and bulbar signs, which appears to improve NIHSS prognostic accuracy in patients with posterior circulation stroke presenting with mild-moderate symptoms. The incorporation of gait ataxia and bulbar signs assessment in a structured tool may help with early prognostication for posterior circulation stroke patients presenting with mild symptoms by identifying those at higher risk of poor outcome. Moreover, POST-NIHSS may help to select patients who are more likely to benefit from reperfusion therapies. For instance, patients presenting with a baseline NIHSS 0-5 or having relative contraindications to intravenous thrombolysis have more finely balanced risks and benefits of thrombolysis to consider. Furthermore, whether endovascular therapy is beneficial for at least some patients with mild deficits is unclear. The BASICS trial results (263) may lead to patients with NIHSS<10 being less likely to receive endovascular therapy. In both these scenarios, POST-NIHSS may identify those patients with lower NIHSS who nonetheless have potentially disabling symptoms such as gait/truncal ataxia or bulbar signs, and who might therefore benefit from thrombolysis and/or thrombectomy.

The decision of whether to offer reperfusion therapies in patients with mild symptoms remains challenging for stroke physicians. The risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis appears to be lower than in more severely affected patients (1.7% with National Institutes of Health Stroke Scale [NIHSS] score 0–4 versus 3.9% with NIHSS score ≥5; p=0.048 in anterior circulation stroke patients) (345) and in those with posterior circulation stroke compared to anterior circulation stroke (odds ratio 0.32, 95% CI 0.21–0.49). (175) Pooled analysis of randomized trials of alteplase suggested benefit in patients with mild but disabling symptoms. Alteplase increased excellent functional outcomes (modified Rankin Scale 0-1) from 59% to 69% of patients with baseline NIHSS score 0 to 4; adjusted odds ratio, 1.48 (1.07–2.06). (159) However, no benefit was detected in the recent PRISMS trial. (346) This randomized controlled trial recruited n=313 patients with a baseline NIHSS 0-5 and non-disabling symptoms. Patients were randomized to either intravenous alteplase 0.9 mg/kg with oral placebo (n =156, intervention arm) or oral aspirin 325 mg with intravenous placebo (n =157, control arm). This study showed that 78.2% in the alteplase group vs 81.5% in the aspirin group achieved an excellent outcome (modified Rankin scale 0-1, adjusted risk difference, −1.1%; 95% CI −9.4%-7.3%). Symptomatic haemorrhage occurred in five alteplase-treated patients (3.2%) vs 0 aspirin-treated patients (risk difference, 3.3%; 95% CI, 0.8%-7.4%). Consistent with these results, current stroke guidelines recommend that intravenous thrombolysis may be reasonable for patients with mild but disabling stroke symptoms within 4.5 hours of symptom onset. (250) Our data provide greater clarity on what constitutes potentially disabling symptoms in posterior circulation strokes and therefore may support increased utilisation of intravenous thrombolysis in this patients' group.

More recently, Saber et al. (347) analysed data from the largest US all-payer inpatient claims-based database. They showed that more than one-half of acute ischemic stroke hospitalizations had mild deficits with NIHSS 0-5 and accounted for 4 of every 10 intravenous thrombolysis and 1 of every 10 mechanical thrombectomy treatments. This is higher than earlier estimates, suggesting an increased implementation of thrombolysis for mild stroke. (348) In this study, intravenous thrombolysis was associated with an increased likelihood of discharge to home (odds ratio, 1.90 [95% CI 1.71–2.13], p<0.001) despite an increased risk of intracranial hemorrhage (odds ratio, 1.41 [95% CI 1.09–1.83], p<0.001). (347) However, the proportion of patients with posterior circulation stroke was not reported in this study.

Data on the effect of endovascular therapy in mildly affected patients are lacking with only 14 patients with NIHSS score 0 to 5 enrolled in the pivotal trials. (239) In a cohort of conservatively managed stroke patients with large vessel occlusion and NIHSS score ≤8 patients, Mokin et al. retrospectively observed an overall rate of death or dependence of 38% which increased to 59% for basilar artery and 45 % for the P1 and P2 segment of the posterior cerebral artery. (349) Recently, Saito et al. performed a post-hoc analysis of n=272 patients with large vessel occlusion and NIHSS 0-5 from a large Japanese multicenter prospective registry. (350) In this cohort, 35% of patients had a posterior circulation stroke. They found that age <75 years (odds ratio, 2.42 [95% CI, 1.30–4.50]), NIHSS score 0-3 (odds ratio, 3.08 [95% CI, 1.59–5.98]), blood glucose level ≤140 mg/dL (odds ratio, 2.37 [95% CI, 1.22–4.60]) and intravenous thrombolysis (odds ratio, 2. 86 [95% CI, 1.32–6.21]) were independently associated with a good outcome (modified Rankin scale 0-2) at 3 months. (350) The effectiveness of intravenous thrombolysis for acute large vessel occlusion stroke with mild symptoms might be attributable to a more peripheral location of the occlusion. (329)

The ENDO-LOW (Endovascular Therapy for Low NIHSS Ischemic Strokes; URL: https://www.clinicaltrials.gov; Unique identifier: NCT04167527) and MOSTE (Minor Stroke Therapy Evaluation; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03796468) are investigating the benefit of endovascular therapy for mildly affected anterior circulation stroke patients. No trial has investigated this issue in basilar artery occlusion, although these patients frequently present with mild or fluctuating symptoms. In the BASICS trial, (263) 15% of patients had a fluctuating onset in the endovascular therapy arm and 14% in the control group.

In a recent multicentre retrospective study of n=57 patients with basilar artery occlusion with NIHSS score 0-5, Seners and colleagues (351) compared bridging therapy and intravenous thrombolysis alone. This study showed that bridging therapy was associated with excellent outcomes (modified Rankin Scale 0-1, adjusted odds ratio 3.37 [95% CI, 1.13–10.03]; p=0.03) compared to intravenous thrombolysis alone. No patient had symptomatic intracranial hemorrhage.

Although patients with NIHSS <10 were included in the work presented in this thesis, the median NIHSS in our derivation and validation cohort was 3 and 2 respectively, a group in whom thrombolysis or endovascular therapy may not routinely be used. Dysphagia and gait/truncal ataxia can be also present in patients with anterior circulation strokes with infarctions in regions such as the frontal lobe, basal ganglia and corona radiata lesions. A validation of the POST-NIHSS in patients with low NIHSS, regardless of the stroke topography, is therefore warranted.

Neurological deterioration in patients with mild symptoms

Disability in mild stroke is not only due to unrecognised disabling deficits at presentation. A proportion of initially mildly affected patients may subsequently deteriorate and become disabled, predominantly patients with large vessel occlusion, (348) and often once the time window for reperfusion therapies has passed.(315) The ongoing TEMPO-2 randomized trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02398656) is testing tenecteplase within 12 hours in ischaemic stroke patients with mild symptoms (including patients with stroke in the vertebrobasilar territory), building on non-randomized data that indicated improved outcomes in patients with mild stroke who had vessel occlusion if they underwent reperfusion. (352) A recent large French-study explored this topic in n=729 consecutive patients with minor stroke (NIHSS score 0-5) and large vessel occlusion intended for intravenous thrombolysis alone. (353) Basilar artery occlusion was present in 4% of patients. Early neurological deterioration of presumed ischaemic origin was defined as ≥4 point deterioration in NIHSS score within 24 hours, without parenchymal hemorrhage on follow-up imaging or another identified cause. This study found that early neurological deterioration of presumed ischaemic origin affected approximately 12% of patients and accounted for approximately 90% of all cases with neurological deterioration. Importantly, patients with early neurological deterioration had significantly poorer 3-month outcome than those without (common odds ratio, 7.37; 95% CI, 4.79- 11.35; p< 0.001), even in patients who underwent rescue thrombectomy (modified Rankin scale 0-1, 48% vs 77.5%, respectively; p< 0.001). In multivariable analysis, more proximal occlusion site (internal carotid artery tandem lesion, adjusted odds ratio 16.0 [95% CI 5.7-44.9]; basilar artery occlusion, adjusted odds ratio 7.2 [95% CI 2.6-20.0] vs distal M1 occlusion, adjusted odds ratio 2.5 [95% CI 1.2-5.1], p<0.001) and longer thrombus length ≥9mm (adjusted odds ratio 3.2, 95% CI 1.8-5.7; p=0.002) were independently associated with early neurological deterioration. The authors of this study subsequently developed and validated a 6-point score to predict early neurological deterioration based on the location of the occlusion and thrombus length. In this score, 2 points should be given for occlusion of the basilar artery, with 1 additional point given if the thrombus is ≥9mm. Analogous to this score developed to predict early neurological deterioration for all large vessel occlusion stroke patients with mild symptoms, the BATMAN score (which assesses the thrombus burden mitigated by the presence of collaterals) may be used to predict early neurological deterioration in patients with basilar artery occlusion presenting with mild symptoms. In a recent small (n=138) retrospective study, Koh et al. (341) showed that incomplete occlusion (odds ratio 6.17, 95% CI 1.1–34.2, p=0.037), lower pc-ASPECTS on DWI (odds ratio 1.96, 95% CI 1.1–3.5, p=0.021) and lower BATMAN score (odds ratio 1.91, 95% CI 1.2–3.5, p=0.009) were significantly associated with neurological deterioration (defined as an increase in the NIHSS score by 4 or more points between the point of admission and discharge) in n=73 patients with vertebrobasilar occlusion who did not undergo reperfusion therapies. (341)

Previous studies reported that almost half of mild stroke patients were treated with endovascular therapy after early in-hospital neurological deterioration. (354) This is probably due to the fear of potential reperfusion complications including the risk of intracerebral hemorrhage that makes physicians await early deterioration before offering endovascular therapy. However, rather than waiting for potential clinical neurological deterioration, putting patients at risk of significant post-stroke disabling symptoms, a thorough clinical assessment to identify those more likely to deteriorate should be performed. As a by-product of testing for gait/truncal ataxia, the upright posture may trigger a worsening of collaterals and temporarily provoke disabling symptoms in patients initially mildly affected. (355) Similarly, the assessment of bulbar symptoms in the acute settings may identify patients at high risk of poor outcome and more likely to benefit from reperfusion therapies. This approach along with the use of more advanced imaging may help to differentiate patients at risk of deterioration and disability from those with a benign natural history for whom revascularization poses an unnecessary risk.

Tenecteplase in basilar artery occlusion

In this thesis, we presented the first series of patients with basilar artery occlusion treated with tenecteplase. Our findings suggest that tenecteplase may be associated with increased reperfusion rates in comparison with alteplase in patients with basilar artery occlusion, with rates of reperfusion similar to the 22% with tenecteplase and 10% with alteplase reported in the EXTEND-IA TNK trial. (203) In contrast to EXTEND-IA TNK, functional outcomes were similar in the two treatment groups but our study was underpowered to detect such differences. Nonetheless, there was a non-significant trend towards higher 3-month excellent outcomes in patients treated with tenecteplase (modified Rankin Scale 0-1 47% vs 37%, p=0.09) compared to alteplase, which did not translate into better outcomes after multivariable analysis adjusted for age and NIHSS (adjusted risk ratio 1.6, 95% CI 0.9-2.7; p=0.1). However, patients treated with tenecteplase were older than those treated with alteplase, likely due to more recent broader age selection criteria for reperfusion therapies, and tended to have higher baseline NIHSS scores (20 (IQR 5-32) for tenecteplase-treated patients versus 15 (IQR 7-32) for alteplase-treated patients, p=0.9). These differences in baseline characteristics would favour improved functional outcomes in the alteplase group. Therefore, our findings may represent a conservative estimate of the clinical benefits associated with tenecteplase. Interestingly, in a recent meta-analysis including five tenecteplase trials (n=1585), (206) the greater effect of tenecteplase was detected when excellent outcomes were used as primary endpoint [(modified Rankin scale 0-1, crude cumulative rates of disability-free 57.9% tenecteplase versus 55.4% alteplase; risk difference 4% (95% CI, −1% to 8%)] compared to good outcomes (modified Rankin Scale score, 0–2, crude cumulative rates of functional independence, 71.9% tenecteplase versus 70.5% alteplase, risk difference 2% (95% CI, −3% to 6%)]. (206)

Although no definitive conclusions about the clinical benefit of tenecteplase can be drawn from our findings, the well-established strong relationship between earlier reperfusion and better functional outcomes, (159, 203) suggests that tenecteplase could improve outcomes. Nonetheless, larger studies are needed to detect treatment effect differences between the two thrombolytic agents, given the likely larger effect of endovascular therapy. Despite this, our findings corroborate the accumulating evidence that suggests superiority of tenecteplase compared to alteplase in large vessel occlusion strokes. A recently published meta-analysis including only patients with large vessel occlusions (4 studies, n=433 patients), (356) showed that patients receiving tenecteplase had higher successful recanalization (odds ratio, 3.05 [95% CI, 1.73–5.40]), higher odds of good outcomes (modified Rankin Scale scores of 0 to 2, odds ratio, 2.06 [95% CI, 1.15–3.69]) and functional improvement defined as 1-point decrease across all modified Rankin Scale (common odds ratio, 1.84 [95% CI, 1.18–2.87]) at 3 months compared with patients with receiving alteplase. (356)

In a recent editorial published in Neurology, (357) our work was valued for its contribution to the field by exploring a promising alternative thrombolytic agent in the treatment of basilar artery occlusion. Among the limitations discussed in the editorial, Lin et al. (357) highlight that the BATMAN registry from where the alteplase-data were extracted, represent historical treatment and that the use of early generation thrombectomy devices and learning curve of interventionalists may have influenced our primary and secondary outcomes. While this may have impacted our secondary outcomes (e.g. 90 days modified Rankin scale score), these factors should not influence the primary outcome of reperfusion on the initial angiogram prior to endovascular therapy. Other factors such as time from thrombolysis to reperfusion assessment, which in our study was in favour of the alteplase group, thrombus location and permeability appear to be independently associated with reperfusion. (329)

The reduced cost and single-bolus administration of tenecteplase versus an hour-long alteplase infusion in patients with basilar artery occlusion who are being transported between hospitals is a major practical advantage. Tenecteplase is given as a single, 5-second intravenous bolus that requires approximately 2 minutes to prepare and administer, whereas alteplase requires preparation of both a bolus syringe containing 10% of the dose and an intravenous pump for infusion of the remaining 90% of the dose over 60 minutes. Moreover, the use of tenecteplase can minimize the risk of error in the preparation and delivery of the thrombolytic drug in the acute setting. Therefore, tenecteplase could be administered more efficiently in patients with basilar artery occlusion, permitting faster commencement of subsequent endovascular therapy, especially in patients treated with intravenous thrombolysis at primary stroke centres and then transferred for endovascular therapy ("drip and ship patients"). These patients may have tenecteplase administered at the primary hospital and then be immediately transferred by a standard ambulance without having to wait for critical care transport with staff expert in continuous infusion pump management and without risking interruption or discontinuation of the alteplase infusion during transit. (206)

In Australia, tenecteplase is slightly cheaper per vial. However, patients >55kg need two vials of alteplase where as only one vial of tenecteplase is required regardless of patient weight, translating to a saving of ~AU$2000 per patient. This is in addition to cost savings from reduced requirement for endovascular thrombectomy when tenecteplase is used and long term savings due to reduced disability. Economic analysis of the EXTEND-IA TNK trial indicated that tenecteplase was dominant (cost-saving) vs alteplase in patients with large vessel occlusion. (358)

Finally, tenecteplase has been reported as a more practical thrombolytic agent during the COVID-19 pandemic. Eliminating the alteplase 1-hour infusion and the required dedicated second intravenous cannula may reduce staff time in proximity to the patient. Moreover, tenecteplase does not need the intravenous infusion pump that accompanies the patient through other hospital departments and wards, presenting an additional surface that could facilitate the transmission of the virus. (206)

Endovascular therapy is highly effective but resource-intensive and access is currently limited in most countries. In Australia, people living in regional areas are 19% more likely to have a stroke. (9) Presently, more than two-thirds of endovascular patients with basilar artery occlusion are referred either from regional hospitals where there are significant barriers to treatment or metropolitan hospitals that do not have endovascular therapy capacity. In rural areas of Australia, delays to the initiation of endovascular therapy are generally 4-6 hours. Patients who initially present to an endovascular therapy-capable centre may still wait at least 60 minutes between hospital arrival and commencement of endovascular therapy, especially patients with basilar artery occlusion who often require intubation before endovascular therapy can be performed. Given each minute reduction in door-to-reperfusion time is associated with a saving of 4.4 disability-adjusted life days, (159) tenecteplase may be a safe and effective treatment to 'buy some time' until endovascular therapy can be performed in these patients, especially in those transferred from regional areas. The EXTEND-IA TNK (part II trial) (204) demonstrated that longer time between thrombolysis with tenecteplase and commencement of endovascular therapy in rural sites was associated with significantly higher reperfusion rates prior to endovascular therapy compared with metropolitan patients. Therefore, tenecteplase may allow treatment of a higher number of patients with a devastating form of stroke such as basilar artery occlusion in regional areas and obviate the need to transfer some patients if there is rapid recanalization with early clinical improvement. During inter-hospital transfer, tenecteplase will have time to act on the occlusion which may facilitate early recanalization and have beneficial effects during transfer to a comprehensive centre for endovascular therapy.

What did we learn from the BASICS and BEST trials and the BASILAR study?

Pending the publication of the complete results of the BASICS trial, several hypotheses can be postulated to explain the better than expected outcome in the standard therapy arm:

1) Time of onset was considered as the estimated time of occlusion of the basilar artery and not as the time of onset of any symptoms. Estimated time of basilar artery occlusion was defined as the time of onset of acute symptoms leading to clinical diagnosis of basilar artery occlusion or if not known last time the patient was seen normal prior to the onset of these symptoms. Approximately 50% of patients were entered under this modified definition of onset time. This approach was adopted to include patients with acute neurological deterioration preceded by mild symptoms but consequently allowed more patients to be treated with intravenous thrombolysis compared to the standard approach of treating patients within 4.5 hours of symptom onset. The BASICS study, therefore, had a very high (nearly 80%) rate of intravenous thrombolysis. Although the same definition of time of onset from the estimated time of occlusion was adopted in the BEST and BASILAR studies, this was only used for endovascular therapy, not for intravenous thrombolysis.
2) Intravenous thrombolysis was performed with overall more inclusive criteria in comparison with the BEST trial and the BASILAR study with a very high rate in the control group (79.5%) but also in the intervention group (79.1%).
3) Intravenous thrombolysis beyond 4.5 hours from the estimated time of occlusion was allowed, although in a small group of n=21 patients.

Given the lack of EVT in the control group, investigators were likely prone to offer a broader treatment with intravenous thrombolysis in the standard medical therapy group in the hope of maximising the chances of survival and reduced disability for these patients. The cross-over rate in the BASICS trial was low (3 patients in the intervention group were treated with best medical management and 7 patients in the best medical management were treated with endovascular therapy). However, a high rate of intravenous thrombolysis was present in the BASICS intervention arm (79.1%). Importantly, most of the patients (n=200/300, 67%) in the BASICS trial were recruited in the Netherlands, where a protocol characterised by intravenous thrombolysis within 4.5 hours of the estimated time of onset has been adopted since the BASICS registry results. Looking at patients recruited in other countries such as Brazil, with different treatment protocols and where endovascular therapy was available only through randomization in the trial, the results appear different. Although in small numbers (n=42) a non-statistically difference of 10% was found for good outcomes (modified Rankin scale 0-2, 33% in the intervention versus 23% in the best medical management arms). Selection bias due to non-consecutive recruitment, with good prognosis patients treated with open-label EVT outside the trial, cannot be ruled out in the BASICS trial. However, the authors of the trial felt that the influence of this bias was small.

The 6.5% absolute risk difference in good outcomes in BASICS, had it been statistically significant, would translate into a number needed to treat of 15.4 to achieve favourable outcomes (modified Rankin scale 0-3). This figure is not so different from the number needed to treat of 14 to achieve excellent outcomes (modified Rankin scale 0-1) in intravenous thrombolysis in the 3.5-4 time window, which is recommended by the current guidelines and routinely performed in clinical practice. In the BEST trial, the number needed to treat in the per-protocol analysis to achieve favourable outcomes (modified Rankin scale 0-3) is 5.3, which is similar to the number needed to treat of 3-7 to achieve good outcomes (modified Rankin scale 0-2) for endovascular therapy among the positive trials in anterior circulation strokes. However, the main legacy of the BASICS trial is that optimising and pushing the boundaries of intravenous thrombolysis delivery in patients with basilar artery occlusion might further improve outcomes. Although both the BASICS and BEST trials were neutral on their primary endpoints, their results provide supporting evidence to push boundaries for treatment with both intravenous thrombolysis and endovascular therapy in basilar artery occlusion patients. Pending the results of the BAOCHE trial, the BASILAR study provides supportive indicators of the possible benefit of endovascular therapy within 24 hours.

In summary:

1) A broader application of intravenous thrombolysis beyond the usual 4.5h after the last known well time might improve outcomes in patients with basilar artery occlusion. Intravenous thrombolysis beyond 4.5 hours appeared safe and may be effective in the absence of extensive baseline ischaemia on non-contrast CT brain in several observational studies. (175, 183, 219)
2) Endovascular therapy may be safe and effective, even when performed up to 24 hours, and particularly in patients with moderate-severe syndromes. The rate of haemorrhagic complications appeared to be acceptable (~7%) after endovascular therapy within 24 hours, even when patients with extensive baseline ischemia and poor collaterals were included.

A reperfusion strategy with both intravenous thrombolysis and endovascular therapy up to 24 hours may be the best option for patients with basilar artery occlusion and significantly improve outcomes in this devastating condition for which no optimal treatment has been identified to date.

Additional factors such as where the patient presents (directly to a comprehensive stroke centre or to a primary stroke centre) should be taken into consideration. Putting the BASICS results in perspective, patients with basilar artery occlusion may be treated more aggressively with intravenous thrombolysis (even beyond 4.5 hours) in settings where endovascular therapy is not immediately available while organising transfer to a comprehensive stroke centre for endovascular therapy. Some patients (e.g. those with milder symptoms and likely good collaterals) may benefit from intravenous thrombolysis while in transfer and achieve earlier reperfusion. On the other hand, patients with moderate or severe clinical syndromes will likely require intervention with endovascular therapy. In these patients, intravenous thrombolysis may work in synergy with endovascular therapy.

Careful assessment of imaging profiles (e.g. extent of baseline ischemia on non-contrast CT brain or CT perfusion maps) and collateral flow on CT Angiography (e.g. BATMAN score or PC-CS) may be performed to exclude patients who are unlikely to benefit from reperfusion therapies in extended time windows, although this approach requires further research in a randomized controlled trial setting. A modified in-hospital workflow for patients with posterior circulation stroke based on the findings of this thesis and the most recent literature evidence is illustrated in Table 5.

Future directions

In light of the above considerations, randomized controlled trials to explore more effective reperfusion strategies in patients with basilar artery occlusion are warranted. BAOCHE is a Chinese-led trial testing EVT (using the Solitaire device) versus standard medical therapy in patients with basilar artery occlusion in the 6-24 hour time window. The primary outcome of this trial is to achieve modified Rankin scale 0-4 (not requiring constant care or better) at 3 months. Subjects enrolled in this study must have a baseline NIHSS≥6 and are either ineligible for intravenous alteplase or have received alteplase therapy without recanalization. Neuroimaging exclusion for this study criteria include:

- pc-ASPECTS< 6 and Pons-midbrain-index of ≥ 3 on NCCT, CTA-SI or MRI.
- CT or MR evidence of haemorrhage
- Complete cerebellar infarct on CT or MRI with significant mass effect and compression of the fourth ventricle.
- Complete unilateral or bilateral thalamic infarction on CT or MRI
- Evidence of vertebral occlusion, high-grade stenosis or arterial dissection in the extracranial or intracranial segment that will prevent access to the intracranial clot or excessive tortuosity of cervical vessels precluding device delivery/deployment.

The estimated sample size is 318 patients. The study was commenced in June 2016. The estimated study completion date is December 2021.

In Australia, current practice is to consider endovascular therapy within 24 hours of symptom onset in basilar artery occlusion, given its dismal prognosis, although there is some variability due to the absence of strong evidence. The Australian guidelines recommend that endovascular therapy should be undertaken in selected stroke patients with basilar artery occlusion, without restricting the time window within 6 hours. However, intravenous thrombolysis in an extended time window in basilar artery occlusion has not been routinely adopted in clinical practice or investigated in a randomized controlled trial. Additionally, the work in this thesis shows that tenecteplase may be associated with increased reperfusion rates compared to alteplase. In a small (n=34) prospective, Canadian study, (359) the feasibility of thrombolysis with tenecteplase up to 24 hours after onset was assessed. Patients were selected using penumbral imaging. This study showed that tenecteplase was associated with clinical improvement (improvement in NIHSS score by ≥4 points) in 56% of cases. (359) Symptomatic intracranial haemorrhage occurred in only one patient (6.3%). (359)

<u>The POST-ETERNAL randomized trial</u>

In light of the recent evidence from the BASICS, BEST, BASILAR studies and our findings on the efficacy of tenecteplase in basilar artery occlusion, we have designed a novel randomized controlled trial, called POST-ETERNAL.

POST-ETERNAL is a multi-arm multi-stage (MAMS) randomised trial that will test the hypothesis that the thrombolytic tenecteplase (TNK, 0.25mg/kg) administered within 24 hours after symptom onset, is superior to current best practice (alteplase, 0.9mg/kg within 4.5 hours or standard care/no lysis) in achieving excellent functional outcomes or return to the premorbid modified Rankin Scale at 90 days in patients with acute ischaemic stroke due to basilar artery occlusion. Endovascular therapy will be allowed in both arms within 24 hours of symptom onset but will not be mandatory. This study will be a MAMS, multicentre, prospective, randomised, open-label, blinded endpoint (PROBE), controlled seamless phase 2b/3 trial, with covariate adaptive randomisation and adaptive sample size re-estimation in patients with stroke due to basilar artery occlusion. Stage 1 will use the surrogate outcome of recanalization without symptomatic intracerebral haemorrhage to establish whether proceeding to Stage 2 is warranted. If results in the first n=202 patients meet success criteria, the trial will seamlessly convert to a phase 3 design using modified Rankin scale 0-1 at 3 months as the primary outcome (minimum n=320 with interim sample size re-estimation at n=240, maximum sample n=688) using the Mehta and Pocock "promising zone" method. (360)

Inclusion Criteria

1. Patients presenting with posterior circulation ischaemic stroke symptoms due to basilar artery occlusion within 24 hours from symptoms onset (or clinical deterioration) or last known well.
2. Patient's age is ≥18 years.
3. Presence of basilar artery occlusion on CT Angiography or MR Angiography. Basilar artery occlusion will be defined as 'potentially retrievable' thrombus in the basilar artery.
4. Premorbid mRS ≤2 (independent function)

Exclusion Criteria

1. Intracerebral haemorrhage (ICH) or other diagnosis (e.g., tumour) identified by baseline imaging.
2. Significant cerebellar mass effect or acute hydrocephalus.
3. Established frank hypodensity on non-contrast CT indicating subacute infarction.
4. Bilateral extensive brainstem ischaemia.
5. High suspicion of underlying intracranial atherosclerotic disease requiring immediate stenting.

Outcome measures

Stage 1 (phase 2b, intermediate outcome):

• Proportion of patients achieving recanalization defined as partial or complete recanalization of the basilar artery using the Arterial Occlusive Lesion scale (AOL 2-3) on initial digital subtraction angiography prior to EVT or CT Angiography in those who do not proceed to endovascular therapy (performed at the time catheter angiography would otherwise have occurred) without sICH.

Stage 2 (phase 3):

Primary:

• Proportion of patients with Modified Rankin Scale (mRS) 0-1 (no disability) or return to baseline mRS (if baseline premorbid mRS =2) at 3 months.

Secondary:

• Proportion of patients with Modified Rankin Scale 0-2 or return to baseline at 3 months.

• Functional improvement of at least 1 point in mRS category (ordinal analysis merging mRS categories 5-6) at 3 months.

• Proportion of patients achieving early clinical improvement (reduction in acute – 72 hour NIHSS score of ≥8 or 72 hour NIHSS 0-1).

• Proportion of patients achieving AOL 2-3 30 on initial digital subtraction angiography run prior to thrombectomy.

Safety

• Proportion of patients with sICH defined as parenchymal haematoma type 2 (PH2) within 36 hours combined with neurological deterioration leading to an increase of ≥4 points on the

NIHSS from baseline.

• Proportion of patients with Modified Rankin Scale (mRS) 5-6 at 90 days (severe disability or death).

• Proportion of patients with death due to any cause.

POST-ETERNAL is the first trial to test a potentially more effective thrombolytic agent prior to endovascular therapy in an extended time window for patients with acute ischaemic basilar artery occlusion. This approach may facilitate early reperfusion to thrombolysis in some patients (e.g. those with milder deficits/better collaterals or in “drip and ship” patients transferred from regional hospitals with long needle-to-arterial puncture times) and obviate the need to transfer some patients, or work in synergy with endovascular therapy in those with moderate-severe syndromes or presenting directly to comprehensive stroke centres. POST-ETERNAL will include regional hospitals with longer transfer times where efficacy of intravenous thrombolysis is particularly critical, allowing treatment of a higher number of patients with this devastating form of stroke in regional areas.

POST-ETERNAL aims to reduce disability by 10-15% with intravenous thrombolysis in extended time window with tenecteplase in basilar artery occlusion patients who have severe disability after stroke with consequent heavy community burden. Based on the current evidence, there is a strong rationale that tenecteplase combined with endovascular therapy within 24 hours of symptom onset is likely to reduce disability and death in basilar artery occlusion. POST-ETERNAL may change practice globally and finally herald a new era of stroke treatment in this under-researched and devastating form of stroke.

Other future directions

We plan to explore the development and possible implementation of an automated version of pc-ASPECTS on CT Perfusion and AI vascular scores (e-BATMAN and e-PC-CS) to be used as a selection criterion for reperfusion therapies in patients with basilar artery occlusion.

We also plan to perform a prospective validation of the POST-NIHSS in anterior and posterior circulation stroke with mild symptoms (NIHSS 0-5) and to test the hypothesis that BATMAN score is associated with neurological deterioration in a large cohort of patients with basilar artery occlusion presenting with mild symptoms.

Table 4. Main results of the BASILAR study, the BASICS and BEST trials.

	BASICS*[258] **Randomized controlled trial**	**BEST [257]** **Randomized controlled trial**	**BASILAR [256]** **Non-randomized prospective study**
Number of patients	300	131	829
Intra-arterial therapy in active arm	Urokinase (max. dose 1.500.000 Units), rt-PA (max. dose 22mg), MERCI, Penumbra, EKOS, Solitaire, Penumbra, Trevo, Revive angioplasty and stenting	• 83% Stent retriever thrombectomy (mainly Solitaire e Trevo) • 5% intra-arterial thrombolytic infusion alone • 4% angioplasty alone • 26% Stent implantation	• 75% Stent-retriever thrombectomy • 3% aspiration • 10% Balloon angioplasty and/or stenting • 12% Intra-arterial medication and/or mechanical fragmentation
Vessel Occlusion (segment occluded active/control)	Basilar artery occlusion	Basilar artery occlusion • 11%/8% Vertebral artery V4 segment • 89%/92% Basilar artery	Basilar artery occlusion • 19%/13% Vertebral artery- V4 segment • 16.5%/8% Proximal basilar artery • 30%/55% Middle basilar artery • 34%/25% Distal basilar artery
Time limit from onset to randomisation	6 hrs	8 hrs	24 hrs

NIHSS limit	Nil	Nil	Nil
Time of onset	Estimated time of BAO defined as time of onset of acute symptoms leading to clinical diagnosis of basilar artery occlusion or if not known last time patient was seen normal prior to onset of these symptoms.	Estimated time of BAO defined as sudden onset of stroke symptoms consistent with acute occlusion of the basilar artery (eg, not considering any preceding minor prodromal symptoms)	Estimated time of BAO defined as the time of onset of symptoms, as described by the patient or witness; consistent with the clinical diagnosis of BAO, on the judgment of the treating physician; or, if the exact time was not known, recorded as the last time the patient was seen well.
Imaging Selection on non-contrast CT brain or MRI	• Lesion consistent with haemorrhage of any degree. • Significant cerebellar mass effect or acute hydrocephalus • Bilateral extended brainstem ischemia.	• no evidence of intracranial haemorrhage • significant cerebellar mass effect or acute hydrocephalus • Extensive bilateral brainstem ischaemia	• evidence of cerebral haemorrhage on baseline non-contrast CT brain
Age, mean or median (active/ control)	67/67	62/68	64/67
NIHSS, median (active/ control)	21/22	32/26	27/26.5
Intravenous thrombolysis rates (active/ control)	79.1%/ 79.5%	27%/32%	18.4%/25.8%
Successful recanalisation (TICI 2b/3) in active arm	-	71%	81%
Modified Rankin Scale 0-3 at 3-months, active vs control [95% CI]	44% vs 37.7% (aRR 1.18 [0.92-1.50])	Intention To-Treat: 42% vs 32% (aOR 1.74 [0.81−3.74]) Per-Protocol: 44% vs 25% (aOR 2.90 [1.20−7.03]) As-Treated: 47% vs 24%	32% vs 9.3% aOR (4.70 [2.53-8.75])

		(aOR 3.02 [1.31−7·00])	
Symptomatic Haemorrhage, active vs control [95%CI]	3.9% vs 0.7% within 72 hours (aRR 5.6 [0.7-45])	8% vs 0% (p=0.06) within 24 hours	7.1% vs 0.5% (p <0 .001) within 48 hours
Mortality at 3 months, active vs control [95%CI]	38.3% vs 43.2% (aRR 0.9 [0.7-1.1])	33% vs 38% (aOR 0.80 [0·37–1·64]); p=0.54	46% vs 71.4% (aOR 2.93 [1.95-4.40])
pc-ASPECTS score active arm (IQR)	-	8 (7–9)	8 (7-9)
Posterior Circulation collateral score	-	-	4 (3-6)

*Unpublished data, detailed methods available on study protocol and results presented at the ESO-WSO 2020. Abbreviations: aOR (adjusted odds ratio); aRR (adjusted relative risk); ASPECTS (Alberta stroke program early CT score); NCCT (non-contrast CT brain); NIHSS (National Institutes of Health Stroke Scale); OR (odds ratio); RR (relative risk); TICI (Treatment In Cerebral Ischemia score).

Table 5. Current and modified in-hospital workflow for patients with posterior circulation stroke.

Workflow step	Current in-hospital workflow	Modified in-hospital workflow proposed on the basis of this thesis and most updated evidence	
Imaging	NCCT/CTA-SI: pc-ASPECTS assessment	CTP: assess pc-ASPECTS on CBV/CBF CTA: assess BATMAN score or PC-CS	
Clinical assessment	Clinical assessment using the NIHSS	In patients with mild symptoms perform POST-NIHSS (if unsure about treatment or for prognostication).	
Treatment with reperfusion therapies			
		Patient presenting to EVT centre	**Patient presenting to primary stroke centre**
Patient presenting within 4.5 hours and eligible for intravenous thrombolysis	Treat with alteplase 0.9mg/kg	Treat with either tenecteplase 0.25mg/kg or alteplase 0.9mg/kg	Treat with either tenecteplase 0.25mg/kg or alteplase

Patient presenting in the 4.5-6 hour time window but no other contraindications for intravenous thrombolysis	Treat with endovascular therapy within 6 hours as recommended by current AHA/ASA guidelines	Treat with endovascular therapy within 6 hours as recommended by current AHA/ASA guidelines Evaluate NCCT/CTA-SI or CT perfusion pc-ASPECTS, BATMAN score or PC-CS for prognostication	If favourable imaging (favourable NCCT/CTA-SI or CT perfusion pc-ASPECTS, favourable BATMAN score or PC-CS): • Consider intravenous thrombolysis (with either tenecteplase or alteplase) while organising transfer for endovascular therapy, especially if long transfer times are expected. If unfavourable imaging (unfavourable NCCT/CTA-SI or CT perfusion pc-ASPECTS, unfavourable BATMAN score or PC-CS): • Transfer for endovascular therapy
Beyond 6 hours up to 24 hours	EVT not recommended by current AHA guidelines but performed in many stroke centres given BAO dismal prognosis	Treat with endovascular therapy. Consider excluding from treatment patients with very poor imaging profiles (e.g. very poor BATMAN score or PC-CS, very poor NCCT/CTA-SI or CT perfusion pc-ASPECTS)	• Consider intravenous thrombolysis (with either tenecteplase or alteplase) ONLY if favourable imaging profiles (e.g. favourable NCCT/CTA-SI or CT perfusion pc-ASPECTS, BATMAN score or PC-CS), while organising transfer for endovascular therapy, especially if long transfer times are expected.

Abbreviations: NNCT non-contrast CT brain; CTA CT Angiography; CTA-SI CT Angiography source images; CTP CT perfusion; EVT endovascular therapy; NIHSS National Institutes of Health Stroke Scale; BATMAN Basilar Artery on Computed Tomography Angiography; PC-CS Posterior circulation collateral score; pc-ASPECTS Posterior circulation Acute Stroke Prognosis Early CT score. BAO basilar artery occlusion

Table 6. Future directions.

Investigate the development and implementation of AI imaging prognostic scores (e.g. e-pc-ASPECTS on CT Perfusion) as selection criteria for reperfusion therapies
Investigate the development and implementation of AI vascular scores (e-BATMAN and e-PC-CS) as selection criteria for reperfusion therapies
Prospective validation of the POST-NIHSS in both anterior and posterior circulation stroke patients with mild symptoms.
Explore the prognostic accuracy of the BATMAN score as predictor of early neurological deterioration in patients with basilar artery occlusion with mild symptoms.
Investigate whether tenecteplase is superior to alteplase prior to endovascular therapy in patients with basilar artery occlusion within 24 hours of symptom onset, in a randomized controlled trial setting.

Table 7. Summary of major thesis conclusions.

Cerebral blood volume pc-ASPECTS may identify patients with basilar artery occlusion at higher risk of disability.
Revascularization is associated with good outcome in patients with basilar artery occlusion with good collaterals and less extensive occlusion, even >6 hours after onset.
POST-NIHSS appears to have higher prognostic accuracy than NIHSS and may be useful to identify posterior circulation stroke patients with mild-moderate symptoms at higher risk of poor outcome.
Tenecteplase may be associated with an increased rate of reperfusion in comparison with alteplase before endovascular therapy in basilar artery occlusion. Randomized controlled trials to compare tenecteplase with alteplase in basilar artery occlusion patients are warranted.

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