Treatment and outcome in basilar artery occlusion

Wouter Schonewille

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Treatment and outcome in basilar artery occlusion

Behandeling en uitkomst bij afsluiting arteria basilaris

(met een samenvatting in het Nederlands)

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Prof.dr. A. Algra

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Contents

Contributing authors

Ale Algra
Professor, Department of Neurology,
Rudolph Magnus Institute of
Neuroscience,
University Medical Centre Utrecht,
Utrecht, Netherlands

Marcel Arnold
Professor, Department of Neurology,
Inselspital, University of Bern,
Bern, Switzerland

Heinrich Audebert
Professor, Department of Neurology,
Center for Stroke Research,
Charité University Medicine Berlin,
Campus Benjamin Franklin,
Berlin, Germany

Eivind Berge
Department of Internal Medicine,
Oslo University Hospital Ullevål,
Oslo, Norway

Alfonso Ciccone
Professor, Department of Neurology and
Stroke Unit,
Carlo Poma Hospital,
Mantua, Italy

Annette Compter
Department of Neurology,
Rudolph Magnus Institute of
Neuroscience,
University Medical Centre Utrecht,
Utrecht, Netherlands

Adriana B. Conforto
Department of Neurology,
Hospital das Clínicas,
São Paulo University,
São Paulo, Brazil

Andrew M. Demchuk
Department of Neurology,
Calgary Stroke Program
University of Calgary,
Calgary, Alberta, Canada

Imanuel Dzialowski
Department of Neurology,
Dresden University Stroke Center,
University of Technology Dresden,
Dresden, Germany

Stefan T. Engelter
Department of Neurology,
University Hospital Basel,
Basel, Switzerland

Oliver Findling
Department of Neurology,
Inselspital, University of Bern,
Bern, Switzerland

Urs Fischer
Department of Neurology,
Inselspital, University of Bern,
Bern, Switzerland

Gabriel de Freitas
Department of Neurology,
University of Rio de Janeiro,
Rio de Janeiro, Brazil

Johannes Gerber
Institute for Medical Informatics and Biometry,
University of Technology Dresden,
Dresden, Germany

Jan Gralla
Professor, Department of Diagnostic and Interventional Neuroradiology,
Inselspital, University of Bern,
Bern, Switzerland

Jacoba P. Greving
Julius Center for Health Sciences and Primary Care,
University Medical Centre Utrecht,
Utrecht, Netherlands

Michael D. Hill
Department of Neurology,
Calgary Stroke Program
University of Calgary,
Calgary, Alberta, Canada

Erik J.R.J. van der Hoeven
Department of Radiology,
St. Antonius Hospital,
Nieuwegein, Netherlands

L. Jaap Kappelle
Professor, Department of Neurology,
Rudolph Magnus Institute of Neuroscience,
University Medical Centre Utrecht,
Utrecht, Netherlands

Andrei Khomenko
Department of Neurology,
Dresden University Stroke Center,
University of Technology Dresden,
Dresden, Germany

Ruediger von Kummer
Professor, Department of Radiology,
Dresden University Stroke Center,
University of Technology Dresden,
Dresden, Germany

Perttu Lindsberg
Professor, Department of Neurology,
Helsinki University Central Hospital and Research Programs Unit, Molecular Neurology, Biomedicum Helsinki
Helsinki, Finland

Heinrich P. Mattle
Professor, Department of Neurology,
Inselspital, University of Bern,
Bern, Switzerland

Mikael Mazighi
Department of Neurology and Stroke Centre,
Bichat University Hospital,
Paris, France

Patrik Michel
Department of Neurology,
Centre Hospitalier Universitaire Vaudois,
Lausanne, Switzerland

Carlos A. Molina
Cerebrovascular Unit,
Department of Neurology,
Hospital Vall d'Hebron,
Barcelona, Spain

Keith W. Muir
Professor, Department of Neurology,
Division of Clinical Neurosciences,
University of Glasgow,
Glasgow, UK

Victor Obach
Department of Neurology,
Comprehensive Stroke Center,
Hospital Clinic de Barcelona,
Barcelona, Spain

Christoph Ozdoba
Department of radiology,
University of Bern,
Bern, Zwitserland

Jorge Pagola
Cerebrovascular Unit,
Department of Neurology,
Hospital Vall d'Hebron,
Barcelona, Spain

Lars-Peder Pallesen
Department of Neurology,
Dresden University Stroke Center,
University of Technology Dresden,
Dresden, Germany

Thomas Pfefferkorn
Department of Neurology,
Klinikum Grosshadern,
University of Munich,
Munich, Germany

Volker Puetz
Department of Neurology,
University of Technology Dresden,
Dresden University Stroke Center
Dresden, Germany

Christina M. Rueckert
Department of Neurology,
St Elisabeth Hospital,
Ravensburg, Germany

Gerhard Schroth
Professor, Department of Diagnostic and
Interventional Neuroradiology,
Inselspital, University of Bern,
Bern, Switzerland

Joaquin Serena
Department of Neurology,
Hospital Universitari
Doctor Josep Trueta,
Girona, Spain

Kristina Szabo
Department of Neurology,
Universitätsklinikum Mannheim,
University of Heidelberg,
Mannheim, Germany

David Tanne
Department of Neurology,
Sheba Medical Center and
Tel Aviv University,
Tel Aviv, Israel

Vincent Thijs
Professor, Department of Neurology,
University Hospitals Leuven and
Vesalius Research Centre, VIB,
Leuven, Belgium

Mervyn D.I. Vergouwen
Department of Neurology,
Rudolph Magnus Institute of
Neuroscience,
University Medical Centre Utrecht,
Utrecht, Netherlands

Jan Albert Vos
Department of Radiology,
St. Antonius Hospital,
Nieuwegein, Netherlands

Christian Weimar
Department of Neurology,
University of Duisburg-Essen,
Essen, Germany

Baerbel Wiedemann
Institute for Medical Informatics and
Biometry,
University of Technology Dresden,
Dresden, Germany

Christine A.C. Wijman
Department of Neurology,
Stanford Stroke Center,
Palo Alto, CA, USA

H. Bart van der Worp
Department of Neurology,
Rudolph Magnus Institute of
Neuroscience,
University Medical Centre Utrecht,
Utrecht, Netherlands

Andrea Zini
Stroke Unit, Department of Neuroscience,
University of Modena and Reggio Emilia,
St. Agostino-Estense Hospital,
Modena, Italy

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General introduction and outline of the thesis

Basilar artery occlusion (BAO) is a rare cause of stroke with a high case fatality rate and an often poor clinical outcome among survivors.

HISTORIC PERSPECTIVE

The first clear-cut clinical description of a patient with basilar artery occlusion is the case of monsieur Noirtier de Villeforte in Alexander Dumas' famous adventure novel *The Count of Monte Cristo* written in 1844.[1] He suffers from a clinical syndrome which we would now call a "locked-in" state after an earlier stroke – described more eloquently by Dumas as "when the soul is trapped in a body that no longer obeys its commands".

"Sight and hearing were the only two senses which, like two sparks, still lit up this human matter, already three quarters moulded for the tomb. Moreover only one of these two senses could reveal to the outside world the inner life, which animated this statue... He was a corpse with living eyes, and at times, nothing could be more terrifying than this marble face out of which anger burned or joy shone."

A more detailed description of the locked-in syndrome can be found in the memoirs of Jean-Dominique Bauby *Le Scaphandre et le Papillon*, the editor-in-chief of the French *Elle* magazine, who suffered a stroke in 1995.[2] After a comatose state of several weeks he "woke-up" with a locked-in syndrome – awake and aware, but unable to speak or move his arms and legs. Only being able to communicate through the blinking of one eye, it took him more than 200,000 blinks to write a book about his experience. The book became a bestseller with millions of copies sold, followed by a movie which won many international awards.

These two cases are dramatic examples of the impact of posterior circulation stroke on the individual sufferer that strike the imagination. The locked-in syndrome is caused by damage to the brainstem usually caused by occlusion of the basilar artery. Fortunately, the locked-in syndrome is a rare "worst case scenario" of the clinical spectrum of stroke. As in the case of Jean-Dominique Bauby it is usually preceded by the acute onset of coma. Vertical eye movement often being the only physical sign of awakening, the locked-in state is not infrequently detected days after awakening by a consulting neurologist at the intensive care unit asked to see a patient with a coma of unknown cause.

The first reports of basilar artery occlusion, well after Dumas clinical description, were all based on post mortem examination.[3-7] Occlusion of the basilar artery was therefore associated for many years with a fatal outcome. In vivo diagnosis of BAO through arterial angiography of the neck vessels became feasible in the 1950s. However, this technique did not become common practise until much later, due to the great risks involved and the lack of therapeutic options. Not surprisingly angiography was generally limited to patients with a persistent severe deficit. As a consequence BAO was therefore considered to be incompatible with independent survival. Although Seldinger already introduced angiography by catherization of the femoral artery in 1953, allowing for selective catherization of all the neck vessels, direct puncture of the involved neck vessel by the neurologists remained common practise up to the 1970s.[8,9] During the 1970s procedures and imaging techniques greatly improved leading to safer and more useful angiography. Together with the introduction of computed tomography (CT imaging), which made it possible to differentiate in vivo between hemorrhagic and ischaemic stroke, this led to the first attempts of recanalization therapy with intravenous (IV) or intra-arterial (IA) thrombolysis. Due to the severity of the disorder there was a strong preference to use IA thrombolysis in patients with BAO. Prior to the initiation of the work on this thesis in 2002 less than 1 out of 10 patients with BAO reported in case series described in the literature was treated with IV as compared to IA thrombolysis.[10]

The first descriptions of the use of IV thrombolysis for BAO are limited to single case reports, the first dating back to 1979.[11,12] It took more than three decades of failed trials, mainly due to a high rate of hemorrhagic complications using strepto- or urokinase, to show the efficacy of intravenous thrombolysis (IVT) in acute ischemic stroke using recombinant tissue plasminogen activator (rtPA) in the North American NINDS trial in 1995.[13] Patients with BAO and a severe deficit were mostly excluded from these trials. As radiologic confirmation of occlusion was not required we do not know how many patients with posterior circulation occlusion with a minor deficit were included in these trials.

Herman Zeumer and his team in Hamburg were among the first (1983) to describe their experience in the treatment of patients with BAO with IA thrombolysis.[14] Their decision to attempt IA thrombolysis was based on the high complication rate of IV thrombolysis, the reluctance to use IVT soon after angiography because of the

risk of local bleeding and the poor outcome of all 17 patients with angiographically diagnosed BAO in the previous 5 years in their own hospital. Furthermore, cardiologic studies had demonstrated that the local use of thrombolytics was more effective than systemic application and that even in high local concentrations the systemic effect was minimal.[15] Two of the 4 patients treated with IA thrombolysis by Zeumer and his team had a good outcome, one died, and one survived in a locked-in state. The first and only prospective study was the Australian Urokinase Stroke Trial in which 16 patients were included with posterior circulation occlusive disease of which 13 had a BAO.[16] All patients were treated with IA thrombolysis. All 5 patients with a persistent occlusion died, compared with only 1 death in 8 patients with sustained recanalization. Five patients had a good outcome.

Thanks to the increasing use of non-invasive technology between the 1980s and 2002, such as transcranial Doppler (TCD), computed tomography angiography (CTA) and magnetic resonance angiography (MRA), we know that the clinical spectrum of patients with BAO is much wider than described above ranging from transient ischemic attacks and minor stroke to coma and death.[17]

THE BIRTH OF A RESEARCH PROJECT

During my residency in neurology at Boston University in the early 90s stroke treatment was still limited to mainly supportive care and the avoidance of stroke recurrence. Acute stroke treatment with IV thrombolysis (Alteplase) was only used as part of clinical trials. IVT was approved by the Federal Drug Administration (FDA) in the United States in 1996 during my Stroke fellowship at the Mount Sinai Hospital in New York. The use of IA thrombolyis was limited to highly selected patients in a few centres worldwide mainly in Germany and the United States. Due to the lack of treatment options specific for the posterior circulation, imaging of the vertebrobasilar arteries was not part of the routine work-up for stroke patients. Ultrasound imaging was mainly used to look for carotid artery disease treatable by carotid endarterectomy.

My interest in the posterior circulation started during the weekly stroke meetings I attended at the New England Medical Centre (NEMC) at Tufts University chaired by Lou Caplan the world authority on the posterior circulation.

Lou Caplan

At the NEMC all patients suspected of posterior circulation ischaemia were studied with ultrasonography of the neck, TCD and/or MRA.[17] Thanks to these stroke meetings I developed a more than average knowledge on the posterior circulation. After one additional year of Stroke fellowship in Barcelona and three years as a general neurologist on Mallorca, I returned to The Netherlands in 2000 and worked at the department of neurology at the University Medical Center Utrecht until 2003 after which I moved to the St. Antonius Hospital in Nieuwegein. In 2002 IVT was approved by the the European Agency for the Evaluation of Medicinal Products (EMEA) for acute ischaemic stroke if given within 3 hours of symptom onset. Prior to the use of IVT, IA thrombolysis was occasionally used in The Netherlands mainly in comatose patients with BAO. Once IV thrombolysis became a more and more routine treatment option in acute ischemic stroke it became harder for clinicians to withhold a potentially beneficial treatment option such as IA thrombolysis in patients with a severe deficit and a radiologically confirmed BAO, especially because most patients were not eligible for IVT as a decreased level of consciousness was considered a contra-indication and treatment was rarely possible within 3 hours. Despite lack of evidence of efficacy IA thrombolysis rapidly became the preferred treatment option in patients with BAO in dedicated stroke centres worldwide. Many considered the performance of a trial on efficacy of IA thrombolysis in patients with

BAO as unethical and compared such a trial with the performance of a trial with randomisation of patients jumping from an aeroplane with or without a parachute, IA thrombolysis being the equivalent of a parachute in patients with BAO. This strong believe in the efficacy of IA thrombolysis among stroke neurologist made it close to impossible to perform a randomised trial. Although the number of stroke neurologist convinced about the efficacy of IA thrombolysis increased dramatically, the number of patients transferred from community hospitals for IA thrombolysis remained very limited. In order to increase awareness we decided to start a registry in 2002 of patients with BAO which I hoped would show such a clear difference in outcome favouring IA thrombolysis that a randomised trial would not be necessary.

EQUIPOISE

Equipoise in epidemiology is defined as a state of uncertainty as to the balance of benefits and harm that may result from two or more therapeutic regimens. A state of equipoise is a prerequisite for a randomized controlled trial. Such uncertainty did not exist in the minds of stroke physicians at the beginning of this century with regards to the efficacy of IV versus IA thrombolysis in patients with BAO, although, this was not supported by the available data in the literature.[10] In case series very few patients had been treated with IV thrombolysis. Studies on the outcome of BAO using a conventional treatment approach (with antiplatelets or anticoagulation) were very small and used very broad definitions, including vertebral and branch artery occlusions. All data had been collected retrospectively from highly selected patients. Detailed information on time to treatment, stroke severity, location of occlusion and vascular risk factors was missing. Differences in outcome among treatment groups could therefore not be adjusted for other important predictors of outcome. No strong conclusions on the efficacy of IA therapy as compared with other treatment options could therefore been drawn from these data.

REGISTRY

In the absence of equipoise a registry is the highest achievable level of evidence. To reach the highest level of evidence a registry should be set up prospectively to be able to avoid the disadvantages of the previously described case series. In order

to be representative of current everyday clinical practice at the time of completion of the registry, data should be collected on a large number of patients, from a large number of centers using a broad spectrum of treatment strategies, in as limited time as possible to avoid major changes in treatment approach. To limit selection bias data should be collected from consecutive patients. The main bias in an observational registry is caused by selection of patients for a specific treatment based on the judgment of the treating physician, a bias which can only be avoided by leaving the choice of treatment to calculated chance or randomization. The collection of detailed data, on as many factors which could potentially influence outcome as possible, facilitates the interpretation of outcome results.

With all these issues in mind we started the Basilar Artery International Cooperation Study (BASICS), the main subject of this thesis. The goal of the registry was to collect data on 500 patients, from 50 centers worldwide, in a 5 years period.

OUTLINE OF THE THESIS

Chapter 2 summarizes our current knowledge on BAO including anatomy, pathophysiology, clinical presentation, imaging techniques and treatment options. Chapter 3 shows the results of a three-center study on the outcome of patients with BAO after conventional treatment. Chapter 4 describes the rationale and design of the BASICS registry. Chapters 5 to 14 describe the results of the registry. Chapter 15 contains the protocol of the ongoing BASICS trial.

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Basilar artery occlusion

Heinrich P. Mattle, Marcel Arnold, Perttu J. Lindsberg,
Wouter J. Schonewille, Gerhard Schroth

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SUMMARY

The clinical presentation of basilar artery occlusion (BAO) ranges from mild transient symptoms to devastating strokes with high fatality and morbidity. Often, non-specific prodromal symptoms such as vertigo or headaches are indicative of BAO, and are followed by the hallmarks of BAO, including decreased consciousness, quadriparesis, pupillary and oculomotor abnormalities, dysarthria, and dysphagia. When clinical findings suggest an acute brainstem disorder, BAO has to be confirmed or ruled out as a matter of urgency. If BAO is recognised early and confirmed with multimodal CT or MRI, intravenous thrombolysis or endovascular treatment can be undertaken. The goal of thrombolysis is to restore blood flow in the occluded artery and salvage brain tissue; however, the best treatment approach to improve clinical outcome still needs to be ascertained.

INTRODUCTION

The vertebral and basilar arteries supply blood to many large and small vessels in the posterior circulation. Occlusions of the posterior circulation arteries cause about a fifth of all strokes. When the basilar artery is occluded, clinical presentation ranges from mild transient symptoms to devastating strokes. Basilar artery occlusion (BAO) is rare. It accounts for about 1% of all strokes and is reported in about 8% of patients with symptomatic vertebrobasilar territory ischaemia.[1,2] At our institutions (since 2004), about ten individuals per year with BAO from Bern, and between ten and 15 from Helsinki, have been treated with thrombolysis. From these numbers, we estimate the incidence of BAO to be about one patient per 100 000 a year, or a maximum of a few individuals per 100 000. Patients are usually elderly, but younger people or even children can have BAO.[3,4]

Abercrombie was probably the first clinician to publish a clinical and pathological description of BAO in 1828,[5] and Hayem is quoted frequently for his detailed clinicopathological report from 1868.[6] Table 1 summarises landmarks in BAO research that have been important for current understanding and advances in management.[5-20] Technical developments during the past few decades have improved the diagnosis and management of BAO greatly. Non-invasive imaging has contributed to a better understanding of clinical-anatomical correlations and serves as a basis for rapid diagnosis and treatment. Furthermore, many recanalisation techniques have been developed that help to reperfuse brain tissue jeopardised by ischaemia and to improve patients' outcomes.

Nevertheless, the disorder is still devastating for many patients and their families, and further research is needed to secure improvements in the diagnosis and treatment of BAO. In this Review, we discuss pathophysiology and causes of BAO and its clinical presentation and diagnosis, and we summarise clinical outcomes and current management of the disorder. We hope that a better understanding of BAO will increase the number of patients who get early and optimum treatment and that the future will bring new treatment options.

Table 1 Advances and landmarks in diagnosis and management of BAO

	Importance
19th century	
Several case reports highlight clinical and pathological features of BAO[5,6]	The main clinical presentation of BAO is known
Era of pathology	
In 1946, Kubik and Adams[7] delineate accurate clinical and pathological features of embolic and thrombotic BAO	BAO is thought to cause a mostly fatal brainstem stroke, although survival is possible; angiography is hardly used for diagnosis of stroke at this time
Era of angiography	
Series of patients with BAO help to delineate a clearer picture of the disease (the most comprehensive review was by Labauge and coworkers in 1981)[8] in 1980, Caplan[9] reviewed the clinical features of distal occlusions of the basilar artery and coined the term "top of the basilar" syndrome	A clearer picture of the clinical manifestation of BAO emerges
Era of non-invasive imaging	
First reports on MR and CT angiography,[10] MR perfusion,[11] and diffusion-weighted imaging in acute stroke[12] are published in the last decade of the 20th century, and development of CT perfusion is reported in the first decade of the 21st century[13]	Multimodal imaging using MR or CT allows rapid and more accurate diagnosis and fast initiation of treatment; angiography is increasingly used for therapeutic interventions and no longer for diagnosis; diffusion-weighted MRI gives an accurate picture of brainstem, cerebellar, and hemispheric areas that are ischaemic as a result of BAO in individual patients
Era of therapeutic interventions	
In 1982, Zeumer and co-workers[14] did successful intra-arterial basilar artery thrombolysis, and Hacke and colleagues[15] showed that successful recanalisation improves clinical outcome	Intra-arterial thrombolysis becomes the gold standard for BAO treatment
Lindsberg and colleagues[16] report a large series of BAO patients treated with intravenous alteplase	The assumption of intra-arterial thrombolysis being the only and optimum treatment for BAO is challenged[17]
The Basilar Artery International Cooperation Study[18] aimed to build the largest registry of BAO patients to assess current diagnosis and management	Findings do not show unequivocal superiority of endovascular treatment over intravenous thrombolysis
Endovascular mechanical recanalisation techniques[19,20]	Several devices, including self-expanding retrievable stents, achieve higher recanalisation rates than pure pharmacological means; various combinations of pharmacological and mechanical recanalisation techniques potentially provide better outcomes than pure intravenous or intra-arterial thrombolysis

BAO=basilar artery occlusion. MR=magnetic resonance.

ANATOMY

The basilar artery is joined to the brainstem via penetrating median, paramedian, and short and long circumferential branches,[21] which are connected by anastomotic channels in 42–67% of people.[22] The section of the basilar artery from the vertebral artery junction to the anterior inferior cerebellar artery is generally referred to as the proximal segment, the middle part from the anterior inferior cerebellar artery to the superior cerebellar artery is called the middle segment, and the area above the orifices of the superior cerebellar artery is known as the distal segment.[23] According to this definition, the anterior inferior cerebellar artery arises from the proximal segment of the basilar artery, and the superior cerebellar artery is present in the distal segment, just before the bifurcation into the posterior cerebral artery. Sometimes the vertebral arteries are asymmetric and one is dominant, causing an elongation of the basilar artery to the opposite side.

The medulla is supplied with blood by the intracranial part of the vertebral arteries and their branches before they join and build the basilar artery. The pons receives its supply from the proximal and middle segments and their branches. The mesencephalon is served by the distal segment of the basilar artery and its branches, including the superior cerebellar artery and the posterior cerebral artery, which can also receive blood from the anterior circulation via the posterior communicating arteries.[24] At the apex of the basilar artery, penetrating arteries supply the median and paramedian portions of the midbrain (Figure 1) and thalamus. The posterior circulation is rich in collaterals and, therefore, clinical manifestations of disturbed basilar artery flow are highly variable (Figure 2).

PATHOPHYSIOLOGY AND CAUSES

The most frequent causes of BAO are atherosclerotic occlusions resulting from local thrombosis due to severe stenosis and embolic occlusions from cardiac and large artery sources. In autopsy series, atherosclerosis was reported as the most common cause of BAO and was usually extensive and not restricted to the basilar artery.[7,25] In studies in which imaging was used for diagnosis of BAO, atherosclerosis was noted in 26–36% of patients, emboli in 30–35%, other causes (including dissection of the vertebral arteries) in 6–8%, and causes were undetermined in 22–35% of

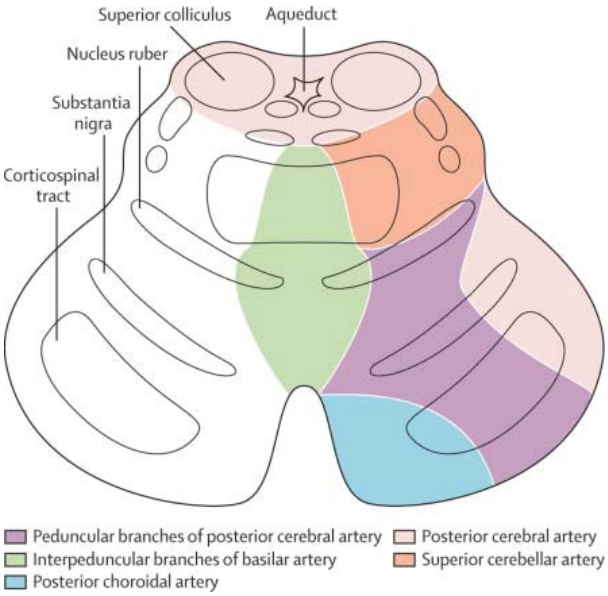

Figure 1 Vascular territories of the midbrain. Reproduced from Caplan,[21] by permission of Louis Caplan.

patients.[18,20] Particularly in young patients, emboli or propagation of a thrombosis from a dissected vertebral artery into the basilar artery are recognised frequently. Atherosclerosis often involves both vertebral arteries and leads mostly to occlusion of the proximal and middle segments of the basilar artery. An embolus reaching the basilar artery is usually flushed to the distal segment, and the combination of a vertebral artery lesion and distal occlusion of the basilar artery is typically indicative of an arterioembolic event.[26,27] Emboli can also become lodged proximally. As the embolus enters the basilar artery, a drop in perfusion pressure takes place downstream, leading to reversed flow from the posterior communicating artery.[26] This reflux might prevent the embolus from proceeding to the distal segment of the basilar artery (Figure 2E, F).

Rare causes of BAO include the following: giant-cell, infectious, and other types of arteritis; meningitis; cervical trauma; upper cervical instability with rheumatoid arthritis; coagulopathy; migraine; aneurysms; dissections and other dilatative arteriopathies of the basilar artery; hereditary arteriopathies; and complications after endovascular procedures and neurosurgery.[21,28-31] In early published work,

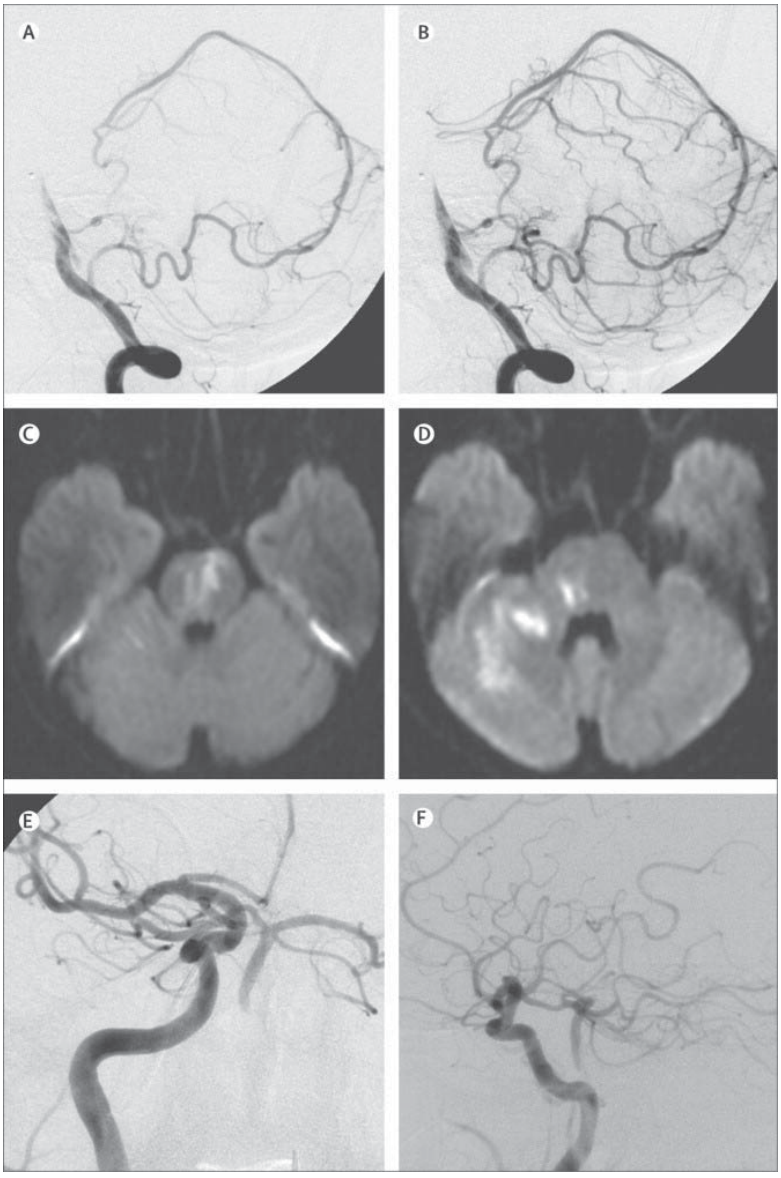

Figure 2 Distal and proximal basilar artery occlusions. In a 12-year-old boy with distal basilar artery occlusion, digital subtraction angiography shows good collaterals: **(A)** filling of the superior cerebellar artery from the posterior inferior cerebellar artery and **(B)** filling of the perforating arterioles in the upper brainstem. The resulting infarcts (hyperintense signal), as seen by diffusion-weighted MRI, are therefore restricted to **(C)** small areas in the midbrain and **(D)** the pons and cerebellum. **(E)** In a 73-year-old man with proximal basilar artery occlusion, right carotid angiography shows filling of the posterior cerebral arteries, the distal basilar artery, and the superior cerebellar arteries from the anterior cerebral circulation via the posterior communicating artery. **(F)** Lateral view of the patient in **(E)**.

BAO resulting from neurosyphilis was reported frequently, and nowadays syphilis is still a rare cause of BAO.[32,33]

ANATOMICAL-CLINICAL CORRELATIONS

Clinical symptoms and signs depend on the location of occlusion in the basilar artery and on the anatomical regions affected by the resulting ischaemia (Table 2). Labauge and colleagues8 surveyed 17 of their own patients and 265 from elsewhere. Of 257 patients with adequate angiograms, 58% were monosegmental, 23% were plurisegmental, and 18% had complete BAO. The extent of the infarct that results from BAO depends mainly on the collaterals (Figure 2). In patients with slowly occluding atherosclerotic lesions, the circulation can adapt so that BAO causes only small ischaemic lesions and transient symptoms. However, sudden embolic or thrombotic occlusions can cause extensive ischaemic damage and severe clinical deficits.

Occlusions of the proximal or middle segments of the basilar artery usually result in large pontine strokes with either hemiplegia or (most usually) quadriplegia. Other effects include reduced consciousness, bilateral extensor plantar sign, dysarthria and dysphagia, horizontal gaze paresis, and other cranial nerve palsies.

Occlusions in the distal segment of the basilar artery cause strokes bilaterally in the mesencephalon and thalamus with decreased consciousness, quadriparesis, and nuclear or supranuclear oculomotor and pupillomotor dysfunctions. Depending on the amount of collateral flow from the carotid system over the posterior communicating artery, the territory of the posterior cerebral artery can be involved or spared. Thalamic involvement is mainly bilateral but, depending on the individual vascular anatomy, thalami can remain intact on one or both sides.[34] Patients with thalamic involvement are often confused and amnestic, and those with posterior cerebral artery occlusions are hemianopic or cortically blind.

The disorder known as top of the basilar syndrome results mostly from embolic occlusions of the distal basilar artery and is characterised by visual, oculomotor, and behavioural abnormalities, often without substantial motor dysfunction.[9,35,36] Somnolence, vivid hallucinations, and dreamlike behaviour can arise. When infarctions at the top of the basilar artery also affect the temporal and occipital lobes

Table 2 Symptoms and signs of basilar artery occlusion and anatomical structures that are involved

	Anatomical structures
Reduced consciousness or coma	Ascending reticular activating system
Hemiparesis or quadriparesis, hemiplegia or quadriplegia, extensor plantar sign	Corticospinal tracts in pons or cerebral peduncles
Unilateral or bilateral hypaesthesia or anaesthesia	Medial lemnisci and spinothalamic tracts, thalamic nuclei
Ataxia, loss of coordination of limbs and posture, loss of balance	Cerebellum, cerebellar peduncles, proprioceptive tracts
Vertigo, loss of balance, directional nystagmus	Vestibular nuclei, labyrinth, vestibulocerebellum
Headache, neck pain	Trigeminal fibres of vessels and meninges
Horner's syndrome	Sympathetic fibres in dorsal longitudinal fascicle
Disturbance of respiration, heart rate, and blood pressure	Medullary autonomic nuclei and efferent and afferent fibres
Incontinence	Parasympathetic hypothalamic nuclei, sympathetic and parasympathetic connecting fibres from frontal micturition centre to spinal cord
Oculomotor nerve palsy	Fascicle of oculomotor nerve
Nuclear oculomotor nerve palsy, vertical gaze paresis, bilateral ptosis, anisocoria, non-reactive pupils, vertical oculocephalic reflex loss	Oculomotor nerve nucleus, rostral interstitial nucleus of the medial longitudinal fascicle, dorsal commissure
Internuclear ophthalmoplegia	Medial longitudinal fascicle
Horizontal gaze paresis, horizontal oculocephalic reflex loss	Abducens nerve nucleus, paramedian pontine reticular formation
Gaze-evoked nystagmus	Cerebellum and its connections to brainstem
Double vision, strabismus, skew deviation	Brainstem oculomotor system, eye nerves
Facial palsy	Corticobulbar tract, facial nerve nuclei
Tinnitus, hearing loss	Inner ear, cochlear nuclei, lateral lemnisci
Dysarthria, dysphagia, anarthria, aphagia	Corticobulbar tracts, cerebellum, caudal cranial nerve nuclei
Hemianopia, blindness	Occipital lobes
Disorientation, confusion, memory disturbance	Thalamic nuclei, medial temporal lobes
Extension rigidity, jerking, shaking episodes, convulsive-like seizures	Pyramidal tracts

on one or both sides, patients will show hemianopia, cortical blindness, aspects of Balint's syndrome, amnestic dysfunction, and agitated behaviour.

A hallmark of BAO is reduced consciousness. The area vital to consciousness is the paramedian tegmental grey matter immediately ventral to the fourth ventricle and

aqueduct, extending from the posterior hypothalamic reticular formation rostrally to about the lower third of the pontine tegmentum caudally.[37] This area forms the anatomical basis of the reticular activating system and is supplied by penetrating branches originating from the basilar artery and thalamo-perforating branches from the posterior communicating and posterior cerebral arteries.[24,38] It is compromised most often when the distal and middle segments of the basilar artery are occluded.[23] Transient hypoperfusion caused by a severe focal stenosis or rapid spontaneous recanalisation of an embolic occlusion can cause transient loss of consciousness without other localising deficits. Kubik and Adams[7] noted large pontine infarcts in patients with basilar artery thrombosis, and in those with emboli to the basilar artery they saw midbrain infarcts.

Large pontine strokes resulting from BAO are the most frequent cause of locked-in syndrome, a condition that can be mistaken for coma or persistent vegetative state. The lesion in the pontine base causes quadriplegia, bilateral facial plegia, anarthria, and aphagia.[39] Typically, the pontine tegmentum is also affected, resulting in horizontal gaze paresis. Only blinking and vertical eye movements remain intact and are the only means of communication for the patient. Patients with locked-in syndrome are awake and alert, as shown by physiological studies.[37,40]

Infarcts are often multifocal, both when they are either arteriosclerotic in origin or embolic and when emboli scatter (Figure 3). In post mortem examinations, nine of 18 patients with BAO had associated cerebellar infarcts, and 20 of 50 cerebellar infarcts with arterial lesions were associated with occlusions of the basilar artery.[7,41]

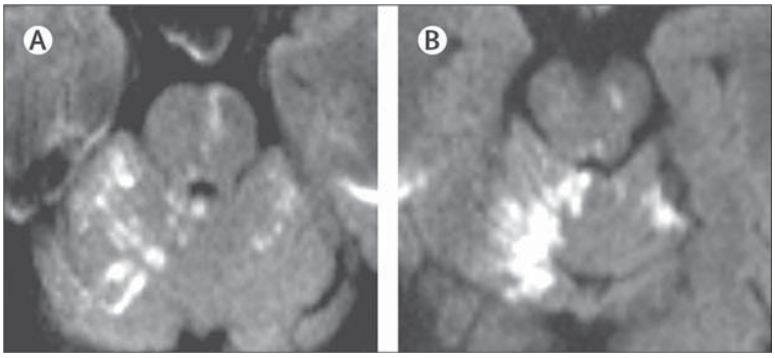

Figure 3 Infarcts shown by diffusion-weighted MRI. **(A)** Scattered cerebellar and pontine infarcts in a 71-year-old woman with distal basilar artery occlusion. **(B)** Midbrain and cerebellar infarcts in the same patient.

Sometimes other proximal or distal vessels are occluded that cause infarcts outside the territory of the basilar artery, which add corresponding symptoms and signs to the clinical picture. In clinical studies, many patients with BAO have infarcts in many regions, including supratentorial and infratentorial areas of the vertebrobasilar circulation.[42] Angiograms of 106 patients from our institution in Bern showed additional occlusions of a vertebral artery in 22% and of a posterior cerebral artery in 16%.[20]

CLINICAL COURSE AND OUTCOME

Prodromal symptoms

Up to two-thirds of patients with BAO have prodromal transient ischaemic attacks, minor strokes, or other symptoms, which are more frequent with atherosclerotic than embolic occlusions.[7,8,26] In the BASICS registry,[18] 19% of patients had prodromal transient ischaemic attacks and 19% had prodromal minor strokes. Vertigo and headaches are the most common prodromal symptoms. Other prodromal symptoms and signs include a decrease in consciousness, yawning, double vision, visual-field deficits, hemiparesis, hemisensory loss, dysequilibrium, dysarthria, dysphagia, facial paresis, tinnitus, hearing loss, drop attacks, convulsions and jerking or shaking episodes, pathological laughter ("fou rire prodromique"), or peduncular hallucinosis.[9,43-46]

Early clinical course of BAO

The onset of symptoms and signs of BAO can be abrupt without preceding events, abrupt with prodromal symptoms, or progressive and stuttering with or without prodromal symptoms. Patients with emboli and distal occlusions most often have abrupt courses without premonitory symptoms, whereas premonitory symptoms and progressive courses arise more frequently with atherosclerotic and more proximal lesions.[7,8,26] Ferbert and colleagues[26] noted sudden onset in 20 patients, sudden but preceded by prodromal symptoms in 11, and progressive onset in 54. Patients with progressive strokes often had bilateral occlusions of the vertebral artery, presumably because of atherosclerosis. Most patients with acute onset had occlusion of the middle and distal basilar artery.

Natural history

In the early years, reports of BAO were based on autopsy and were biased towards fatal cases.[7,47,48] However, even after the advent of angiography, survival after BAO was rare. More than 85% of patients died, and BAO was regarded as mostly fatal.[8] Increasing numbers of surviving patients were reported only after the introduction of antithrombotic treatment and non-invasive imaging with CT and MR techniques. In the international BASICS registry,[18] 41% of patients had non-devastating strokes and did quite well irrespective of the treatment they received.

In some series, patients with distal BAO have been reported to have better functional recovery than do those with proximal occlusion, but important neurobehavioural abnormalities often remain.[36] In other series, no such difference is mentioned.[8,20,49]

Long-term outcome

Long-term outcome of patients with BAO was reported in two large series.[16,20] Many patients were still improving after 3 months, especially those with low modified Rankin scale (mRS) scores at 3 months. However, in rare cases, even patients with locked-in syndrome regain independence after prolonged rehabilitation.[50] This occurrence underlines the importance of rehabilitation for patients with BAO who survive with a handicap. Having survived the acute phase, individuals with severe handicaps, including locked-in syndrome, often perceive their quality of life to be similar to that of age-matched controls and better than that judged by medical professionals.[51,52] Their demand for euthanasia is infrequent.[51]

DIFFERENTIAL DIAGNOSIS

Several disorders can mimic BAO (Table 3). When recognised early, the outcome of BAO can be improved with thrombolysis. Therefore, rapid diagnosis is essential. Whenever a patient with decreased consciousness shows brainstem signs such as cranial nerve palsy combined with contralateral or bilateral long-tract signs, BAO should be considered. Extensor jerks and spasms and decerebrate posturing arising with BAO are sometimes mistaken for grand mal seizures and postictal state,[43,53] and acute headaches at the onset of BAO can mimic subarachnoid haemorrhage.

Table 3 Differential diagnosis of basilar artery occlusion and ancillary investigations, by disorder

	Ancillary investigations
Subarachnoid haemorrhage	Head CT, CT or MR angiography, CSF
Non-convulsive status epilepticus or postictal state	Clinical findings, history, EEG
Hypoglycaemic or other metabolic coma, intoxication	Clinical findings, history, blood chemistry, EEG
Hypoxic-ischaemic encephalopathy	Clinical findings, history, ECG, EEG, diffusion-weighted MRI
CNS infection (meningitis, encephalitis)	Clinical findings, cerebrospinal fluid, MRI
Bilateral hemispheric stroke	Head CT or MRI, carotid ultrasound, cardiac ultrasound
Cardiogenic or haemorrhagic circulatory shock	Haemodynamics, ECG, chest radiography, cardiac ultrasound
Guillain-Barré syndrome or cranial neuritis, Miller-Fisher syndrome, Bickerstaff encephalitis, botulism, myasthenic crisis	Clinical findings (reflexes), CSF, nerve conduction studies, serum antibodies
Basilar-type migraine	History, clinical course, MRI

MR=magnetic resonance. CSF=cerebrospinal fluid. EEG=electroencephalogram. ECG=electrocardiogram.

Supratentorial mass lesions with transtentorial herniation can falsely suggest localisation to the upper brainstem. Any rapidly progressive clinical condition with multiple cranial nerve dysfunctions—such as cranial polyradiculitis, Miller-Fisher syndrome, Bickerstaff encephalitis, botulism, or myasthenic crisis—can potentially be mistaken for a brainstem lesion. Acute lesions affecting the brainstem, such as haemorrhage, can be differentiated from BAO only by imaging. The same is true for basilar-type migraine when a patient is seen during an attack.[54] Metabolic or toxic encephalopathy can also mimic BAO when the onset of coma is not witnessed and coma is deep enough to interfere with brainstem reflexes.

NEUROIMAGING

CT and CT angiography, MRI and magnetic resonance (MR) angiography, and transcranial doppler and colour-coded duplex sonography allow non-invasive or minimally invasive diagnosis in the acute stage of BAO.[55] Moreover, CT perfusion imaging and diffusion-weighted and perfusion-weighted MRI provide information

on haemodynamics in the capillaries of ischaemic tissue. A combination of these techniques is referred to as multimodal CT or multimodal MRI, and they are standard care at many comprehensive European stroke centres.[56] A drawback of these techniques is that they have been developed mostly in studies of anterior circulation strokes and they are not well validated for use in the posterior circulation.

Multimodal CT

Hypoattenuation delineates tissue with ischaemic damage on non-contrast CT, and a hyperdense basilar artery can be an indirect sign of acute BAO (Figure 4A).[57] A drawback of non-contrast CT is its low sensitivity to show acute ischaemic damage in the posterior circulation. A dense basilar artery sign is visible in only about two-thirds of patients, but when present it is highly specific for BAO.[20,58] Contrast injection greatly enhances the sensitivity and specificity of CT. On cross-sectional images, BAO is seen as a filling defect within the vessel, and angiographic reconstruction of source images readily shows the missing part of the basilar artery. Contrast injection is also needed to produce CT perfusion images.[59] CT perfusion imaging provides information about capillary-level haemodynamics of brain parenchyma. It has the potential to roughly distinguish severely hypoperfused but

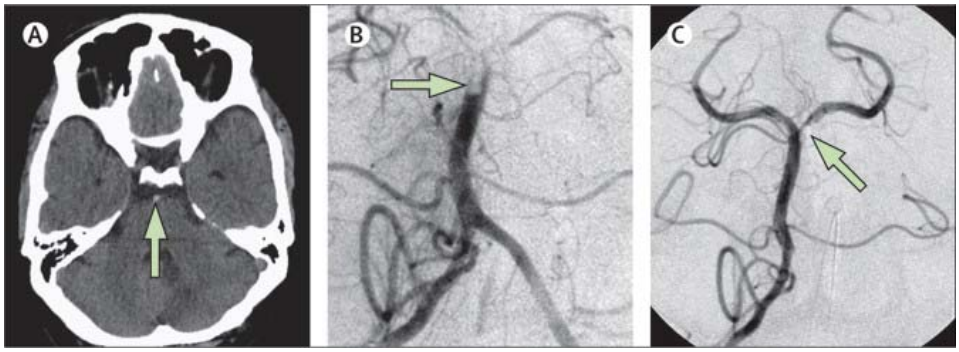

Figure 4 CT and digital subtraction angiography of a patient with distal basilar artery occlusion. **(A)** A dense basilar artery (arrow) indicates a clot in this area in a 52-year-old man. **(B)** Angiography shows both vertebral arteries, the right posterior inferior cerebellar artery, both anterior inferior cerebellar arteries, and the clot obstructing the distal basilar artery (arrow). **(C)** After intra-arterial urokinase, the basilar artery was recanalised. Angiography shows both posterior cerebral arteries and the right superior cerebellar artery, while some thrombotic material remains at the origin of the left superior cerebellar and posterior cerebral arteries (arrow).

salvageable tissue (penumbra) from irreversibly damaged (core) and hypoperfused but metabolically stable tissue (benign oligaemia). Measures of mean transit time and time to peak are increased and cerebral blood flow is decreased both in the penumbra and core, but cerebral blood volume is reduced in the core and is normal or raised in the penumbra.

Multimodal MR techniques

Loss of flow void on spin-echo and fluid-attenuated inversion recovery (FLAIR) images is an early sign of BAO.[10] On MR angiography, the occluded segment is missing because of insufficient blood flow to generate signal.[10,60] Cytotoxic brain oedema resulting from ischaemia restricts diffusion of protons, which can be visualised on diffusion-weighted MRI much sooner than can changes on spin-echo and FLAIR images.[12] Using diffusion-weighted imaging, the apparent diffusion coefficient can be calculated and depicted on images. Apparent diffusion coefficient images indicate ischaemic damage with high sensitivity and specificity and show the extent of early ischaemic damage resulting from BAO. Capillary blood flow can be seen on perfusion-weighted images, although the spatial resolution is sometimes inadequate to show a small perfusion reduction in the brainstem, and perfusion-weighted imaging is less well validated in the posterior than in the anterior circulation.[11] The mismatch between brain volumes with diffusion restriction and reduced perfusion represents an estimation of the penumbra with salvageable tissue.[61] Conversely, hyperintense signal on T2-weighted spin-echo and FLAIR images is probably the best imaging marker of the final infarct, but use of this marker requires further validation.[62,63]

Transcranial doppler and colour-coded duplex sonography

Absence of signal on transcranial doppler and colour-coded duplex sonography in the basilar artery and indirect signs such as abnormal waveforms in the vertebral arteries and collateral flow (eg, reversed flow in the precommunicating segment of the posterior cerebral artery) are indicative of BAO.[64,65] Transcranial doppler and colour-coded duplex sonography are both user-dependent techniques. Because of low sensitivity, they cannot be used to rule out BAO with certainty.[55] However, their advantages are that they can be used at the bedside and for follow-up examinations.

Digital subtraction angiography

Digital subtraction angiography is the gold standard for imaging of BAO. Biplane angiography systems can give a stereoscopic view of cerebral vessels with a spatial resolution as low as 200 μm. Generally, digital subtraction angiography is used only after non-invasive imaging for therapeutic recanalisation.

Predictive value of imaging

The hyperdense basilar artery sign has conflicting prognostic importance, but the extent of hypoattenuation on plain CT is helpful to predict death and functional outcome.[57,66,67] Furthermore, when diffusion-weighted imaging is used in a scoring system, it has predictive value.[68,69] Both CT perfusion and the combination of diffusion-weighted and perfusion-weighted imaging have the potential to be used for selection of patients who are likely to benefit from reperfusion therapies.[59,61]

Electrophysiological tests

Electrophysiological tests have been used to assess more precisely functional systems in the brainstem and prognosis of individual patients in coma.[70] Somatosensory-evoked potentials indicate that sensory function is more often affected than is apparent from clinical assessment.[26] Motor-evoked potentials have been used to predict recovery of paretic limbs.[71] Electroencephalography is helpful to assess consciousness. In locked-in syndrome resulting from BAO, predominant reactive alpha activity has been seen.[40,71]

MANAGEMENT

Table 4 summarises BAO outcomes after various treatments and interventions.[17-20,49,72-82] Figure 5, based on studies listed in Table 4, presents data on recanalisation, survival, and functional outcomes.

Table 4 Course of basilar artery occlusion according to major intervention studies* and publications

	Patients (n)	Time to treatment (h)‡	Good outcome (mRS 0–2 or independence) [%]	Moderate-to-good outcome (mRS 0–3) [%]	Mortality (%)	Symptomatic haemorrhages (%)	Recanalisation rate (%)	Remarks
Antithrombotics								
Schonewille et al.[72]	82	..	..	20	40	..	N/A	Patients from 3 centres
BASICS[18]	104 (mild-to-moderate deficit)	..	37	58	13	0	..	Multicentre registry; outcome assessed at 1 month
BASICS[18]	79 (severe deficit)	..	3	8	54	1	..	Multicentre registry; outcome assessed at 1 month
Intravenous thrombolysis								
Lindsberg and Mattle[17]	76	N/A	22	..	50	11	53‡	Systematic analysis of publications up to 2005
BASICS[18]	49 (mild-to-moderate deficit)	N/A	53	63	16	6	71‡	Multicentre registry; 40 of 121 intravenous thrombolysis patients received rescue intra-arterial thrombolysis; outcome assessed at 1 month
BASICS[18]	72 (severe deficit)	N/A	21	26	46	6	66‡	Multicentre registry; 40 of 121 intravenous thrombolysis patients received rescue intra-arterial thrombolysis; outcome assessed at 1 month
Sairanen et al.[49]	116	8·7	26	36	41	16	65	Large single-centre consecutive intravenous thrombolysis series

Table 4 continues on next page.

Table 4 *Continued*

	Patients (n)	Time to treatment (h)[‡]	Good outcome (mRS 0–2 or independence) [%]	Moderate-to-good outcome (mRS 0–3) [%]	Mortality (%)	Symptomatic haemorrhages (%)	Recanalisation rate (%)	Remarks
Intra-arterial thrombolysis								
Lindsberg and Mattle[17]	344	N/A	24	..	55	8	65	Systematic analysis of publications up to 2005
BASICS[18]	92 (mild-to-moderate deficit)	N/A	30	43	23	14[§]	83[‡]	Multicentre registry; outcome assessed at 1 month
BASICS[18]	196 (severe deficit)	N/A	11	17	49	14[§]	69[‡]	Multicentre registry; outcome assessed at 1 month
Renard et al.[73]	16	9·2 (3–22)	31	..	50	0	69	Intra-arterial thrombolysis without endovascular mechanical recanalisation
Kashiwagi et al.[74]	18	4·5 (1·3–24·5)	39	..	6	6	94	Intra-arterial thrombolysis with on-demand percutaneous transluminal angioplasty
Yu et al.[75]	52	3–48	42	..	38	12	77	Intra-arterial thrombolysis with on-demand stenting
Chandra et al.[76]	40	7·2	35	50	33	13	83	Intra-arterial thrombolysis with on-demand percutaneous transluminal angioplasty and Merci Retriever (Concentric Medical, Hertogenbosch, Netherlands) endovascular mechanical recanalisation
Jung et al.[20]	106	5·5 (1·3–24·5)	33	44	41	1	70	Intra-arterial thrombolysis with on-demand endovascular mechanical recanalisation

Endovascular mechanical recanalisation								
Lutsep et al.[77]	27	5·4 (1·2–17·3)	33	41	44	19	78	56% received undescribed adjunctive treatments
Pfefferkorn et al.[19]	26	6·0 (1·5)	38	50	31	8	85	Full-dose intravenous alteplase as bridging agent; Penumbra (Penumbra, Alameda, CA, USA), Angiojet (MedRad, Warrendale, PA, USA), or Merci (Concentric Medical) used in 16/26 patients
Miteff et al.[78]	10	4 (0–48)	20	20	30	10	100	Intra-arterial thrombolysis with on-demand microwire disruption or Merci (Concentric Medical) endovascular mechanical recanalisation
Costalat et al.[79]	16	<24	44	..	25	2	81	10/16 patients treated with full-dose intravenous alteplase before endovascular treatment; Solitaire (Microtherapeutics, Irvine, CA, USA) stent used in all
Abciximab as bridging agent to intra-arterial thrombolysis								
Eckert et al.[80¶]	47	6·0 (3·4–14·2)	..	34	38	13	72	Percutaneous transluminal angioplasty or stenting also used in 15 patients
Nagel et al.[81]	43	5 (2–12)	19	35	58	14	84	..
Barlinn et al.[82]	20	7 (3·5–13)	15	15	45	15	85	..

Studies with a large portion of occlusions at the level of vertebral artery were not included because outcome data were not reported separately for basilar artery.
* Number of participants greater than ten. † Data for time to treatment are either median (range) or mean. ‡ Recanalisation was assessed at end of angiography with intra-arterial thrombolysis, but at a later timepoint with intravenous thrombolysis. § Number for patients with mild-to-moderate and severe deficits. ¶ Good outcome defined as mRS 0–3. mRS=modified Rankin scale. N/A=not applicable.

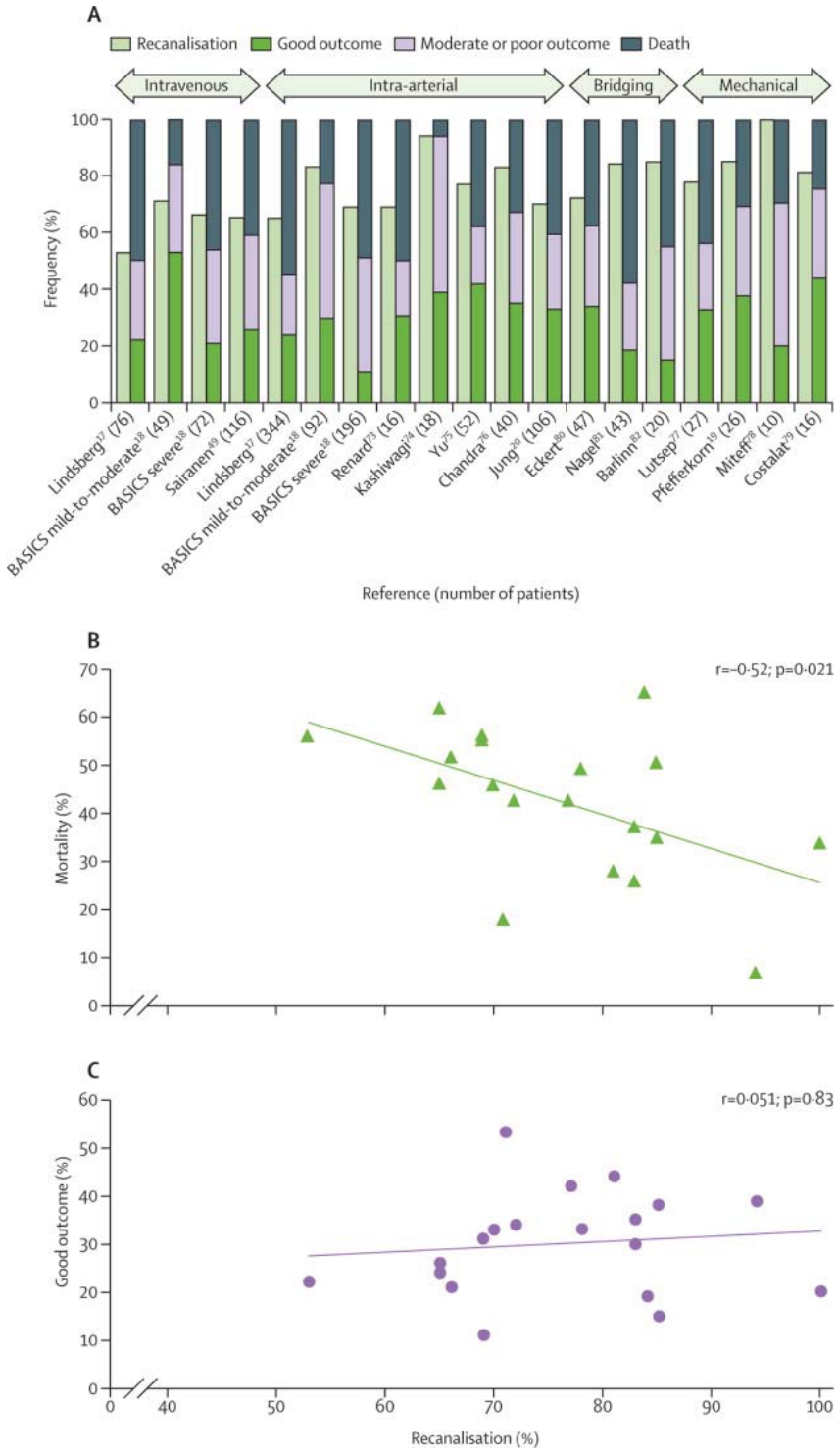
A
Recanalisation
Good outcome
Moderate or poor outcome
Death
Intravenous
Intra-arterial
Bridging
Mechanical
Frequency (%)
Lindsberg[17] (76)
BASICS mild-to-moderate[18] (49)
BASICS severe[18] (72)
Sairanen[49] (116)
Lindsberg[17] (344)
BASICS mild-to-moderate[18] (92)
BASICS severe[18] (196)
Renard[73] (16)
Kashiwagi[74] (18)
Yu[75] (52)
Chandra[76] (40)
Jung[20] (106)
Eckert[80] (47)
Nagel[81] (43)
Barlinn[67] (20)
Lutsep[77] (27)
Pfefferkorn[19] (26)
Miteff[78] (10)
Costalat[79] (16)
Reference (number of patients)
B
r=–0·52; p=0·021
Mortality (%)
C
r=0·051; p=0·83
Good outcome (%)
Recanalisation (%)

Figure 5 Recanalisation, survival, and functional outcomes in series of patients with basilar artery occlusion. Figure based on studies listed in Table 4. **(A)** Endovascular protocols seem to give higher recanalisation rates than intravenous thrombolysis, but better outcomes with endovascular treatment are not shown clearly. Deaths fell over time with all forms of treatment. The Eckert study80 used mRS 0–3 as good outcome whereas all others used mRS 0–2. Intravenous=intravenous thrombolysis. Intra-arterial=intra-arterial thrombolysis. Bridging=bridging therapy. Mechanical=mechanical recanalisation. mRS=modified Rankin scale. **(B)** Recanalisation is important for survival. A significant negative correlation is shown between recanalisation rate and mortality. **(C)** Recanalisation is probably the most important factor for outcome; however, alone it does not guarantee good outcome and independence (mRS 0–2).

Anticoagulation or antiplatelet agents

Aspirin affords a small absolute benefit (around 1%) in patients with acute stroke and causes fewer haemorrhages than does heparin.[83] However, comparative studies of antithrombotics versus placebo in people with BAO are not available. In hospital-based series of patients with BAO treated with antithrombotics, outcomes were good in 20% to 59% of patients[2,72,84] however, in a large series, case fatality was still 40%.[83] Among survivors, 65% remained dependent (mRS 4–5). Good outcome (mRS 0–3) was reached by only 20%. Table 5 lists predictors of outcome from these series.[2,72,84-86]

In the BASICS registry,[18] patients with mild-to-moderate deficits (n=245) had better outcomes than did those with severe deficits (n=347). Coma, locked-in state, or tetraplegia was defined as severe stroke and any deficit that was less than severe as mild to moderate. Outcome was assessed at 1 month (Table 4).[73,74,76,92-94]

Intravenous thrombolysis

Findings of randomised trials with intravenous alteplase show a beneficial effect in patients with stroke up to 4·5 h after stroke onset.[95] Only patients with very mild or very severe strokes may potentially not benefit from intravenous thrombolysis.[96] Individuals with posterior circulation strokes were included in these trials, but angiographic assessment was not done. Therefore, these trials do not provide information about the effectiveness of intravenous thrombolysis in BAO. Several researchers have reported promising results with intravenous alteplase in BAO, with similar outcomes to intra-arterial thrombolysis (Table 4).[16,49,97] By 3 months, 48 of 116 Finnish patients (41%) were dead and 30 (26%) had good outcomes (mRS 0–2).[49]

Table 5 Predictors of outcome in patients with basilar artery occlusion who received antithrombotic or thrombolytic treatment

	Predictors of favourable outcome	Predictors of unfavourable outcome
Antithrombotics[2,18,72,84-86]	Younger age Minor stroke Mild-to-moderate deficit Acute onset Feeding arteries to the posterior circulation on MR angiography Reversed basilar flow Single-sector strokes	Progressive onset Severe stroke Coma Pupillary abnormalities Dysarthria Lower cranial nerve involvement Tetraparesis
Intravenous and intra-arterial thrombolysis[20,49,58,73,74,76,87-91]	Recanalisation Younger age Low NIHSS Mild-to-moderate deficit Short time to treatment Short occlusion length Low thrombus volume Distal clot location Good collaterals on angiography	Symptomatic haemorrhage Coma Severe deficit Quadriplegia Proximal basilar occlusion Poor collaterals Diabetes

MR=magnetic resonance. NIHSS=National Institutes of Health stroke scale.

In the BASICS registry,[18] 121 patients received primary intravenous thrombolysis and 40 of them had subsequent intra-arterial thrombolysis. Results for antithrombotics and intravenous thrombolysis were similar for patients with mild-to-moderate deficits, but individuals with severe deficits fared better with intravenous thrombolysis than with antithrombotics (Table 4).

Intra-arterial thrombolysis

The result of intra-arterial thrombolysis is shown in Figure 4. Hacke and coworkers[15] published a series of 43 patients with BAO who received intra-arterial thrombolysis and 22 who were treated conventionally (eg, with anticoagulants or antiplatelets). Of patients in the thrombolysis group, those who had recanalisation (n=19) had better chances of survival and more favourable outcomes than did those with persistent occlusions (n=24). Quality of outcome and survival were significantly better in patients having thrombolysis compared with those receiving conventional treatment.[15] Hacke's study initiated interest in endovascular treatment and the belief that BAO has to be treated with intra-arterial thrombolysis. However, to date, intra-arterial thromboylsis has been tested in only one small (n=16) randomised trial of

BAO, in which immediate intra-arterial thrombolysis and urokinase plus full-dose heparin was compared with immediate full-dose heparin (control).[98] More severe strokes were reported in the intra-arterial thrombolysis arm than in the control arm; good outcomes were noted in four of eight patients allocated to receive intra-arterial thrombolysis compared with one of eight controls.

Findings of uncontrolled studies, mostly done with intra-arterial urokinase, have confirmed the correlation between recanalisation and outcome.[20,58,87-89] Recanalisation seems to be almost a prerequisite for favourable functional outcome. Additional outcome predictors identified with multivariate analyses of large series are shown in Table 5.[20,58,87-91] Patients with good collaterals seem to tolerate ischaemic symptoms for a longer time than those with poor collaterals.

Intra-arterial thrombolysis in the BASICS registry[18] comprised thrombolysis with alteplase or urokinase, mechanical thrombectomy, stenting, or a combination of these approaches (Table 4, Figure 5). Compared with antithrombotic treatment, intra-arterial thrombolysis improved outcomes for patients with severe deficits.

Mechanical endovascular treatment

Several mechanical devices have been used for endovascular recanalisation of large intracranial vessels.[77-79,99-101] One device is based on a self-expanding retrievable stent (Solitaire; Microtherapeutics, Irvine, CA, USA), which is deployed at the site of the thrombus, withdrawn, and removed with the clot caught within the struts. In three pilot studies,[79,94,101] a total of 29 patients with BAO were treated and at least a 90% recanalisation rate was achieved. Nine of 29 (31%) patients died and 13 (45%) regained independence (mRS 0–2). Recanalisation rates with mechanical techniques were high (68–82%) and outcome was significantly better when recanalisation was achieved. However, clinical outcomes for BAO were reported adequately in only one trial:[79] seven of 16 patients (44%) had good outcomes (mRS 0–2) after 3 months and four (25%) died. Ten (62%) were treated with full-dose intravenous thrombolysis (0·9 mg/kg) followed by rescue mechanical endovascular treatment after failed recanalisation with intravenous thrombolysis.

Jung and colleagues[20] compared outcomes of 49 patients with BAO treated with intra-arterial thrombolysis from 1992 to 2003 with those of 57 individuals treated

from 2004 to 2010. From 2004 to 2010, most patients had some form of mechanical recanalisation, with or without intra-arterial urokinase. Good outcomes (mRS 0–3) were recorded in 35% of patients treated from 1992 to 2003 and in 52% of those treated from 2004 to 2010; mortality was 43% and 39%, respectively (p=0·076). Free use of mechanical recanalisation techniques is the most likely explanation for the better outcomes between 2004 and 2010.

Bridging therapy

Today's multimodal approach to recanalise a blocked artery can include many techniques. Various intravenous agents can be given quickly and complemented later with intra-arterial thrombolysis or endovascular mechanical therapy, or both. Such an approach is called bridging. Intravenous alteplase in variable doses (mostly 0·6–0·9 mg/kg bodyweight) or glycoprotein IIb/IIIa inhibitors, such as abciximab and tirofiban, have been used as bridging agents before use of intra-arterial thrombolysis. For endovascular treatment, alteplase or urokinase have mostly been used with or without thrombus aspiration or mechanical retriever devices.

In three studies with intravenous abciximab as a bridging agent before use of intra-arterial thrombolysis,[80-82] good outcome (mRS 0–3) ranged from 15% to 35% and mortality from 38% to 58%. Tirofiban as a bridging agent might be safer than abciximab owing to its shorter half-life, but experience with BAO is restricted to a few patients.[19,102] In a series with full-dose intravenous alteplase (0·9 mg/kg) as the bridging agent,[19] good outcome (mRS 0–3) was 50% and mortality 31%. In all studies, time to intra-arterial thrombolysis was 5 h or longer—ie, intra-arterial thrombolysis was done rather late.

Comparisons of thrombolytic and bridging therapies

To date, no direct comparisons have been published of intravenous versus intra-arterial thrombolysis or of intra-arterial thrombolysis with and without bridging therapy for BAO. In a systematic analysis of uncontrolled series of patients with BAO,[17] no difference was seen in clinical outcome after intra-arterial versus intravenous thrombolysis (Table 4). Recanalisation was achieved more frequently with intra-arterial thrombolysis than with intravenous thrombolysis, despite similar

clinical outcomes. Without recanalisation, the likelihood of good outcome was low (2%).

In the BASICS registry,[18] patients with a mild or moderate deficit had a worse outcome after intra-arterial thrombolysis compared with primary intravenous thrombolysis (adjusted risk ratio 1·49 [95% CI 1·00–2·23]), whereas outcomes for individuals with severe deficits were similar after treatment with intra-arterial or intravenous thrombolysis (1·06 [0·91–1·22]). The main limitation of this comparison is that a third of patients counted in the intravenous thrombolysis group received this treatment as bridging therapy before intra-arterial thrombolysis. Outcomes for men and women did not differ.[103]

Findings of studies with intravenous abciximab as the bridging agent given before intra-arterial thrombolysis are conflicting: in one study of bridging therapy with intravenous abciximab followed by intra-arterial thrombolysis, good outcomes and low mortality were reported;[82] however, in another study, mortality increased.[80] Results of bridging with tirofiban followed by intra-arterial thrombolysis (n=9) were similar to results obtained with intra-arterial thrombolysis only (n=15).[19]

In a non-randomised comparison of intra-arterial thrombolysis and bridging therapy with full-dose intravenous alteplase, 23% of patients who received intra-arterial thrombolysis alone and 50% of patients who received bridging therapy with intravenous alteplase before intra-arterial thrombolysis had good outcomes (mRS 0–3) and mortality was 54% and 31%, respectively.[19] Rubiera and colleagues[92] reported increased recanalisation rates with intravenous thrombolysis as bridging therapy before intra-arterial thrombolysis and microwire disruption (intravenous thrombolysis bridging to intra-arterial thrombolysis 56% *vs* intravenous thrombolysis alone 28%); however, mortality (67% *vs* 50%) and independent 3-month outcome (mRS 0–2; 22% *vs* 33%) were worse in the group who received intravenous thrombolysis as bridging therapy before intra-arterial thrombolysis. The limitation of this comparison is the low number of patients (n=9).[92]

CONSIDERATIONS FOR IMPROVING MANAGEMENT

Systematic analyses have shown that most patients with BAO receive intra-arterial thrombolysis[17,18] however, unlike the expectations of many investigators, results

do not support unequivocal superiority of the intra-arterial over intravenous technique.[17,18] The effect of intravenous thrombolysis is probably not much different from that of intra-arterial thrombolysis, and in patients with mild-to-moderate deficits, intravenous thrombolysis might even be superior. However, undoubtedly, intravenous thrombolysis has a pharmacological ceiling effect, which drives efforts to improve overall unsatisfactory therapeutic results by systematic endovascular procedures.

In multivariate analyses of large series of patients with BAO who have undergone thrombolysis,[15,20,58] the main independent predictors of outcome are the following: stroke severity (assessed with the National Institutes of Health stroke scale); age; location and length of the occlusion; time to treatment; recanalisation; and collaterals as seen on angiography. Of these, only time to treatment and recanalisation rates can be enhanced by acceleration of the treatment chain and improvement of recanalisation techniques. All other factors are patient-led and cannot be changed.

Enhancing recanalisation rates

At present, the most discussed approach to enhance recanalisation rates is bridging treatment. Some groups advocate abciximab as a bridging agent to intra-arterial thrombolysis. However, on the basis of analysis of results with intravenous or intra-arterial thrombolysis, we would not advocate such a treatment approach. High rates of symptomatic haemorrhage (13–15%) are a deterrant. Results of bridging with intravenous alteplase to intra-arterial thrombolysis are more promising. Bridging will be studied further in the BASICS trial,[104] in which efficacy and safety of additional intra-arterial treatment in patients with persistent BAO after intravenous thrombolysis will be assessed.

Another promising approach to enhance recanalisation rates and chances for good outcomes is mechanical recanalisation. Aspiration of thrombotic material with a catheter and a syringe is usually successful. Advanced, expensive, and technically more effective devices for mechanical recanalisation are constantly entering into preclinical development and clinical use. Self-expanding retrievable stents are the most promising devices. Use of thrombectomy devices shortens time to recanalisation significantly compared with pharmacological recanalisation.[105] The skilled interventionist will manoeuvre the guidewire and the stent into the basilar artery

along the pontine vessel wall, from where most of the perforating arteries emerge. When the stent is expanded, flow is restored immediately, thrombotic material will be pushed towards the opposite vessel wall and retained by the stent struts when retrieved.[106] With such an approach, the origin of the perforators will not be blocked by thrombotic material. Conversely, devices that capture the thrombus at the distal end of the basilar artery with a basket-like structure compact the thrombus while being pulled back.[107] Therefore, thrombotic material can irritate the vessel wall, obstruct the origins of perforators, or might be lost into the perforators and enlarge infarcts.[107]

Other treatment considerations

Recanalisation treatment is only part of the management of acute BAO. Nursing and medical treatment according to stroke guidelines are important as well. Many patients need intubation and ventilation, analgesia-based sedation, and a nasogastric tube; furthermore, prevention of common complications should be initiated during the acute phase. Successful recanalisation is necessary to permit survival, but reocclusion and other threats need to be monitored closely. In patients with large cerebellar infarcts, swelling and compression of the brainstem can take place and worsen the initial ischaemic damage. As soon as such a complication is recognised, ventriculostomy or surgical decompression should be considered.[56]

In patients with locked-in syndrome, the issue of end-of-life decision-making is often raised and discussed with the patient and their family. However, in the acute stage, an exact prognosis cannot be made and discussions about outlook are generally too early.[108] Only when patients with locked-in syndrome are medically stabilised and informed are they then competent to consent to or refuse life-sustaining treatment. They should not be denied the right to refuse treatment and to die and, more importantly, they should also be given the right to live with the best possible rehabilitation, pain, and symptom management, and with dignity.[52]

The question of whether the time window for recanalisation and reperfusion in BAO is longer than in the case of occlusion of the anterior circulation has generated much interest. A high proportion of white matter in the brainstem might make it more resistant to ischaemia than other brain tissue, and better collaterals in the posterior than in the anterior circulation might preserve penumbral tissue for a longer period. However, this issue is not resolved. Multivariate analyses of large

series of patients have indicated that there are many independent predictors of outcome. Time to treatment seems to be less important than severity of the clinical deficit before treatment and the presence of collaterals.

At present, we select patients with BAO for treatment according to clinical findings and multimodal MR or CT imaging. When coma has not been prolonged and imaging does not show extensive infarcts in the brainstem, the patient receives intravenous alteplase followed by arteriography or CT angiography and subsequent mechanical thrombectomy when necessary. Such a strategy can also be realised in a stroke network. To avoid treatment delays, intravenous thrombolysis should be initiated in the referring hospital before transfer to the intervention centre.

Challenges for future research

Higher recanalisation rates decrease mortality (Figure 5B) but do not necessarily translate into better outcomes (Figure 5C). Therefore, different treatment strategies should be tested against each other in randomised trials. Bridging therapy with intravenous alteplase before endovascular treatment should best be tested against intravenous thrombolysis alone and direct endovascular treatment.

Two outcomes of bridging therapy are possible. First, some patients will recanalise after intravenous thrombolysis and will not need subsequent endovascular treatment. Second, those who do not recanalise after intravenous thrombolysis will receive endovascular treatment (also referred to as rescue therapy). If only individuals receiving rescue therapy are counted, their outcome will probably differ from that of all patients, including those who recanalise after intravenous thrombolysis.

Another limitation of direct comparison of variable treatment modalities is the rapid evolution of endovascular techniques that inherently creates learning curves for mastering the use of novel interventions and devices, which are also selected for use on an individual basis. Owing to this heterogeneity, appropriate randomised controlled studies comparing various treatment modalities are very difficult to undertake in this uncommon disease. Intuitively, it seems that the rate of recanalisation as a strong predictor of good outcome could act as a relevant surrogate marker, but weighing the benefit of different treatments according to avoidance of death or disability is important.

CONCLUSIONS

During the past few decades, BAO has evolved from an almost uniformly fatal disease to a treatable disorder. Prompt recanalisation of the basilar artery can substantially enhance a patient's chances of survival and good functional recovery. However, the best recanalisation approach has not been defined in randomised trials. Current endovascular techniques recanalise 80–90% of all blocked basilar arteries. Nevertheless, many recanalisation procedures are futile, so the outlook for many patients with BAO is bleak. Further medical research, training of doctors and other health professionals, and improved public awareness are needed to hone the treatment process for BAO at various points to provide a better outlook for patients.

Search strategy and selection criteria

We searched PubMed (from 1990 to August, 2011) with the terms "basilar artery occlusion" and "basilar artery thrombosis". We also identified relevant published work by searching the reference lists of articles retrieved by our search and from our own files. Reports published in English, Finnish, French, German, Italian, and Swedish were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

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3

Outcome in patients with basilar artery occlusion treated conventionally

Wouter J. Schonewille, Ale Algra, Joaquin Serena, Carlos A. Molina, L. Jaap Kappelle

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ABSTRACT

Background Most data on the outcome of basilar artery occlusion are from recent case series of patients treated with intra-arterial thrombolysis. The limited knowledge on the outcome after a conventional treatment approach comes from a few small case series of highly selected patients.

Objective To provide more data on the outcome of conventional treatment.

Methods Data were analysed on patients from three centres with symptomatic basilar artery occlusion treated conventionally. Conventional therapy was defined as treatment with antiplatelets, anticoagulation, or both.

Results Data were available on 82 patients. The case fatality was 40%. Among survivors, 65% remained dependent (Rankin score 4–5). Patients younger than 60 years (odds ratio=3.1 (95% confidence interval, 1.0 to 9.5)) and those with a minor stroke (OR=3.1 (1.0 to 9.6)) were more likely to have a good outcome (Rankin score 0–3). Patients with a progressive stroke were less likely to have a good outcome (OR=0.3 (0.08 to 1.2)) than patients with a maximum deficit at onset or fluctuating symptoms at presentation.

Conclusions Conventional treatment of symptomatic basilar artery occlusion is associated with a poor outcome in almost 80% of patients, which emphasises the importance of the search for a more effective treatment approach.

INTRODUCTION

Unlike the anterior circulation, the posterior circulation depends on one main artery. The basilar artery supplies the occipital lobes, part of the temporal lobes, the thalami, the cerebellum, and most importantly the brain stem. Acute occlusion of the basilar artery has been associated with a high case fatality rate and morbidity, although reliable data about the natural history are lacking. Studies on the outcome of basilar artery occlusion using a conventional treatment approach have been small and have described the outcome of highly selected patients or used very broad definitions, including vertebral and branch artery occlusions.[1-10] Hacke et al, in the largest study to date with detailed individual angiographic data (n=22), found a case fatality of 86% in patients treated conventionally.[11,12] Recently several uncontrolled larger case series of patients treated with intra-arterial thrombolysis have found case fatality rates ranging between 20% and 70%.[11-25] More data are needed on the outcome of conventional treatment to validate these results.

METHODS

Three centres participated in our database search: the University Medical Centre Utrecht, Netherlands; Hospital Universitari Doctor Josep Trueta in Girona, Spain; and Hospital Vall d'Hebron in Barcelona, Spain. All are academic hospitals with a special interest in stroke. The databases used in the three centres were constructed in similar fashion, with comparable definitions and outcome measures. Patients' records were reviewed for details of clinical presentation. Patients were included in the study if they fulfilled at least one of the following diagnostic criteria:

(A) acute neurological deficit attributable to the posterior circulation and basilar artery occlusion on angiography, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or necropsy;

(B) acute "classic" symptoms of basilar artery occlusion including alternating hemiplegia/tetraplegia with brain stem deficits, leading to a locked-in state, coma, or death;

(C) coma or loss of consciousness and acute posterior circulation infarction on computed tomography (CT) or magnetic resonance imaging (MRI).

Patients were considered to have been treated conventionally if they had not received any specified treatment, or if they had been treated with antiplatelets, anticoagulation, or a combination of the two. During the time period studied, thrombolytic treatment was not a standard option in these three centres. Most studies of intravenous or intra-arterial thrombolysis in acute stroke have used a modified Rankin score of 0–1 or 0–2 to define good outcome. Because of the poor natural history of basilar artery occlusion we used a modified Rankin score of 0–3 as a measure of independence and good outcome. Outcome was assessed at the time of discharge or in-hospital death, without knowledge of baseline characteristics pertinent to the outcome. Stroke severity at the time of presentation was considered minor if a patient was non-comatose and was not tetraplegic, intubated, or locked-in.

We distinguished three different types of clinical presentation: fluctuating symptoms with alternating periods of neurological worsening (at least one) and improvement, without full recovery; progressive stroke with a progressive worsening of deficit, stepwise or gradual, but without intermittent periods of improvement; and maximum deficit from onset with or without subsequent improvement or fluctuating symptoms.

Data analysis

We assessed the relation between potential prognostic factors and outcome by univariate logistic regression. The strength of a relation was expressed as an odds ratio (OR) with corresponding 95% confidence interval (CI) to describe its precision.

RESULTS

On our database search we found 82 patients with the clinical diagnosis of symptomatic basilar artery occlusion, treated conventionally, over a period of 20 database years (11 years for Utrecht, 5 years for Girona, and 4 years for Barcelona), ending in 2002 (Table 1). Eleven patients with basilar artery occlusion treated with intravenous (n=2, from two centres) or intra-arterial thrombolysis (n=9, three in each centre) where excluded from the study. These were all treated within the first three hours in cases of intravenous treatment or within 12 hours in cases of intra-arterial thrombolysis. Fifty three patients were treated in Utrecht, 20 in Girona, and

Table 1 Patient characteristics and outcome: three centre database search (n=82)

			Rankin score		
Patient characteristics	n	%	0–3 (n (%))	4–5 (n (%))	Death (n (%))
All	82		17 (21)	32 (39)	33 (40)
Age <60 years	35	43	11 (31)	18 (51)	6 (17)
Male sex	44	54	12 (27)	15 (34)	17 (39)
Fluctuating symptoms	13	16	3 (23)	7 (54)	3 (23)
Progressive stroke	29	35	3 (10)	10 (35)	16 (55)
Maximum from onset	40	49	11 (28)	15 (38)	14 (35)
Coma	28	34	6 (21)	7 (25)	15 (54)
Locked-in/tetraplegia	18	22	0	10 (56)	8 (44)
Intubated	18	22	3 (17)	4 (22)	11 (61)
Minor stroke	35	43	11 (31)	15 (43)	9 (26)
Previous TIAs*	16	20	4 (25)	9 (56)	3 (19)
Previous stroke*	16	20	1 (6)	8 (50)	7 (44)
Use of antiplatelet agents	55	67	10 (18)	22 (40)	23 (42)
Use of anticoagulation	27	33	7 (26)	10 (37)	10 (37)
Diagnostic category A†	25	30	9 (36)	6 (24)	10 (40)
Diagnostic category B‡	26	32	0	13 (50)	13 (50)
Diagnostic category C§	31	38	8 (26)	13 (42)	10 (32)

* Posterior circulation. † Diagnostic criteria A, B, and C are defined in the text.

nine in Barcelona. Of these 82 patients, 25 were categorised in diagnostic group A, 26 in group B, and 31 in group C. All patients in group B had a poor outcome (Rankin score 4–6), 74% had a poor outcome in group C, and 64% in group A. The small number of patients who had necropsy (n=2) did not cause a bias towards a worse outcome in group A.

The poor outcome in patients with basilar artery occlusion did not improve in more recent years (82% in 1997 to 2002 *v* 74% in 1991 to 1996), despite more patients being diagnosed with a minor stroke (47% *v* 35%). The mean time to assessment was 28 days (range 1 to 280) for all patients. Twenty nine per cent of the deaths occurred within the first 48 hours and 53% within the first week, with a mean time to death of 12 days (range 1 to 76). Discharge of the 42 survivors was after a mean of 40 days (range 3 to 280); 61% were discharged within a month, 84% within two months, and 91% within three months. There was a clear trend towards a better

Table 2 Predictors of good outcome: three centre database search (n=82)

	Good outcome		
Characteristic	Present	Absent	OR (95% CI)
Age ≤60 years	31% (11/35)	13% (6/47)	3.1 (1.0 to 9.5)
Male sex	27% (12/44)	13% (5/38)	2.5 (0.8 to 7.8)
Fluctuating stroke	23% (3/13)	20% (14/69)	1.2 (0.3 to 4.9)
Progressive stroke	10% (3/29)	26% (14/53)	0.3 (0.08 to 1.2)
Maximum from onset	28% (11/40)	14% (6/42)	2.3 (0.8 to 6.9)
Coma	21% (6/28)	20% (11/54)	1.1 (0.3 to 3.3)
Minor stroke	31% (11/35)	13% (6/47)	3.1 (1.0 to 9.6)
Previous TIAs*	25% (4/16)	20% (13/66)	1.4 (0.4 to 4.9)
Previous stroke*	6% (1/16)	24% (16/66)	0.2 (0.03 to 1.7)

* Posterior circulation. CI, confidence interval; OR, odds ratio; TIA, transient ischaemic attack.

outcome in patients younger than 60 years (odds ratio (OR)=3.1 (95% confidence interval, 1.0 to 9.5)) and patients with a minor stroke (OR=3.1 (1.0 to 9.6)). Patients who presented with a progressive stroke were less likely to have a good outcome than patients presenting with fluctuating symptoms or a maximum deficit from onset (OR=0.3 (0.08 to 1.2) (Table 2).

DISCUSSION

Basilar artery occlusion has generally been associated with a high mortality and morbidity. Among the patients from our database search—the largest series to date on patients treated conventionally—almost 80% had a poor outcome, with a case fatality of 40% and the presence of a severe residual deficit in more than 65% of survivors.

The results of our study should be interpreted with caution. Outcome in our study was assessed after a mean of 28 days. This information, however, is lacking in the previous case series, possible explaining the different findings among studies, because outcome tends to be better after a longer follow up. The three diagnostic groups recognised in the database search by no means represent the whole range of patients with basilar artery occlusion. However, we believe that with a combination

Table 3 Case series on the outcome of basilar artery occlusion treated conventionally

			Rankin score		
Study	Year	n	0–3	4–5	6
Moscow[7]	1973	9	44	22	33
Archer[8]	1977	20	5	25	70
Hacke[11]	1988	22	14		86
Devuyst[9]	2002	9	66	22	11
Present study	2004	82	21	39	40
Total		142	21	28	49

of strict clinical and simple frequently used imaging techniques as inclusion criteria for our database search, our patient group is more representative of the conventional treatment approach than most previously published series in which individual patient data were described (Table 3). These series included cases confirmed by MRA or conventional angiography. It is unlikely that, in a disorder for which no specific treatment other than anti-thrombotic agents was available, all consecutive patients with the possible clinical diagnosis of basilar artery occlusion had radiological confirmation of their occlusion, while a few would have been imaged within the first 24 hours, causing an important selection bias. This is especially true for the older case series done at a time when non-invasive vascular imaging was not an option.[8,11] In our database review, basilar artery occlusion was only confirmed by radiological imaging in 30% of patients (group A). Interestingly these patients had the best outcome, despite having similar stroke severity at onset. One possible explanation for the better outcome in patients who had radiological confirmation of their occlusion is that most were imaged more than 24 hours after the time of occlusion and had already survived the most critical phase. Our patient groups B and C, presenting with a severe progressive deficit or an acute loss of consciousness, are probably most representative of the way most physicians would think of a typical patient with basilar artery occlusion. However, this latter group excludes an important subgroup of patients with a minor stroke, causing a bias towards the inclusion of patients with a more severe deficit.

The more frequent use of non-invasive vascular imaging in the two most recent studies could have caused an increase in the number of patients diagnosed with

basilar artery occlusion with a minor deficit.[9,10] Voetsch et al[10] described the outcome of 87 patients with occlusive basilar artery disease including patients with basilar artery stenosis and 32 patients with basilar artery occlusion documented by transcranial Doppler, MRA, or conventional angiography. They found an overall case fatality of only 2.3%. No individual patient data were described concerning stroke severity, treatment, or time to radiological confirmation. Most patients had a minor stroke, and only five had tetraparesis or tetraplegia; one patient was locked-in and 16 had a decreased level of consciousness. The only data available on the subgroup of patients with basilar artery occlusion described a poor outcome (death or major disability) in 40% of patients with an atherosclerotic occlusion.

The severity of deficit in the 20 patients described by Archer and Horenstein8 seems comparable to our patient group. In contrast to our results, they found coma to be an important predictor of poor outcome. This difference might reflect improved monitoring and treatment options in comatose patients, as on average our patients were treated 25 years later. The mayor difference in outcome with the study of Hacke et al is more difficult to explain, as all their patients had minimal symptoms (n=2) or a stable moderate brain stem stroke (n=20).[11,12]

The numbers of patients described by Moscow and Newton[7] and Devuyst et al[9] are too small for a meaningful comparison, but interestingly both studies describe the same possible positive influence on outcome of previous TIAs as found in our study.

The emphasis in our study was on the outcome in relation with the clinical presentation; because of the low rate of vascular imaging the aetiology could not reliably be assessed. We identified three potentially important predictors of good outcome in patients treated conventionally: young age, limited stroke severity, and a presentation with fluctuating symptoms or a maximum deficit from onset (Table 2). Age could influence both the spontaneous recanalisation rate and the quality of collateral flow, as the rate of atherothrombotic disease increases with age. Initial stroke severity could be an indicator of the quality of collateral flow at the time of occlusion, and progression of deficit could represent failure of augmentation of collateral flow or growth of the thrombus.

In conclusion, the outcome of patients with basilar artery occlusion treated conventionally varies considerably among case series. Considering our limited knowledge on the outcome of patients treated conventionally, future studies on

the outcome of basilar artery occlusion should not be limited to patients receiving more aggressive treatment.

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4

The Basilar Artery International Cooperation Study (BASICS)

Wouter J. Schonewille, Christine A. C. Wijman, Patrik Michel, Ale Algra, L. Jaap Kappelle; on behalf of the BASICS Study Group

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ABSTRACT

Basilar artery occlusion is a rare cause of stroke with a high case fatality rate and an often poor clinical outcome among survivors. Our limited knowledge on the outcome in patients with basilar artery occlusion comes from small case series of selected patients.

Study aim The main purpose of the registry is to collect preliminary data that will help direct the design of a future clinical treatment trial. The target number of patients included is 500.

Design BASICS is a prospective, observational, multi-center, international registry of consecutive patients presenting with a symptomatic and radiologically confirmed basilar artery occlusion.

Study outcomes From November 2002 until December 2006 data have been collected on 400 patients, from 42 centers in 12 countries. Most patients were treated with IA therapy (55%), followed by antithrombotics (29%) and IV thrombolysis (6%). The overall mortality was 45%.

Posterior circulation stroke accounts for about 20% of all ischemic strokes. Unlike the anterior circulation, the posterior circulation depends on one main artery. The basilar artery supplies most of the brainstem and the occipital lobes, and part of the cerebellum and thalami. The clinical presentation of basilar artery occlusion is highly variable ranging from transient ischemic attacks (TIAs) or minor stroke to rapidly progressive brainstem dysfunction or coma at onset. These differences in presentation may represent differences in the etiology, localization of occlusion and severity of ischemia.

In a disease with such a variety of presentations and etiologies, it is possible that some subgroups of patients will respond better to a specific treatment than others. Numerous case series have failed to identify a superior treatment strategy in patients with basilar artery occlusion. The overall case fatality rate is 40–50% in patients treated with antithrombotics (antiplatelets or heparin), intravenous (i.v.) thrombolysis or intraarterial (IA) thrombolysis.[1-18] The interpretation of outcome results has been as varied as the outcome results themselves. Data in these case series have been collected retrospectively on small numbers of selected patients using different definitions and treatment strategies. Owing to the retrospective nature of these case series, data collection has been limited to a few basic items not allowing for multivariable analysis.

There has been only one attempt to perform a randomized trial (Australasian Urokinase Stroke Study) comparing heparin with heparin plus IA urokinase, which was terminated prematurely because of a low recruitment rate.[19]

We need a better understanding of the natural history of basilar artery occlusion and the differences in treatment responses among patients before we can embark on a prospective randomized clinical trial.

Treatment options in basilar artery occlusion

Owing to the absence of a clearly effective therapy, current treatment approaches for acute basilar artery occlusion differ considerably among stroke centers both within and between countries. Many stroke centers use an 'all-inclusive' treatment protocol for patients with acute stroke that does not distinguish between anterior and posterior circulation stroke, based on results from randomized treatment trials of patients with mainly anterior circulation stroke.

There have been several randomized treatment trials studying the efficacy and safety of i.v. recombinant tissue plasminogen activator (rtPA) in patients with acute ischemic stroke.[20-22] The results of these trials suggest a potential benefit of i.v. thrombolysis up to 6 h from symptom onset, but this benefit is clearly greater the sooner a patient is treated.[23] Intravenous rtPA received approval from the US Food and Drug Administration and conditional approval from the European Agency for the Evaluation of Medicinal Products for the treatment of acute ischemic stroke within 3 h of symptom onset in 1996. Furthermore, there has been one randomized trial showing the efficacy and safety of IA thrombolysis in anterior circulation stroke within the 0–6-h time window and several smaller trials showing the feasibility of a combined i.v.–IA approach.[24-26]

Patients with posterior circulation stroke were either excluded from the randomized i.v. thrombolysis trials, or their number was small or undetermined.[20-22] The largest dataset on outcome of patients with basilar artery occlusion treated with i.v. thrombolysis is a case series of 50 patients.[16] The protocol allowed treatment up to 12 h from stroke onset for patients with a sudden onset of decreased level of consciousness or tetraparesis and up to 48 h in patients with a progressive stroke with a lesser deficit.

The data available from case series of patients with basilar artery occlusion do not suggest a significant difference in treatment response in patients with posterior circulation stroke as compared with stroke in the anterior circulation. Nevertheless, many centers allow for a 6–12-h treatment delay in patients with basilar artery occlusion resulting in severe neurological deficit and up to several days for patients with a progressive stroke with a lesser deficit. As in anterior circulation stroke, time to treatment is probably the most important determinant of a favorable outcome in patients with basilar artery occlusion. If extension of the treatment window in unselected basilar artery occlusion patients beyond 6 h offers a benefit, this is likely to be small.

Whether advanced imaging methods will help to identify patients with symptomatic basilar artery occlusion who will benefit from treatment in delayed time windows is unknown. Preliminary data suggest that such a strategy may be useful in anterior circulation stroke patients using diffusion and perfusion magnetic resonance imaging.[27-30] However, these imaging techniques in the posterior circulation have been explored very little.[31]

The Basilar Artery International Cooperation Study (BASICS) registry

The BASICS is a prospective, observational, multi-center, international registry of consecutive patients presenting with a symptomatic and radiologically confirmed basilar artery occlusion.

The main purpose of the BASICS study is to collect preliminary data that will help direct the design of a future clinical treatment trial. The target number of patients included in the registry is 500, which should be sufficient to answer several predetermined questions (see Box 1). For example, for a baseline characteristic with a prevalence of 30%, a relative risk of 1·4 could be assessed with sufficient precision – the corresponding 95% confidence interval would range from 1·1 to 1·7. Likewise, on the basis of 50% of the patients being treated with IA therapy and about 30% with antithrombotics alone, a crude relative risk reduction by IA of 23% would have a 95% confidence limit from 2% to 39%. The latter estimate would be of importance for the design of a clinical trial.

The advantages of the BASICS registry over data derived from case series will be the large number of patients included, the prospective and detailed data collection and the inclusion of consecutive patients treated with different treatment strategies. The detailed data available on a large number of patients will enable the evaluation of several potential predictors of outcome. Patients will be divided into three treatment

Box 1 The BASICS registry is designed to collect preliminary data aimed at answering the following predetermined questions

- What is the relationship between functional outcome and
  - Type of clinical presentation
  - Duration of symptoms before treatment
  - Presence of early ischemic changes on pretreatment CT scan
  - Location of occlusion
  - Type of treatment
  - The presence of recanalization
  - Stroke etiology?
- What are the most common treatment complications for the three different treatment groups (antithrombotic treatment alone, IV. thrombolysis, IA therapy)?
- What is the clinical outcome; vessel patency, stroke recurrence, and quality of life of survivors at 1-year follow up?

groups for analysis: antithrombotic treatment alone, i.v. thrombolysis and IA therapy. Predictors of outcome will be identified comparing patients who died and with poor clinical outcome (modified Rankin score of 4–5) at 1 month with patients with good clinical outcome (defined as a modified Rankin score of 0–3). In addition, a separate follow-up study will assess clinical outcome at 3 and 12 months.

Patients are eligible for entry in the registry if they present with symptoms and signs attributable to the posterior circulation in the presence of basilar artery occlusion confirmed by computed tomography angiography, magnetic resonance angiography or conventional contrast angiography. BASICS is a purely observational study. Patients will receive treatment as determined by the treating physician. There are no exclusion criteria.

Detailed data are recorded on estimated time of occlusion, prodromal phase, and type of presentation, pretreatment imaging, type and timing of treatment, neurological deficit at time of treatment, follow-up imaging, risk factors, presumed etiology and outcome. The follow-up study will record data on clinical outcome, basilar artery patency, stroke recurrence, and living situation at 1 year. Data entry is performed electronically through a website that is accessible through a center-specific login and password that only gives access to the data entered by that specific center. Data entry by fax or regular mail is optional.

Current status

From November 2002 until December 2006, data have been collected on 400 patients, from 42 centers in 12 countries. Sixty-two per cent of the patients are male and the mean age is 63 years. Sixty-one per cent of the patients had a severe stroke defined as a National Institute of Stroke Scale of ≥20 at the time of treatment. Most patients were treated with IA therapy (55%), followed by antithrombotics alone (29%) and i.v. thrombolysis (6%). Ten per cent received no acute treatment. Patients who received no acute treatment were either having a TIA or a minor stroke while taking antithrombotics or had such a severe stroke that acute treatment other than supportive care was considered futile. Overall mortality was 45%. After 1 month, 29% of the patients had a good outcome defined as a modified Rankin score of 0–3. With the current recruitment, we anticipate to reach our goal of 500 patients by the end of 2007. We are still welcoming additional centers to participate in the registry.

Interested centers are invited to contact the principal investigator at w.j.schonewille@umcutrecht.nl.

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5

Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study

Wouter J. Schonewille, Christine A.C. Wijman, Patrik Michel, Christina M. Rueckert, Christian Weimar, Heinrich P. Mattle, Stefan T. Engelter, David Tanne, Keith W. Muir, Carlos A. Molina, Vincent Thijs, Heinrich Audebert, Thomas Pfefferkorn, Kristina Szabo, Perttu J. Lindsberg, Gabriel de Freitas, L. Jaap Kappelle, Ale Algra;
on behalf of the BASICS Study Group

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ABSTRACT

Background Treatment strategies for acute basilar artery occlusion (BAO) are based on case series and data that have been extrapolated from stroke intervention trials in other cerebrovascular territories, and information on the efficacy of different treatments in unselected patients with BAO is scarce. We therefore assessed outcomes and differences in treatment response after BAO.

Methods The Basilar Artery International Cooperation Study (BASICS) is a prospective, observational registry of consecutive patients who presented with an acute symptomatic and radiologically confirmed BAO between November 1, 2002, and October 1, 2007. Stroke severity at time of treatment was dichotomised as severe (coma, locked-in state, or tetraplegia) or mild to moderate (any deficit that was less than severe). Outcome was assessed at 1 month. Poor outcome was defined as a modified Rankin scale score of 4 or 5, or death. Patients were divided into three groups according to the treatment they received: antithrombotic treatment only (AT), which comprised antiplatelet drugs or systemic anticoagulation; primary intravenous thrombolysis (IVT), including subsequent intra-arterial thrombolysis; or intra-arterial therapy (IAT), which comprised thrombolysis, mechanical thrombectomy, stenting, or a combination of these approaches. Risk ratios (RR) for treatment effects were adjusted for age, the severity of neurological deficits at the time of treatment, time to treatment, prodromal minor stroke, location of the occlusion, and diabetes.

Findings 619 patients were entered in the registry. 27 patients were excluded from the analyses because they did not receive AT, IVT, or IAT, and all had a poor outcome. Of the 592 patients who were analysed, 183 were treated with only AT, 121 with IVT, and 288 with IAT. Overall, 402 (68%) of the analysed patients had a poor outcome. No statistically significant superiority was found for any treatment strategy. Compared with outcome after AT, patients with a mild-to-moderate deficit (n=245) had about the same risk of poor outcome after IVT (adjusted RR 0·94, 95% CI 0·60–1·45) or after IAT (adjusted RR 1·29, 0·97–1·72) but had a worse outcome after IAT compared with IVT (adjusted RR 1·49, 1·00–2·23). Compared with AT, patients with a severe deficit (n=347) had a lower risk of poor outcome after IVT (adjusted RR 0·88, 0·76–1·01) or IAT (adjusted RR 0·94, 0·86–1·02), whereas outcomes were similar after treatment with IAT or IVT (adjusted RR 1·06, 0·91–1·22).

Interpretation Most patients in the BASICS registry received IAT. Our results do not support unequivocal superiority of IAT over IVT, and the efficacy of IAT versus IVT in patients with an acute BAO needs to be assessed in a randomised controlled trial.

INTRODUCTION

Stroke is the leading cause of disability in developed countries.[1] Posterior circulation stroke accounts for about 20% of all ischaemic strokes. The basilar artery, which is the main vessel of the posterior circulation, supplies most of the brainstem and occipital lobes and part of the cerebellum and thalami. Owing to different degrees of involvement of the brainstem, patients with acute basilar artery occlusion (BAO) can present with symptoms that vary from isolated cranial nerve palsies or hemiplegia to the locked-in state or coma. Despite recent advances in the treatment of acute stroke, the rate of death or disability associated with BAO is almost 80%.[2-4]

Randomised trials have shown the safety and efficacy of intravenous thrombolysis (IVT) given within 4·5 h of the onset of the symptoms of acute ischaemic stroke and intra-arterial thrombolysis given within 6 h.[5-10] Unfortunately, the results of these randomised acute stroke trials do not directly apply to patients with an acute BAO because only few, if any, of these patients were included. BAO has not been studied in isolation in randomised clinical trials because of its low incidence: only about 5% of all patients who have thrombolysis for stroke have BAO.[4,11] We are aware of only one randomised trial of treatment in patients with an acute BAO, which was terminated prematurely because of poor recruitment.[12] Case series of patients with BAO found the outcomes of patients treated with antithrombotic therapy (AT), IVT, or intra-arterial therapy (IAT) were similar.[2,13] The primary aim of the Basilar Artery International Cooperation Study (BASICS) was to obtain a better understanding of outcomes after acute BAO and to study potential differences in treatment response in anticipation of a definitive randomised controlled trial of acute treatment in these patients.

METHODS

Patients

BASICS was a prospective, observational, international registry of consecutive patients aged 18 years or older who presented with an acute symptomatic and radiologically confirmed BAO.[14] Patients were eligible for entry if they presented with symptoms or signs attributable to disruption of the posterior circulation,

and had a BAO as confirmed by CT angiography (CTA), magnetic resonance angiography (MRA), or conventional contrast angiography. BAO was defined as complete obstruction of flow in the proximal, middle, or distal portion of the basilar artery. Patients with bilateral vertebral artery occlusions with retrograde filling of the basilar artery were excluded. Treatments were allocated at the discretion of the treating physician. The BASICS protocol was approved by the ethics committee of the University Medical Center Utrecht, Netherlands. The requirement for additional local ethical approval differed between participating countries and was obtained if required. Verbal or written informed consent was obtained from the patient or patient's representative, as required by national and local guidelines. The BASICS registry opened on November 1, 2002, and closed on October 1, 2007.

Procedures

Detailed data were recorded in a web-based data entry form that included information on baseline characteristics, stroke risk factors, estimated time of BAO, clinical presentation, pretreatment and post-treatment imaging findings, type and timing of treatment, neurological deficits at time of treatment, complications, presumed cause of stroke, cause of death, and outcome at 1 month. Data were entered with a centre-specific login and password. Definitions of the variables collected were incorporated in the electronic data entry form and specified in a separate guideline, which was available at all participating centres.

Stroke severity at time of treatment was dichotomised as severe or mild to moderate. Patients in a coma, with tetraplegia, or in a locked-in state were classed as having a severe stroke, whereas mild-to-moderate stroke was defined as any deficit that was less than severe. Neurological deficit at the time of treatment was further assessed with the National Institutes of Health stroke scale (NIHSS). Estimated time of BAO was 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; if the exact time was not known, the time of onset was recorded as the last time the patient was seen by any witness before symptom onset. Transient ischaemic attack (TIA) or minor stroke in the hours or days before the index event were not counted as the time of the occlusion but were recorded under the prodromal phase. For example, the estimated time of occlusion for a patient who was admitted with an

acute minor cerebellar stroke but who developed a severe deficit the next day that was consistent with the clinical diagnosis of an acute BAO was recorded as the time of the onset of the severe deficit. All pertinent data from the centres that recorded all consecutive patients were included in the registry.

The primary outcome measure was poor outcome at 1 month. In view of the high risk of death and disability in patients with BAO, poor outcome was defined as a modified Rankin scale (mRS) score of 4 or 5 (severe disability) or death.[15] Haemorrhagic changes seen on the first post-treatment CT image or the occurrence of symptomatic intracranial haemorrhage at any time during the first month were systematically recorded as a treatment complication and, if applicable, as a cause of death. The registry did not predefine symptomatic intracranial haemorrhage as an outcome measure, and the reporting of symptomatic intracranial haemorrhage was done entirely on the basis of each investigator's judgment. For the primary analysis, patients were divided into three groups according to treatment: only AT (ie, received antiplatelet drugs or systemic anticoagulation); primary IVT, including subsequent IAT; or only IAT, which comprised thrombolysis, mechanical thrombectomy, stenting, or a combination of these procedures. These three treatment groups were deemed to represent conventional therapy before IVT was approved (AT), the current standard of care available to all patients (IVT), and the treatment available only at dedicated stroke centres (IAT). Patients who received both IVT and IAT were included in the IVT group because IVT was the intended initial treatment.

Statistical analysis

The target number of patients to be included in BASICS was 500, which was deemed to be sufficient to answer several predetermined questions.[14] Assuming that 50% of patients were being treated with IAT and about 30% with AT, a crude relative risk reduction of 23% with IAT would have a 95% CI of 2–39%. The frequency of poor outcome was compared among treatment groups with risk ratios and 95% CI. Adjusted risk ratios were calculated with Poisson regression. Adjustments are reported for only those factors that changed the crude risk ratios by more than 5%. Additionally, we report simultaneous adjustments for the three factors that had most influence, as well as for all six factors that affected the crude risk ratio. For the treatment comparisons that include AT, we also show the two-factor and

five-factor adjustments because the variable time to treatment was not accurately assessed for patients treated with AT. Missing baseline data (<5% for each variable) were imputed with regression imputation for optimal adjustment for baseline differences in the assessment of treatment effects.[16] We prespecified separate analyses for patients with a mild-to-moderate deficit and for those with a severe deficit. Modification of treatment effect by severity of disease and time to treatment was assessed by calculation of the p value of the treatment by effect modifier terms in Poisson regression.

Role of the funding source

BASICS was an independent, investigator-initiated registry, and no external support was received. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

619 patients from 48 centres in Europe (41), South America (3), North America (2), Australia (1), and the middle east (1) were included in the registry. Participating centres and the number of patients recruited per centre are listed at the end of the paper. One centre was excluded from participation in the registry because not all pertinent data on consecutive patients were being recorded.

183 patients were treated with AT, 121 with IVT, and 288 with IAT. Of the patients treated with IVT, 80 were treated with only IVT and 41 were treated with additional IAT. 179 patients in the IAT group were treated with only pharmacological thrombolysis, 79 patients were treated with pharmacological thrombolysis in conjunction with mechanical thrombectomy, and 30 were treated with only mechanical thrombectomy. 347 patients had severe deficits and 245 patients had mild-to-moderate deficits. 592 patients completed 1 month of follow-up. 27 patients were not analysed because they did not receive AT, IVT, or IAT; these patients were either comatose (n=26) or tetraplegic (n=1) at the time of presentation. 26 of these patients died, and the patient who survived (who had been comatose) had a mRs score of 5 at 1 month.

Table 1 shows baseline characteristics. Patients who received IVT were more commonly treated within 3 h of a BAO than were the patients who received IAT (RR 2·38, 95% CI 1·83–3·10). The time to treatment in patients treated with only AT was not recorded accurately. Patients treated with IAT more often had a severe deficit than did the patients who received AT (RR 1·58, 1·31–1·90) and the patients

Table 1 Baseline characteristics by type of treatment

	All (n=592)	AT (n=183)	IVT (n=121)	IAT (n=288)
Age (years)	63 (15)	64 (15)	65 (14)	62 (15)
Age ≤50 years	114 (19%)	36 (20%)	19 (16%)	59 (21%)
Age ≥70 years	219 (37%)	74 (40%)	46 (38%)	99 (34%)
Women	218 (37%)	71 (39%)	44 (36%)	103 (36%)
Hypertension	365 (62%)	126 (69%)	70 (59%)	169 (59%)
Diabetes mellitus	128 (22%)	43 (24%)	17 (14%)	68 (24%)
Hyperlipidaemia	163 (28%)	64 (35%)	31 (26%)	68 (24%)
Atrial fibrillation	126 (21%)	28 (15%)	30 (25%)	68 (24%)
Coronary artery disease	106 (18%)	31 (17%)	19 (16%)	56 (19%)
Prodromal TIA	111 (19%)	36 (20%)	18 (15%)	57 (20%)
Prodromal minor stroke	112 (19%)	41 (22%)	16 (13%)	55 (19%)
Time to treatment				
0–3 h	179 (30%)	45 (25%)*	67 (55%)	67 (23%)
3–6 h	190 (32%)	39 (21%)*	32 (26%)	119 (41%)
7–9 h	84 (14%)	28 (15%)*	7 (6%)	49 (17%)
>9 h	139 (24%)	71 (39%)*	15 (12%)	53 (18%)
Deficit at time of treatment				
Mild to moderate†	245 (41%)	104 (57%)	49 (41%)	92 (32%)
Severe‡	347 (59%)	79 (43%)	72 (60%)	196 (68%)
NIHSS score	22 (11–30)	15 (6–28)	21 (12–28)	25 (15–30)
NIHSS score >20	310 (52%)	72 (39%)	64 (53%)	174 (60%)
Cause of stroke				
Embolic	215 (36%)	55 (30%)	48 (40%)	112 (39%)
Atherosclerotic	209 (35%)	77 (42%)	38 (31%)	94 (33%)
Dissection	32 (5%)	11 (6%)	8 (7%)	13 (5%)
Other	6 (1%)	1 (<1%)	1 (1%)	4 (1%)
Unknown	130 (22%)	39 (21%)	26 (22%)	65 (23%)

Data are mean (SD), number (%), or median (IQR). AT=antithrombotic therapy. IVT=primary intravenous thrombolysis, with or without additional IAT. IAT=immediate intra-arterial therapy. TIA=transient ischaemic attack. NIHSS=National Institutes of Health stroke scale score.

* Time to treatment was not reported as reliably as it was in the IVT and IAT groups. †Any deficit that was less than severe. ‡Coma, locked-in syndrome, or tetraplegia.

who received IVT (RR 1·14, 0·97–1·35). The mean NIHSS score was 10·7 (SD 7·3) in the patients with a mild-to-moderate deficit and 28·0 (7·2) in the patients with a severe deficit.

402 (68%) of the 592 patients who received treatment had a poor outcome at 1 month and 214 (36%) patients died. Figure 1 shows the outcomes of patients according to the severity of their deficit and treatment modality.

Figure 1 Outcome at 1 month according to severity of initial disease and treatment. **(A)** Outcome according to severity of deficit at time of treatment. **(B)** Outcome according to type of treatment in patients with a mild-to-moderate deficit at time of treatment. **(C)** Outcome according to type of treatment in patients with a severe deficit at time of treatment. Note that the treatment comparisons in panels B and C are based on crude data; Table 2 shows adjusted comparisons. mRS=modified Rankin scale.

Table 2 shows the risk ratios for poor outcome when the three treatment modalities are compared by stroke severity, including adjustments for imbalances in baseline variables and time to treatment. After adjustment for age, NIHSS score, time to treatment, prodromal minor stroke, location of the BAO, and diabetes mellitus (6 factors), we could not show a difference in the risks of patients with a mild-to-moderate deficit with respect to poor outcome after IVT compared with AT (RR 0·94, 95% CI 0·60–1·45) or after IAT compared with AT (RR 1·29, 0·97–1·72). There were no differences in patients with a severe deficit, although their risk of poor outcome after IVT (RR 0·88, 0·76–1·01) or IAT (RR 0·94, 0·86–1·02) was slightly lower than their risk after AT. Adjustment for sex, the presence of prodromal symptoms, hyperlipidaemia, smoking status, and a history of peripheral artery or coronary artery disease did not influence the treatment risk ratios. The treatment effects of IAT versus AT were significantly different between the two strata of disease severity (p=0·03 after adjustment for 6 factors).

When time to treatment was removed from the multivariable adjustment, because the accuracy of the recording of this variable was uncertain among patients treated with AT, the findings changed only slightly and any similarity of outcomes between the IVT and IAT treatment groups were unchanged (adjustment for two factors and fi ve factors in Table 2). After adjustment for five factors, patients with a severe deficit had a significantly worse outcome when treated with AT compared with those treated with IAT or IVT (RR 0·88, 95% CI 0·81–0·96)

In a direct comparison of IAT with IVT (Table 2), patients with a mild-to-moderate deficit had a higher risk of a poor outcome after adjustment for six factors when treated with IAT (RR 1·49, 95% CI 1·00–2·23), whereas patients with a severe deficit had similar outcomes when treated with either IAT or IVT (1·06, 0·91–1·22). The results of these comparisons were the same if a poor outcome was defined as an mRS score of 3–5 or death; the risk ratios adjusted for six factors were 1·36 (0·96–1·93) for patients with a mild-to-moderate deficit and 1·07 (0·95–1·21) for those with a severe deficit.

Table 3 shows the risk ratios for poor outcome in patients treated with IAT compared with those treated with IVT, stratified by time to treatment. There was no statistically significant difference in outcome between IVT and IAT at any time window; however, the number of patients in each stratum was small. None of the

Table 2 Adjusted risk ratios for poor outcome according to treatment comparisons by severity of initial disease

	IVT *vs* AT*	IAT *vs* AT*	IAT *vs* IVT†
Mild-to-moderate deficit			
Total	49	92	92
Poor outcome	18 (37%)	52 (57%)	52 (57%)
Unadjusted	0·87 (0·57–1·34)	1·34 (1·00–1·78)	1·54 (1·02–2·32)
Age (years)	0·90 (0·59–1·36)	1·37 (1·03–1·82)	1·53 (1·03–2·25)
NIHSS	0·79 (0·51–1·23)	1·13 (0·86–1·50)	1·47 (0·97–2·24)
Time to treatment (h)	0·95 (0·61–1·49)	1·37 (1·03–1·82)	1·46 (0·96–2·23)
Prodromal minor stroke	0·93 (0·61–1·42)	1·41 (1·06–1·87)	1·51 (1·01–2·25)
Location of occlusion	0·87 (0·56–1·33)	1·37 (1·03–1·83)	1·63 (1·09–2·45)
Diabetes mellitus	0·88 (0·57–1·35)	1·31 (0·98–1·75)	1·48 (0·98–2·24)
3 factors‡	0·92 (0·58–1·44)	1·23 (0·93–1·62)	1·35 (0·90–2·02)
6 factors§	0·94 (0·60–1·45)	1·29 (0·97–1·72)	1·49 (1·00–2·23)
2 factors¶	0·81 (0·52–1·25)	1·17 (0·88–1·54)	..
5 factors‖	0·85 (0·55–1·30)	1·25 (0·93–1·66)	..
Severe deficit			
Total	72	196	196
Poor outcome	53 (74%)	162 (83%)	162 (83%)
Unadjusted	0·80 (0·68–0·93)	0·89 (0·82–0·98)	1·12 (0·96–1·31)
Age (years)	0·80 (0·68–0·93)	0·90 (0·82–0·98)	1·14 (0·98–1·33)
NIHSS	0·81 (0·70–0·94)	0·90 (0·82–0·98)	1·11 (0·96–1·28)
Time to treatment (h)	0·84 (0·72–0·97)	0·92 (0·85–1·00)	1·08 (0·93–1·26)
Prodromal minor stroke	0·80 (0·69–0·93)	0·89 (0·82–0·98)	1·11 (0·96–1·29)
Location of occlusion	0·80 (0·69–0·93)	0·89 (0·82–0·98)	1·12 (0·96–1·30)
Diabetes mellitus	0·81 (0·69–0·94)	0·90 (0·82–0·98)	1·11 (0·95–1·29)
3 factors‡	0·86 (0·74–0·99)	0·94 (0·86–1·03)	1·09 (0·94–1·25)
6 factors§	0·88 (0·76–1·01)	0·94 (0·86–1·02)	1·06 (0·91–1·22)
2 factors¶	0·81 (0·70–0·94)	0·90 (0·82–0·99)	..
5 factors‖	0·82 (0·71–0·95)	0·90 (0·83–0·98)	..

Data are number (%) or risk ratio (95% CI). Poor outcome=modified Rankin scale score of 4 or 5, or death. IVT=primary intravenous thrombolysis, with or without additional IAT. IAT=immediate intra-arterial therapy. AT=antithrombotic treatment with aspirin or heparin. NIHSS=National Institutes of Health stroke scale score. ..=not available. * Compared with the AT group risk ratios of 1·0 (reference). Of the 104 people with a mild-to-moderate deficit who received AT, 44 (42%) had a poor outcome; of the 79 with a severe deficit who received AT, 73 (92%) had a poor outcome. † Compared with the IVT group risk ratios of 1·0 (reference). Of the 49 people with a mild-to-moderate deficit who received IVT, 18 (37%) had a poor outcome; of the 72 with a severe deficit who received IVT, 53 (74%) had a poor outcome. ‡ Adjustment for age, NIHSS at time of treatment, and time to treatment. § Adjustment for age, NIHSS at time of treatment, time to treatment, prodromal minor stroke, location of occlusion, and diabetes mellitus. ¶ Adjustment for age and NIHSS at time of treatment. ‖ Adjustment for age, NIHSS at time of treatment, prodromal minor stroke, location of occlusion, and diabetes mellitus.

Table 3 Risk ratios for poor outcome according to severity/initial disease and time to treatment

	Patients	Poor outcome		IAT vs IVT (crude)*	IAT vs IVT (adjusted)*
		IVT	IAT		
Mild-to-moderate deficit					
Time to treatment					
0–3 h	43	11/27	7/16	1·07 (0·52–2·20)	1·15 (0·51–2·61)
4–6 h	55	5/14	22/41	1·50 (0·70–3·21)	1·52 (0·69–3·32)
7–9 h	16	1/3	7/13	1·62 (0·30–8·65)	2·84 (0·99–8·10)
>9 h	27	1/5	16/22	3·64 (0·62–21·4)	3·00 (0·61–14·8)
p value for interaction‡	..	..	..	0·15	0·09
Severe deficit					
Time to treatment					
0–3 h	91	28/40	37/51	1·04 (0·80–1·35)	0·96 (0·74–1·24)
4–6 h	96	12/18	62/78	1·19 (0·84–1·68)	1·17 (0·83–1·65)
7–9 h	40	3/4	32/36	1·19 (0·67–2·11)	1·20 (0·76–1·88)
>9 h	41	10/10	31/31	1·00 (NE)	NE
p value for interaction‡	..	..	..	1·00	0·42

Data are number (%) or crude or adjusted relative risk (95% CI) for total numbers/patients who had the stated disease severity and time to treatment. * Adjusted for five variables: age, NIHSS, prodromal minor stroke, location/occlusion, and diabetes mellitus. † Interaction between treatment and time to treatment. NA=not applicable. NE=not estimable. IVT=primary intravenous thrombolysis, with or without additional IAT. IAT=immediate intra-arterial therapy. NIHSS=National Institutes of Health stroke scale score.

41 patients with a severe deficit had a good outcome when treatment was started beyond 9 h after the estimated time of occlusion. Patients with a mild-to-moderate deficit had the worst outcome with IAT if the time to treatment was longer than 9 h (interaction between treatment and time to treatment p=0·09 after multivariable adjustment).

72% (207) of patients treated with IAT had partial or complete recanalisation of the basilar artery (corresponding to a thrombolysis in myocardial infarction [TIMI] score of 2 or 3) at the end of the angiographic procedure. Recanalisation protected against poor outcome after IAT (RR 0·75, 95% CI 0·66–0·85). Of the patients treated with IVT, 182 (88%) had a CTA, MRA, transcranial Doppler (TCD), or conventional angiogram hours to days after treatment, and these showed a mean overall vessel patency rate of 67%. The precise timing of recanalisation in the IVT group, however, is unknown. Basilar artery patency also protected against poor outcome in the IVT group (RR 0·67, 0·49–0·92).

Symptomatic intracranial haemorrhage was more commonly reported in patients treated with IAT (39 of 288 [14%], 95% CI 10–18%) than in those treated with IVT (7 of 121 [6%], 3–11%), and by fewer than 1% (1 of 183) of patients in the AT group. Intracranial haemorrhage was the cause of death in 11 (9%) of 117 patients after IAT, 3 (7%) of 41 patients treated with IVT, and 1 (2%) of 56 patients treated with AT.

DISCUSSION

This is a prospective, international observational study of consecutive patients who presented with an acute symptomatic BAO. Although, to date, no data from a randomised controlled trial support the use of IAT for BAO, IAT was by far the most commonly used treatment type in our registry. Almost 50% of patients were treated with primary IAT: 56% of patients with a severe deficit and 38% of patients with a mild-to-moderate deficit. Additionally, 7% were treated with IVT followed by IAT.

Our results suggest there is a difference in the efficacy of treatment strategies in patients with an acute BAO, depending on the severity of the stroke. Patients with a mild-to-moderate deficit more often had a poor outcome if they were treated with IAT rather than with IVT. In a direct (unadjusted) comparison of IAT with IVT in these patients, the absolute increase in the risk of death or dependency associated with IAT was 20% (Figure 1). The better outcome in the IVT group was not attributable to the patients with a mild-to-moderate deficit who received IAT in addition to IVT, because these patients generally fared worse than those who received only IVT. Conversely, patients with a severe deficit seemed to benefit from both IVT and IAT; absolute risk of death or dependency was 19% (IVT) and 10% (IAT) lower than the risk with AT (Figure 1). The overall rate of death or dependency in this group was 93% in those who were treated with only AT.

We found a non-significantly lower rate of symptomatic intracranial haemorrhage after IVT compared with after IAT, and the overall rates of haemorrhage were similar to those seen in intervention trials of anterior circulation stroke. Rates of mortality due to intracranial haemorrhage were similar after IVT or IAT.

In our analyses, we used an estimated time to treatment from the onset of symptoms consistent with a clinical diagnosis of BAO, rather than the more commonly used time of onset of any symptom to treatment. Previous studies have shown that BAO

is preceded by prodromal symptoms in more than 60% of patients.[17,18] Most of these patients would be excluded from a potential trial that has the time of onset of any symptom to treatment as an inclusion criterion. Because the data in our registry suggest differences in the response to different treatment types, we believe our results support use of the estimated time of BAO, rather than the time of onset of any symptom, to treatment as an inclusion criterion for a future randomised treatment trial in patients with an acute symptomatic BAO.

Interpretation of the results from a previously published meta-analysis of 15 small case-series and from retrospectively collected data has been hampered by the use of different functional scales, heterogeneity in the timing of outcome assessments, and patchy recording of baseline characteristics.[2] Another important limitation of that meta-analysis was that all the patients who were treated with IVT came from only three centres and most were from one centre. The 121 patients treated with IVT in BASICS came from 23 centres, which reduced the chance of selection bias.

Our study is observational and has all the limitations of a non-randomised study. The interpretation of our results is hampered by the absence of a treatment protocol for all patients who entered the study. The reasons for clinicians to select a specific treatment option are more complex than can be covered by the scope of a prospective registry. Multivariable analyses can never adjust completely for systematic differences between treatment groups, which is the aim of randomisation in clinical trials. We suspect that a bias towards more aggressive treatment in patients who were thought to have a worse prognosis might have influenced outcome in the IAT group, and that the restriction of treatment to only AT in patients with a severe deficit might have been an expression of a more palliative approach. More vigilant searching for intracranial haemorrhage in patients who received thrombolysis than in those who received AT might have exaggerated the differences between the IVT, IAT, and AT treatment groups. Crossover to another treatment group because of clinical worsening or the absence of treatment response was not taken into account. Most patients with AT and IVT were diagnosed with BAO on the basis of only non-invasive imaging (as opposed to arterial angiography). We cannot exclude the possibility that some of these patients had a false-positive CTA or MRA, introducing a potential bias in favour of the AT and IVT groups. There might be variables that we did not measure that are relevant to outcome but are unbalanced between groups. In the

design of our data entry form, we tried to take into account all factors that could affect outcome, but we did not record possible relevant imaging or laboratory findings. Furthermore, data collection in a registry is generally not as accurate as it is in a randomised treatment trial. Nevertheless, standard neurological and functional scores and risk factor data were collected from all sites. In the analyses, we have adjusted for baseline imbalances among the treatment groups as much as possible, to help readers to interpret our data. Finally, we are of the opinion that our dataset is representative of the current practice in dedicated stroke centres around the world for patients with an acute symptomatic BAO.

Our observations underscore the continued absence of a proven treatment modality for patients with an acute BAO and that current clinical practice varies widely. Furthermore, the often-held assumption that IAT is superior to IVT in patients with an acute symptomatic BAO is challenged by our observations. Therefore, we believe that a randomised controlled trial to compare IVT with IAT in patients with acute symptomatic BAO is a high priority.

In the meantime, our results should encourage clinicians to treat patients who have acute symptomatic BAO and a mild-to-moderate deficit with IVT. In case of subsequent acute worsening, additional IAT can be considered. Patients who present with a severe deficit can be treated with IVT or IAT. Treatment should be initiated as soon as possible. Our data do not enable any recommendations to be made on the time window within which IVT or IAT should be used in patients with BAO. In centres that cannot provide IAT, we recommend starting IVT while the transfer of the patient to a centre that is able to provide additional IAT if needed is being arranged. Because the chance of a favourable response to therapy will probably decrease with time, the initiation of IVT should not be delayed while waiting for IAT.

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6

Acute basilar artery occlusion in the Basilar Artery International Cooperation Study. Does gender matter?

Marcel Arnold, Urs Fischer, Annette Compter, Jan Gralla, Oliver Findling, Heinrich P. Mattle, L. Jaap Kappelle, David Tanne, Ale Algra, Wouter J. Schonewille; on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose Randomized trials suggested a different benefit of intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT) between men and women with anterior circulation stroke because of a worse outcome of women in the control group.

Methods We compared outcome and recanalization in men and women with basilar artery occlusion treated with antithrombotic treatment alone, IVT or combined IVT–IAT, or IAT in the Basilar Artery International Cooperation Study.

Results Overall, 389 male and 226 female patients were analyzed. In the antithrombotic treatment group, 68 of 111 (61%) men and 47 of 70 (67%) women had a poor outcome defined as a modified Rankin Scale score of 4 to 6 (adjusted risk ratio [aRR], 0.96; 95% CI, 0.75 to 1.24), in the IVT/combined IVT–IAT group, 47 of 77 (61%) men and 24 of 43 (56%) women (aRR, 1.19; 95% CI, 0.89 to 1.60), and in the IAT group, 142 of 185 (77%) men and 71 of 102 (70%) women (aRR, 1.01; 95% CI, 0.88 to 1.17). Mortality was not different between men and women in the antithrombotic treatment group (aRR, 0.80; 95% CI, 0.55 to 1.16), the IVT/combined IVT–IAT group (aRR, 1.11; 95% CI, 0.72 to 1.73), or in the IAT group (aRR, 1.01; 95% CI, 0.75 to 1.36). Insufficient recanalization after combined IVT–IAT or IAT was similar in men and women (23% versus 22%; aRR, 0.92; 95% CI, 0.58 to 1.46).

Conclusions In patients with acute basilar artery occlusion, no significant gender differences for outcome and recanalization were observed, regardless of treatment modality.

INTRODUCTION

In previous studies on patients with acute stroke, gender-based differences have been observed with respect to clinical presentation, management, and outcomes.[1] Studies on patients with ischemic stroke not treated with thrombolysis reported less favorable outcomes for women than for men.[2] Further, it has been reported that women benefited more from intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT) than men.[3,4] The main reason for this difference in favor of women was that nonthrombolyzed women in the control group had a worse outcome than nonthrombolyzed men, whereas in patients undergoing IAT or IVT, outcome was similar in men and women.[3,4]

Large studies on differences between men and women with acute basilar artery occlusion (BAO) are lacking. The Basilar Artery International Cooperation Study (BASICS) is the largest observational study of consecutive patients with acute BAO and provides multicenter data for secondary analyses.[5,6]

The aim of this study was to determine the association between gender and outcome in patients from the BASICS registry.

METHODS

BASICS was a prospective, observational, international registry of consecutive patients presenting with an acute symptomatic and radiologically confirmed BAO. Details of the protocol have been published previously.[5,6]

For the analyses of gender differences in outcome and mortality, patients were divided into 3 groups: (1) antithrombotic treatment (AT; antiplatelets or systemic anticoagulation) alone, (2) IVT or combined IVT–IAT (cIVT-IAT), and (3) IAT (including thrombolysis, mechanical thrombectomy, stenting, and a combination of these). Risk ratios and corresponding 95% CIs were calculated according to gender for poor clinical outcome (modified Rankin scale score 4 to 6), for death within the 3 treatment subgroups, and for insufficient vessel recanalization (Thrombolysis in Myocardial Infarction grade 0 or 1) after cIVT-IAT and after IAT. Adjusted risk ratios (aRRs) were calculated with Poisson regression. Simultaneous adjustments for the 3 and 4 factors that affected the crude risk ratio most were

performed. Missing baseline data (<5% for each variable) were imputed with regression imputation for optimal adjustment for differences between men and women.[7]

RESULTS

A total of 619 patients from 48 centers were included in BASICS. Four patients were not included because of missing data for gender, and 27 were excluded for further

Table 1 Baseline characteristics of patients according to gender

	Female (n=215)	Male (n=373)
Mean age, y (SD)	64 (17)	63 (13)
Age ≤50 y	53 (25%)	61 (16%)
Age ≥70 y	102 (47%)	114 (31%)
Hypertension	125 (58%)	237 (64%)
Diabetes mellitus	39 (18%)	86 (23%)
Hyperlipidemia	48 (22%)	113 (30%)
Atrial fibrillation	50 (23%)	74 (20%)
Coronary artery disease	23 (11%)	83 (22%)
Smoking	23 (11%)	78 (21%)
Prodromal minor stroke	36 (17%)	73 (20%)
Treatment		
AT	70 (33%)	111 (30%)
IVT	28 (13%)	51 (14%)
cIVT-IAT	15 (7%)	26 (7%)
IAT	102 (47%)	185 (50%)
Time to treatment		
0–3 hours	69 (32%)	108 (29%)
4–6 hours	72 (34%)	118 (32%)
6–9 hours	23 (11%)	61 (16%)
>9 hours	51 (24%)	86 (23%)
Severe deficit at time of treatment*	127 (59%)	218 (58%)
Median NIHSS score	21 (11–28)	22 (12–30)
NIHSS score >20	113 (53%)	194 (52%)
Cause of stroke		
Embolic	90 (42%)	123 (33%)
Atherosclerotic	61 (28%)	147 (39%)
Dissection	12 (6%)	19 (5%)
Other	3 (1%)	3 (<1%)
Unknown	49 (23%)	81 (22%)

Data are mean (SD), No. (%), or median (interquartile range).
NIHSS indicates National Institutes of Health Stroke Scale.
*Coma, locked-in state, or tetraplegia.

analysis because they did not receive any AT, IVT, or IAT. Of these 27 patients, 26 died and 1 survived, with a modified Rankin Scale score of 5. Of the remaining 588 patients (373 [63%] men; 215 [37%] women), 181 received AT alone, 120 IVT (n=79) or cIVT-IAT (n=41), and 287 IAT. Table 1 shows baseline characteristics of men and women.

Unadjusted risk ratios and aRRs for poor outcome at 1 month according to gender for each treatment group are shown in Table 2. In the AT group, 68 of 111 (61%) men and 47 of 70 (67%) women had a poor outcome (aRR, 0.96; 95% CI, 0.75 to 1.24), in the IVT/cIVT-IAT group, 47 of 77 (61%) men and 24 of 43 (56%) women (aRR, 1.19; 95% CI, 0.89 to 1.60), and in the IAT group, 142 of 185 (77%) men and 71 of 102 (70%) women (aRR, 1.01; 95% CI, 0.88 to 1.17). The Figure shows detailed clinical outcomes in men and women.

Mortality did not differ between men and women in any group (AT group [aRR, 0.80; 95% CI, 0.55 to 1.16]; IVT/cIVT-IAT group [aRR, 1.11; 95% CI, 0.72 to 1.73]; IAT group [aRR, 1.01; 95% CI, 0.75 to 1.36]).

Table 2 Unadjusted risk ratios and aRRs for poor clinical outcome for gender according to treatment

	AT male vs female	IVT/cIVT-IAT male vs female	IAT male vs female
Total	181	120	287
Poor clinical outcome	68/111 (61%) vs 47/70 (67%)	47/77 (61%) vs 24/43 (56%)	142/185 (77%) vs 71/102 (70%)
Unadjusted	0.91 (0.73–1.14)	1.09 (0.79–1.51)	1.10 (0.95–1.28)
Age (y)	0.92 (0.73–1.14)	1.24 (0.92–1.67)	1.11 (0.95–1.28)
Diabetes mellitus	0.91 (0.73–1.13)	1.09 (0.79–1.50)	1.09 (0.94–1.27)
Hyperlipidemia	0.93 (0.74–1.15)	1.11 (0.81–1.52)	1.12 (0.96–1.30)
Smoking	0.93 (0.74–1.16)	1.16 (0.84–1.60)	1.12 (0.97–1.31)
Prodromal minor stroke	0.91 (0.73–1.13)	1.05 (0.76–1.43)	1.10 (0.95–1.27)
Time to treatment (hours)	0.91 (0.73–1.14)	1.08 (0.79–1.49)	1.09 (0.94–1.26)
Deficit at time of treatment	0.94 (0.74–1.20)	1.12 (0.82–1.53)	1.10 (0.96–1.27)
NIHSS score	0.95 (0.78–1.15)	1.13 (0.84–1.51)	1.07 (0.92–1.23)
Location of occlusion	0.91 (0.73–1.13)	1.09 (0.79–1.50)	1.04 (0.89–1.21)
3 factors*	0.95 (0.78–1.15)	1.21 (0.91–1.62)	1.00 (0.87–1.16)
4 factors†	0.96 (0.75–1.24)	1.19 (0.89–1.60)	1.01 (0.88–1.17)

Data are No. (%) or risk ratio (95% CI).
Poor clinical outcome indicates a modified Rankin scale score of 4 or 5 or death.
*Adjustment for age, National Institutes of Health Stroke Scale (NIHSS) score at time of treatment, and location of occlusion; †adjustment for age, NIHSS score at time of treatment, location of occlusion, and deficit at time of treatment.

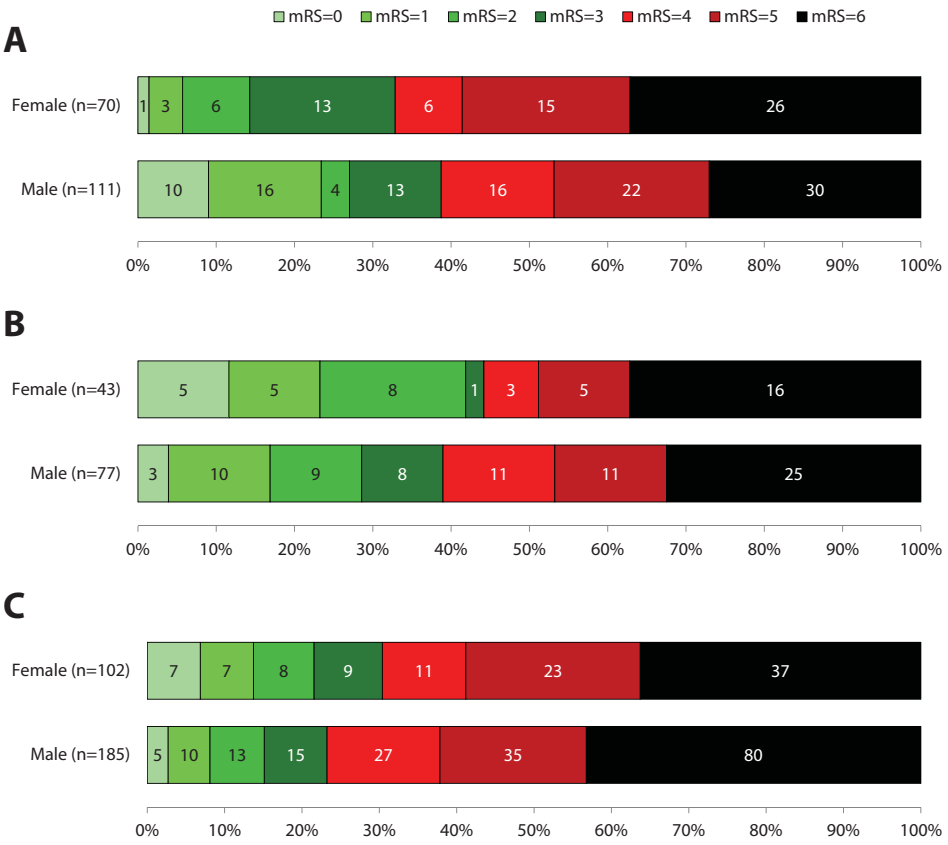

Figure 1 Clinical outcome at 1 month according to gender and treatment. **(A)** Outcome according to gender in patients with AT. **(B)** Outcome according to gender in patients with IVT or cIVT-IAT. **(C)** Outcome according to gender in patients with IAT. Note that comparisons between men and women are based on crude data; Table 2 shows adjusted comparisons. mRS indicates modified Rankin Scale score.

Recanalization was investigated in 37 of 44 (91%) patients after cIVT-IAT and in 252 of 287 (88%) patients after IAT. Insufficient recanalization (Thrombolysis in Myocardial Infarction score of 0 or 1) after cIVT-IAT or IAT was similar in men and women (23% versus 22%; aRR, 0.92; 95% CI, 0.58 to 1.46). The rate of symptomatic intracranial hemorrhage was equal in men (30 of 343; 8%) and women (17 of 215; 8%).

DISCUSSION

In this secondary analysis of BASICS, no significant gender differences in clinical outcome were observed, regardless of treatment modalities. Recanalization rates after IAT and cIVT-IAT were similar for men and women.

The lack of an association between gender and outcome for patients treated with IVT, IAT, or cIVT-IAT is in line with the results of previous studies.[3,4,8] However, the similar outcome of men and women with BAO in the AT group is in contrast with previous studies performed on patients with mainly or exclusively anterior circulation stroke. In a pooled analysis of randomized trials of acute stroke patients, women treated with IV recombinant tissue plasminogen activator derived a greater benefit than men independently of other variables.[3] This effect of gender on outcome was caused primarily by a worse outcome of women among the control patients who were not treated with thrombolysis.

Similar results were reported in patients treated with intra-arterial pro-urokinase for acute ischemic stroke resulting from M1 or M2 segment occlusion of the middle cerebral artery.[4] In a secondary analysis of the PROACT-2 study, an association between gender and treatment effect was demonstrated, with women showing a larger benefit (20% absolute risk reduction for achieving a modified Rankin Scale score ≥2) compared with men (10% absolute risk reduction).[4] Again, the reason for this difference was that in the control group, women had a worse outcome than men, whereas in the thrombolytic group, outcome was similar in men and women. This gender-based effect in the PROACT-2 trial was not attributable to differences in vessel recanalization rates between women and men, and the reasons for these differences remained unexplained. An observational study including patients with middle cerebral artery or internal carotid artery occlusion showed no difference between men and women of recanalization rate and clinical outcome after IAT with urokinase and is in line with the PROACT-2 data.[9] In contrast, a smaller observational study showed higher recanalization rates and more frequent early clinical neurological improvements after intravenous recombinant tissue plasminogen activator among women than men.[10]

The Canadian Alteplase for Stroke Effectiveness Study reported similar clinical outcome and mortality for men and women treated with IVT.[11]

The reasons for the differences between the gender-based analyses of BASICS with regard to treatment effect of AT therapy and those of previous studies are difficult to explain. Differences in coagulation and endogenous fibrinolysis between men and women were reported previously and might contribute to different outcomes according to gender in patients with acute stroke treated with AT.[12,13] Higher factor VII:C levels in women than men have been described in healthy persons and in patients with noninsulin-dependent diabetes mellitus.[14,15] Moreover, plasminogen activator inihibitor-1 levels were shown to be higher in women than men with diabetes mellitus.[15] However, it is difficult to understand why such gender differences would have different effects in acute ischemic stroke in the anterior and posterior circulation, and it seems unlikely that differences of coagulation and the fibrinolytic system exist between patients with anterior and posterior circulation stroke. In the absence of a pathophysiological explanation of the contrary, we believe our study suggests a lack of a difference in treatment response between men and women with BAO.

BASICS was an observational registry and has the inherent limitations of a non-randomized study. Therefore, our results are prone to known and unknown biases that limit the strength of the evidence and preclude definite conclusions on gender differences in patients with BAO. However, we did adjust for age, National Institutes of Health Stroke Scale score at time of treatment, location of occlusion, and deficit at time of treatment in multivariable analyses, whereas no major imbalance was found among other patient characteristics between men and women overall and in the AT group specifically.

In conclusion, in this observational study, men and women with acute BAO did not show any significant differences in clinical outcome and vessel recanalization regardless of treatment modalities.

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7

Predicting outcome after acute basilar artery occlusion based on admission characteristics

Jacoba P. Greving, Wouter J. Schonewille, Christine A.C. Wijman, Patrik Michel, L. Jaap Kappelle, Ale Algra; on behalf of the BASICS Study Group

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ABSTRACT

Objective To develop a simple prognostic model to predict outcome at 1 month after acute basilar artery occlusion (BAO) with readily available predictors.

Methods The Basilar Artery International Cooperation Study (BASICS) is a prospective, observational, international registry of consecutive patients who presented with an acute symptomatic and radiologically confirmed BAO. We considered predictors available at hospital admission in multivariable logistic regression models to predict poor outcome (modified Rankin Scale [mRS] score 4–5 or death) at 1 month. We used receiver operator characteristic curves to assess the discriminatory performance of the models.

Results Of the 619 patients, 429 (69%) had a poor outcome at 1 month: 74 (12%) had a mRS score of 4, 115 (19%) had a mRS score of 5, and 240 (39%) had died. The main predictors of poor outcome were older age, absence of hyperlipidemia, presence of prodromal minor stroke, higher NIH Stroke Scale (NIHSS) score, and longer time to treatment. A prognostic model that combined demographic data and stroke risk factors had an area under the receiver operating characteristic curve (AUC) of 0.64. This performance improved by including findings from the neurologic examination (AUC 0.79) and CT imaging (AUC 0.80). A risk chart showed predictions of poor outcome at 1 month varying from 25 to 96%.

Conclusion Poor outcome after BAO can be reliably predicted by a simple model that includes older age, absence of hyperlipidemia, presence of prodromal minor stroke, higher NIHSS score, and longer time to treatment.

Posterior circulation stroke accounts for about 20% of all ischemic strokes. Unlike the anterior circulation, the posterior circulation depends on one main artery. The basilar artery supplies most of the brainstem and the occipital lobes and part of the cerebellum and thalami. The clinical presentation of basilar artery occlusion (BAO) is highly variable, ranging from TIAs or minor stroke to rapidly progressive brainstem dysfunction or coma at onset. Despite recent advances in the treatment of acute stroke, the rate of death or disability is almost 80%.[1-3]

Predicting outcome after BAO may be helpful to determine which therapeutic interventions should be given and to inform patients and their families about prognosis, but accurate prognostic models with admission data are not available. We describe a basic model that includes easily accessible clinical variables and additional models that include findings from the neurologic examination (NIH Stroke Scale [NIHSS]) and from CT imaging.

METHODS

Study population

The Basilar Artery International Cooperation Study (BASICS) is a prospective, observational, international registry of consecutive patients aged 18 years or older who presented with clinical features of an acute symptomatic and radiologically confirmed BAO. Detailed characteristics of this registry have been described elsewhere.[4,5] In summary, 619 patients with BAO from 48 centers in Europe (41), South America (3), North America (2), Australia (1), and the Middle East (1) were included in the registry from November 2002 to October 2007. Patients were eligible for entry in the registry if they presented with symptoms or signs attributable to disruption of the posterior circulation and had a BAO confirmed by CT angiography, magnetic resonance angiography, or conventional contrast angiography. BAO was defined as complete obstruction of flow in the proximal, middle, or distal portion of the basilar artery. The choice of treatment was left to the discretion of the treating physician.

Standard protocol approvals, registrations, and patient consents

The BASICS protocol was approved by the ethics committee of the University Medical Center Utrecht (Utrecht, the Netherlands). The requirement for additional local ethics approval differed between participating countries and was obtained if required. Verbal or written informed consent was obtained from the patient or patient's representative, as required by national and local guidelines.

Data collection

Detailed data were recorded in a Web-based data entry form that included information on demographics, stroke risk factors, stroke severity assessed by the NIHSS score, estimated time of BAO, and CT imaging findings before treatment. Slightly hypodense lesions with vague borders were classified as early ischemic changes, and lesions that were clearly hypodense and with sharp borders were classified as old infarctions. Estimated time of BAO was the time of onset of symptoms consistent with the clinical diagnosis of an acute BAO, as described by the patient or witness, or, if unknown, the time that the patient was last seen without such symptoms. TIA or minor stroke in the hours or days before the index event was not counted as the time of the occlusion but was recorded under the prodromal phase. For example, the estimated time of occlusion for a patient who was admitted with an acute minor cerebellar stroke but who developed a severe deficit the next day that was consistent with the clinical diagnosis of an acute BAO was recorded as the time of the onset of the severe deficit.

Outcome

The primary outcome measure was poor outcome at 1 month. In view of the high risk of death and disability in patients with BAO, poor outcome was defined as a modified Rankin Scale (mRS) score of 4 or 5 (severe disability) or death.[6] The mRS score at 1 month was assessed in person during admission or as an outpatient or through a telephone interview with the patient or caregiver. All patients had complete follow-up data.

Model development

We considered predictors that could be determined easily and readily within the first few hours after BAO. For consecutive models, we presented groups of variables for inclusion according to the order in which information generally becomes available in clinical practice. Three prognostic models were defined: model 1 was based on demographics and stroke risk factors; model 2 had information on neurologic examination (NIHSS) added; and model 3 had imaging data from noncontrast CT and CT angiography added. Restricted cubic spline functions and graphs were used to determine whether continuous variables could be analyzed as linear terms or required transformation.[7,8]

Missing values of patient characteristics were imputed as determined by the correlation between patient characteristics with missing values with the other variables by means of single regression imputation.[9] Logistic regression analysis was performed with poor outcome as the outcome variable. Candidate predictors were considered for entrance into multivariable regression models irrespective of their univariable association with poor outcome.[8] All candidate predictors were included in a multivariable logistic regression model and were step by step excluded if the likelihood ratio test had $p>0.15$. Interaction terms between predictors were examined with likelihood ratio tests, but none was of sufficient relevance to extend the models beyond the main effects for each predictor.

Model performance

We evaluated both calibration and discrimination of the 3 models.[10] The discriminative performance, i.e., the extent to which the prognostic models enable discrimination between patients with and without poor outcome, was described by area under the receiver operating characteristic curve (AUC). The AUC varies between 0.5 (a noninformative model) and 1.0 (a perfect model). The predictive accuracy of the prognostic models, i.e., the agreement of observed outcomes with predicted risk, was assessed by the Hosmer-Lemeshow test and graphically with a calibration plot.

Model validation

Prognostic models derived from multivariable regression analysis are known to overestimate regression coefficients. This results in too extreme predictions when applied in new patients.[7,10] Therefore, we internally validated our model with bootstrapping techniques, where in each bootstrap sample the entire modeling process was repeated.[10] This resulted in a shrinkage factor for the regression coefficients.[7] The bootstrap procedure was also used to estimate the AUC corrected for overoptimism. The corrected AUC may be considered an estimate of discriminative ability expected in future similar patients.

Application in clinical practice

Based on the independent predictors from the model with the highest discriminatory value, a risk chart was developed to display the risks for poor outcome in patients with or without these predictors. Data were analyzed with SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL) and R (version 2.10.1; http://www.r-project.org) with help of the libraries Hmisc and Design of Harrell.[11]

RESULTS

Study population

Admission characteristics of the 619 patients are presented in Table 1. Mean age at admission was 64 years (range, 19–95 years). Of the patients, 429 (69%) had a poor outcome at 1 month: 74 (12%) had a mRS score of 4, 115 (19%) had a mRS score of 5, and 240 (39%) had died.

Prognostic models

The multivariable models for prediction of poor outcome at 1 month after BAO are presented in Table 2. Predictors of poor outcome were older age, absence of hyperlipidemia, presence of prodromal minor stroke, higher NIHSS score, longer time to treatment, proximal and middle vs distal location of the BAO, and presence of old posterior circulation stroke or early ischemic changes on CT. A poor outcome

Table 1 Baseline characteristics of the 619 patients with acute basilar artery occlusion (BAO)

	Good outcome mRS 0–3 (n=190)[a]		Poor outcome mRS 4–6 (n=429)[a]	
Demographic characteristics				
Male[b]	117	62%	275	64%
Age (years; mean ± SD)[b]	61	14	65	15
Stroke risk factors				
Hypertension	116	61%	267	62%
Diabetes	35	18%	100	23%
Hyperlipidemia	70	37%	97	23%
Atrial fibrillation	41	22%	92	21%
Coronary artery disease	29	15%	80	19%
Valvular heart disease	6	3%	10	2%
Peripheral vascular disease	8	4%	22	5%
Alcohol abuse	10	5%	12	3%
Current smoking	46	24%	59	14%
Prodromal TIA	42	22%	71	17%
Prodromal minor stroke[c]	20	11%	98	23%
Neurological examination				
Severe deficit[d]	59	31%	314	73%
NIHSS score (mean ± SD)[b]	13	11	24	10
NIHSS score >20	49	26%	288	67%
Time to treatment (h)[c,e]				
0–3 h	61	32%	106	25%
4–6 h	61	32%	125	29%
7–9 h	26	14%	57	13%
10–12 h	14	7%	49	11%
13–24 h	20	11%	46	11%
>24 h	8	4%	46	11%
Imaging findings				
Location of occlusion[b]				
Distal third	82	43%	119	28%
Middle third	36	19%	111	26%
Proximal third	72	38%	199	46%
Dense basilar[f]	59	31%	139	32%
Old posterior circulation stroke	14	7%	54	13%
Early ischemic changes	40	21%	154	36%
Treatment				
Antithrombotic therapy	66	35%	117	27%
Primary intravenous thrombolysis with or without intra-arterial therapy	50	26%	71	17%
Immediate intra-arterial therapy	74	39%	214	50%
No treatment	0	0%	27	6%

Abbreviation: NIHSS = NIH Stroke Scale. [a] At 1 month. [b] <10% missing data. [c] 21%-22% missing data. [d] Coma, locked-in syndrome, or tetraplegia. [e] 27 patients who did not receive treatment were classified as time to treatment longer than 24h. [f] 12% missing data.

occurred in particular for those with higher NIHSS scores and older age. Type of treatment and CT imaging findings had no additive contribution to the prediction of poor outcome.

Model performance

The discriminatory ability of the models became larger with increasing complexity. The AUC corrected for overoptimism was 0.64 for the model restricted to

Table 2 Multivariable predictors of poor outcome at 1 month after BAO in a series of three prognostic models of increasing complexity based on admission characteristics[a]

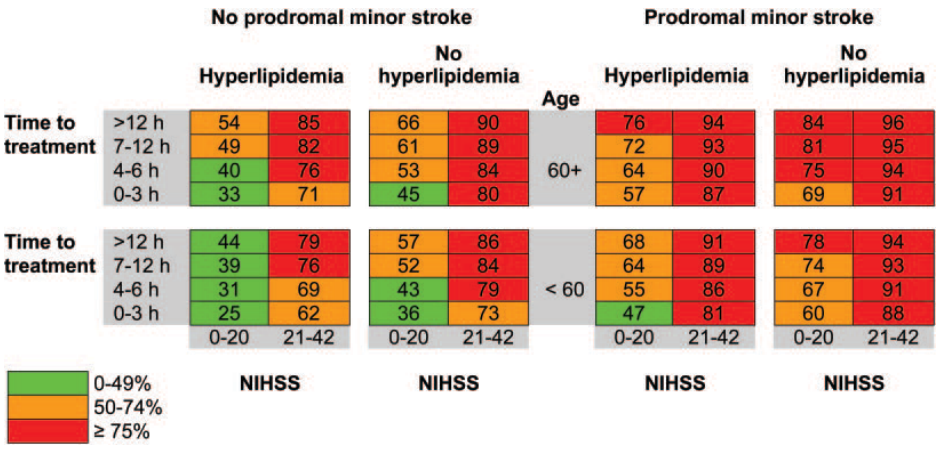
	Odds ratio (95% confidence interval)		
	Model 1[b]	Model 2[b]	Model 3[b]
Demographic characteristics			
Age (per year above 60)	1.03 (1.01–1.05)	1.03 (1.01–1.06)	1.04 (1.01–1.07)
Stroke risk factors			
Hyperlipidemia	0.55 (0.37–0.81)	0.65 (0.42–1.01)	0.60 (0.38–0.94)
Current smoking	0.69 (0.44–1.10)		
Prodromal minor stroke	2.26 (1.33–3.85)	2.83 (1.55–5.19)	2.20 (1.18–4.12)
Neurological examination			
NIHSS score (per point)		1.17 (1.09–1.26)	1.16 (1.08–1.26)
Time to treatment (h)			
0–3 h		1.00 (referent)	1.00 (referent)
4–6 h		1.33 (0.79–2.23)	1.29 (0.76–2.19)
7–9 h		1.60 (0.83–3.07)	1.57 (0.80–3.09)
10–12 h		3.12 (1.38–7.07)	2.66 (1.17–6.07)
>12 h		2.65 (1.41–5.01)	1.98 (1.02–3.87)
Imaging findings			
Location of occlusion			
Distal third			1.00 (referent)
Middle third			2.11 (1.20–3.73)
Proximal third			1.83 (1.12–2.99)
Old posterior circulation stroke			2.10 (0.98–4.50)
Early ischemic changes			1.84 (1.12–3.02)
AUV curve[c]	0.64 (0.59–0.68)	0.79 (0.76–0.83)	0.80 (0.77–0.84)

Abbreviations: AUC area under the receiver operating characteristic curve; NIHSS NIH Stroke Scale. [a] The absolute risk of 1 month poor outcome was calculated as $1/(1 + e^{-LP})$, where LP refers to the linear predictor in our second logistic regression model. $LP_{poor\ outcome}$ = -1.99 + 0.032 x (age-60) - 0.429 (if hyperlipidemia present) + 1.042 (if prodromal stroke present) + 0.157 x NIHSS score - 0.002 x NIHSS score^2 + 0.286 (if time to presentation 0–3 h) + 0.467 (if time to presentation 4–6 h) + 1.138 (if time to presentation 7–12 h) + 0.976 (if time to presentation >12h). Dichotomous variables are coded 1 if presented and 0 if absent. [b] Models after adjustment for overfitting by shrinkage (regression coefficients were shrunk by 19% in model 1, 13% in model 2 and 17% in model 3). [c] Adjusted for optimism with bootstrapping techniques.

demographics and stroke risk factors only, 0.79 for that also using information about stroke severity (NIHSS) and time to treatment, and 0.80 for the model using a combination of demographics, stroke risk factors, and findings from the neurologic examination and from CT imaging. Calibration of the 3 models was good (Hosmer-Lemeshow tests, p>0.30) (Figure e-1 on the Neurology® Web site at www.neurology.org).

Clinical application

Because the second model had almost the same discriminatory performance as the third model, we developed a risk chart on the basis of the second model. Figure 1 systematically displays the predicted 1-month risk of poor outcome for each combination of the 5 predictors from model 2. These risks range from 25% for a patient younger than 60 years with hyperlipidemia, a low NIHSS score, and no prodromal minor stroke to 96% for a patient older than 60 years with a high NIHSS score and prodromal minor stroke. The AUC corrected for overoptimism of the risk chart was 0.75 (95% confidence interval 0.71–0.79).



NIHSS = NIH Stroke Scale.

Figure 1 Predicted probablities of poor outcome at 1 month after basilar artery occlusion for each combination of the main 5 independent predictors. NIHSS=NIH Stroke Scale.

DISCUSSION

We described the development of a series of prognostic models of increasing complexity, based on admission characteristics, to predict the risk of poor outcome at 1 month in patients with an acute symptomatic BAO. The largest amount of prognostic information could be obtained with a set of 5 predictors: age, stroke severity, time to treatment, presence of prodromal minor stroke, and hyperlipidemia.

To the best of our knowledge, this is the first study that identified independent predictors for poor outcome after acute BAO and combined these clinical variables into a simple risk chart. Obviously, risk charts will be more reliable if they include predictors that are already well-established risk factors for poor outcome after stroke. Older age, time to treatment, and stroke severity are such risk factors.[2,12] Patients with hyperlipidemia had a lower risk of poor outcome after BAO. This was an unexpected finding but might be explained by potential benefits of treatment with statins.[13] However, we do not have data on statin use in our patients. The underlying mechanism of this association is uncertain and deserves further study, although prognostic factors do not necessarily need to have a causal association with the outcome.

We found limited or no added value of CT imaging findings and type of treatment for the prediction of poor outcome. This does not mean that treatment and CT imaging findings are not important; instead, these variables have limited added value for the prediction of poor outcome when data on demographics, stroke risk factors, and clinical stroke severity are already accounted for. Hence, we consider it unlikely that our prediction model has been influenced importantly by withdrawal of life-sustaining interventions. The limited role of type of treatment as a predictor of outcome is probably caused by the lack of a clearly superior treatment strategy in patients with BAO.[5]

An important strength of our study lies in the large number of patients from which the models were derived. Second, we believe our dataset is representative of the current practice in dedicated stroke centers around the world for patients with an acute symptomatic BAO. Standard neurologic and functional scores and risk factor data were systematically collected from all sites. Furthermore, all measurements were obtained in routine clinical practice. Therefore, the predictors in our model are well defined, easily measured clinical variables already available at admission.

Our study has certain limitations. First, we might not have captured all variables related to outcome. In the design of our data entry form, however, we tried to take into account all factors that could affect outcome. Second, there were some missing values in our database. Regression imputation was used to predict missing values with information from other predictors. Both theoretical and empirical support is growing for the use of imputation methods instead of traditional complete case analysis.[14] Third, some misclassification may have occurred in classification of poor vs good outcome. However, the mRS is widely used and has the advantage that it suffers little from such potential bias. Furthermore, our models are based on clinical outcome at 1 month, which is too early a time point to capture a patient's full neurologic recovery from an acute symptomatic BAO. Some patients with an acute BAO have been described to experience remarkably good long-term functional outcomes despite an initial locked-in state and extensive brainstem infarction.[15] Thus, it is likely that some patients labeled as having a poor outcome at 1 month would have shifted to having a good outcome if studied at a later time point. The most important drawback of this study is the lack of validation of the risk chart in another population than that in which it was derived (external validation). Although bootstrapping techniques were applied to shrink regression coefficients to correct for overoptimism (internal validation), there might be an overestimation of the true performance. Future studies are needed to confirm the validity of our risk chart.

Prognostic models are particularly useful for a more efficient design of randomized controlled trials. For example, we can exclude those with a very good or very poor prognosis. In addition, these models can be useful for stratification and covariate adjustment of a treatment effect in clinical trials. The proposed risks may also guide clinicians in their initial assessment of the prognosis of a patient who presents with an acute symptomatic BAO. We note, however, that prognostic models can only augment, not replace, clinical judgment.

Our study shows that poor 1-month outcome after BAO can be reliably predicted by a simple model that includes older age, absence of hyperlipidemia, presence of prodromal minor stroke, higher NIHSS score, and longer time to treatment. The model predictions may support clinical practice and research, including the design and analysis of randomized controlled trials.

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8

Outcomes of basilar artery occlusion in patients aged 75 years or older in the Basilar Artery International Cooperation Study

Mervyn D.I. Vergouwen, Annette Compter, David Tanne, Stefan T. Engelter, Heinrich Audebert, Vincent Thijs, Gabriel de Freitas, Ale Algra, L. Jaap Kappelle, Wouter J. Schonewille; on behalf of the BASICS Study Group

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ABSTRACT

Patients with an acute basilar artery occlusion (BAO) have a high risk of long-lasting disability and death. Only limited data are available on functional outcome in elderly patients with BAO. Using data from the Basilar Artery International Cooperation Study, we aimed to determine outcomes in patients ≥75 years. Primary outcome measure was poor functional outcome (modified Rankin scale score 4–6). Secondary outcomes were death, insufficient vessel recanalization (defined as thrombolysis in myocardial infarction score 0–1) and symptomatic intracranial hemorrhage (SICH). Patients were divided into four age-groups, based on quartiles: 18–54, 55–64, 65–74, and ≥75 years. Outcomes were compared between patients ≥75 years and patients aged 18–54 years. Risk ratios with corresponding 95 % confidence intervals (CI) were calculated and Poisson regression analyses were performed to calculate adjusted risk ratios (aRR). We included 619 patients [18–54 years n=153 (25 %), 55–64 years n=133 (21 %), 65–74 years n=171 (28 %), and ≥75 years n=162 (26 %)]. Compared with patients aged 18–54 years, patients ≥75 years were at increased risk of poor functional outcome [aRR 1.33 (1.14–1.55)] and death [aRR 2.47 (1.75–3.51)]. Nevertheless, 35/162 (22 %, 95 % CI 15–28 %) of patients ≥75 years had good functional outcome. No significant differences between age groups were observed for recanalization rate and incidence of SICH. Although patients ≥75 years with BAO have an increased risk of poor outcome compared with younger patients, a substantial group of patients ≥75 years survives with a good functional outcome.

INTRODUCTION

Patients with an acute basilar artery occlusion (BAO) have a high risk of long-lasting disability and death.[1,2] Although higher age, analyzed as a continuous variable, has been associated with poor functional outcome after BAO, only limited data are available on functional outcome in elderly patients.[3-8] One small case series suggested that all patients ≥75 years have poor functional outcome.[6] In another study, the eldest surviving patient in whom recanalization was successful was 63-year-old.[3] We analysed data from the Basilar Artery International Cooperation Study (BASICS) to determine outcomes in patients with BAO ≥75 years.

METHODS

BASICS is a prospective, observational, registry of 619 consecutive patients ≥18 years with an acute symptomatic BAO.[2,9] The protocol was approved by the ethics committee of the University Medical Center Utrecht, the Netherlands. Embolic BAO was defined as complete recanalization on follow-up and no indication of dissection, or maximum deficit from onset and cardiac or vertebral source of embolism, or maximum deficit from onset with complete absence of other atherosclerotic cerebrovascular lesions. Atherosclerotic BAO was defined as known symptomatic basilar artery stenosis (>50%) prior to occlusion, or residual stenosis after recanalization and no evidence of cardiac or vertebral artery source of embolism, or prior TIAs or stroke in the basilar artery territory and no evidence of cardiac or vertebral artery source of embolism. Dissections were not predefined, but scored according to the investigators.

Primary outcome was poor functional outcome after 1 month [predefined as modified Rankin scale (mRS) score 4–6]. Secondary outcomes were death, insufficient vessel recanalization [defined as thrombolysis in myocardial infarction (TIMI) score 0–1] and symptomatic intracranial hemorrhage (SICH). We also investigated if our conclusions changed if poor functional outcome was defined as an mRS of 3–6. SICH was not predefined by the registry, and the reporting of SICH was done on the basis of each investigator's judgment. For the purpose of this study, patients were divided into four age-groups, based on quartiles: 18–54, 55–64, 65–74, and ≥75 years. Outcomes were compared between patients ≥75 years

and patients aged 18–54 years. Risk ratios (RR) and corresponding 95% confidence intervals (CI) were calculated. Variables that affected the crude risk ratio most were used simultaneously in Poisson regression analyses to calculate adjusted risk ratios (aRR).[2] Missing baseline data (<5% for each variable) were imputed with regression imputation.[10] Finally, we explored the incidence of poor functional outcome in patients 75–79, 80–84, 85–89, and 90 years or older.

RESULTS

Baseline characteristics are listed in Table 1. In total, 162 patients (26% of total cohort) were ≥75 years. In this group of patients, the most common cause of stroke was embolism and 64% had an NIHSS score >20. Treatment of any kind was initiated in 148 patients (91%).

Modified Rankin Scale scores for all age groups are presented in Figure 1. Patients ≥75 years had a higher risk of poor functional outcome [aRR 1.33 (1.14–1.55), Table 2] and death [aRR 2.47 (1.75–3.51), Table 3] than patients aged 18–54 years. Nevertheless, 35 patients (22%, 95% CI 15–28%) of those ≥75 years had a good functional outcome. No significant differences between age groups were observed for insufficient recanalization [patients ≥75 vs. 18–54 years aRR 1.69 (0.95–3.03)] and SICH [patients ≥75 vs. 18–54 years RR 1.77 (0.77–4.06)]. Since SICH occurred in only 42 (7%) patients, no further analyses were performed for this outcome measure.

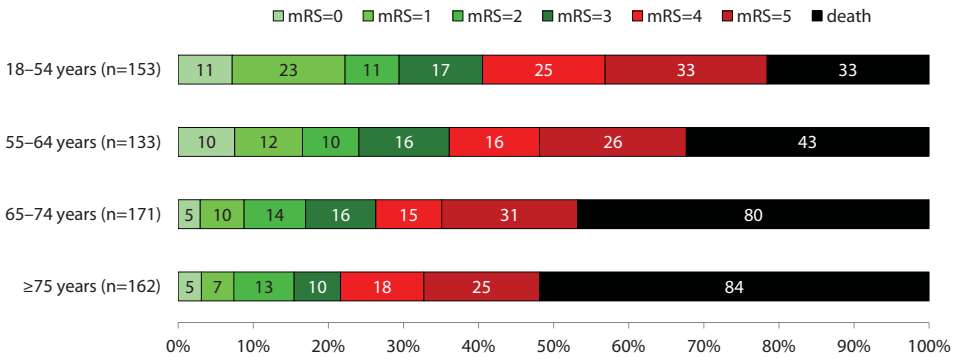

Figure 1 Modified Rankin scale scores according to age group. mRS modified Rankin scale score.

Table 1 Baseline characteristics according to age group

Variable	All patients n=619	18–54 years n=153	55–64 years n=133	65–74 years n=171	≥75 years n=162
Male sex	390 (63 %)	94 (61 %)	105 (79 %)	116 (68 %)	75 (46 %)
Hypertension	383 (62 %)	41 (27 %)	87 (65 %)	133 (78 %)	122 (75 %)
Diabetes mellitus	135 (22 %)	13 (8 %)	31 (23 %)	49 (29 %)	42 (26 %)
Hyperlipidemia	167 (27 %)	30 (20 %)	45 (34 %)	55 (32 %)	37 (23 %)
Atrial fibrillation	133 (21 %)	3 (2 %)	20 (15 %)	42 (25 %)	68 (42 %)
Coronary artery disease	109 (18 %)	12 (8 %)	21 (16 %)	35 (20 %)	41 (25 %)
Location of basilar artery occlusion					
Distal third	202 (33 %)	42 (27 %)	30 (23 %)	55 (32 %)	75 (46 %)
Middle third	143 (23 %)	37 (24 %)	29 (22 %)	46 (27 %)	31 (19 %)
Proximal third	274 (44 %)	74 (48 %)	74 (56 %)	70 (41 %)	56 (35 %)
Median NIHSS score (IQR)	22 (12–30)	20 (9–30)	20 (12–30)	22 (13–28)	25 (16–30)
NIHSS score >20	336 (54 %)	73 (48 %)	66 (50 %)	93 (54 %)	104 (64 %)
Type of treatment					
Antithrombotics	183 (30 %)	47 (31 %)	33 (25 %)	52 (30 %)	51 (31 %)
IV tPA or IV tPA/IAT	121 (20 %)	25 (16 %)	37 (28 %)	24 (14 %)	35 (22 %)
IAT only	288 (47 %)	78 (51 %)	59 (44 %)	89 (52 %)	62 (38 %)
No treatment	27 (4 %)	3 (2 %)	4 (3 %)	6 (4 %)	14 (9 %)
Time to treatment					
0–3 h	179 (29 %)	41 (27 %)	39 (29 %)	49 (29 %)	50 (31 %)
4–6 h	190 (31 %)	45 (29 %)	37 (28 %)	58 (34 %)	50 (31 %)
7–9 h	84 (14 %)	22 (14 %)	19 (14 %)	26 (15 %)	17 (10 %)
10–12 h	57 (9 %)	14 (9 %)	14 (11 %)	16 (9 %)	13 (8 %)
13–24 h	55 (9 %)	17 (11 %)	15 (11 %)	9 (5 %)	14 (9 %)
>24 h	27 (4 %)	11 (7 %)	5 (4 %)	7 (4 %)	4 (2 %)
Cause of stroke					
Embolism	224 (36 %)	42 (27 %)	38 (29 %)	59 (35 %)	85 (52 %)
Atherosclerosis	215 (35 %)	39 (25 %)	57 (43 %)	72 (42 %)	47 (29 %)
Dissection	32 (5 %)	24 (16 %)	5 (4 %)	3 (2 %)	0 (0 %)
Other	6 (1 %)	2 (1 %)	1 (1 %)	2 (1 %)	1 (1 %)
Unknown	142 (23 %)	44 (29 %)	30 (23 %)	31 (18 %)	27 (17 %)

NIHSS national institutes of health stroke scale, IQR interquartile range, IV intravenous, tPA tissue plasminogen activator, IAT any intra-arterial treatment (either intra-arterial tPA, mechanical clot disruption, or both).

If poor functional outcome was defined as an mRS of 3–6, the proportion of patients with poor functional outcome in each age group was 108/153 (71%) in patients 18–54 years of age, 101/133 (76%) in patients 55–64 years, 142/171 (83%) in patients 65–74 years, and 137/162 (85%) in patients ≥75 years. Also when this definition

Table 2 Poor functional outcome (mRS 4–6) according to age-group

	18–54 years[a]	55–64 years	65–74 years	≥75 years
Total	153 (25%)	133 (21%)	171 (28%)	162 (26%)
Poor outcome	91/153 (60%)	85/133 (64%)	126/171 (74%)	127/162 (78%)
Unadjusted	1	1.08 (0.90–1.29)	1.24 (1.06–1.45)	1.32 (1.13–1.54)
Adjusted				
Male sex	1	1.06 (0.88–1.28)	1.23 (1.05–1.45)	1.33 (1.14–1.55)
Location of occlusion	1	1.06 (0.89–1.27)	1.26 (1.08–1.47)	1.37 (1.18–1.60)
NIHSS	1	1.06 (0.90–1.25)	1.22 (1.06–1.41)	1.23 (1.06–1.41)
Time to treatment (h)	1	1.08 (0.90–1.30)	1.26 (1.07–1.49)	1.33 (1.13–1.56)
Type of treatment	1	1.07 (0.89–1.29)	1.24 (1.05–1.46)	1.32 (1.12–1.55)
3 factors[b]	1	1.05 (0.89–1.24)	1.24 (1.07–1.43)	1.28 (1.11–1.48)
5 factors[c]	1	1.06 (0.90–1.25)	1.28 (1.10–1.49)	1.33 (1.14–1.55)

[a] Reference group. Data are number (%) or risk ratio (95% CI). [b] Adjustment for national institutes of health stroke scale (NIHSS) score, sex, and location of occlusion. [c] Adjustment for NIHSS score, sex, location of occlusion, time to treatment, and type of treatment.

Table 3 Mortality according to age group

	18–54 years[a]	55–64 years	65–74 years	≥75 years
Total	153 (25%)	133 (21%)	171 (28%)	162 (26%)
Mortality	33/153 (22%)	43/133 (32%)	80/171 (47%)	84/162 (52%)
Unadjusted	1	1.50 (1.02–2.21)	2.17 (1.54–3.05)	2.40 (1.72–3.37)
Adjusted				
Male sex	1	1.48 (1.002–2.19)	2.16 (1.53–3.04)	2.43 (1.73–3.40)
Location of occlusion	1	1.47 (0.998–2.16)	2.22 (1.58–3.11)	2.55 (1.83–3.56)
NIHSS	1	1.46 (1.008–2.12)	2.13 (1.55–2.94)	2.16 (1.57–2.98)
Time to treatment (h)	1	1.56 (1.04–2.35)	2.28 (1.59–3.27)	2.41 (1.68–3.46)
Type of treatment	1	1.55 (1.03–2.34)	2.24 (1.56–3.21)	2.42 (1.68–3.47)
3 factors[b]	1	1.47 (1.02–2.12)	2.22 (1.61–3.05)	2.31 (1.68–3.17)
5 factors[c]	1	1.56 (1.05–2.31)	2.41 (1.71–3.39)	2.47 (1.75–3.51)

[a] Reference group. Data are number (%) or risk ratio (95% CI). [b] Adjustment for national institutes of health stroke scale (NIHSS) score, sex and location of occlusion. [c] Adjustment for NIHSS score, sex, location of occlusion, time to treatment, and type of treatment.

was used, patients ≥75 years had a higher risk of poor functional outcome [aRR 1.21 (1.07–1.36)] than patients aged 18–54 years.

Baseline characteristics of patients ≥75 years and their relationship with functional outcome are shown in Table 4. The following variables were associated with an increased risk of poor functional outcome after 1 month: male sex (RR 1.18, 95%

Table 4 Characteristics of patients ≥75 years and risk of poor functional outcome

Variable	Risk of poor functional outcome (mRS 4–6)		
	Characteristic present	Characteristic absent	RR (95% CI)
Male sex	64/75 (85%)	63/87 (72%)	1.18 (1.00–1.38)
Hypertension	98/122 (80%)	29/40 (73%)	1.11 (0.90–1.37)
Diabetes mellitus	29/42 (69%)	98/120 (82%)	0.85 (0.68–1.05)
Hyperlipidemia	27/37 (73%)	100/125 (80%)	0.91 (0.74–1.13)
Atrial fibrillation	57/68 (84%)	70/94 (74%)	1.13 (0.96-1.32)
Coronary artery disease	35/41 (85%)	92/121 (76%)	1.12 (0.96–1.32)
Location of basilar artery occlusion[a]			
Proximal third	43/56 (77%)	56/75 (75%)	1.03 (0.85–1.25)
Middle third	28/31 (90%)	56/75 (75%)	1.21 (1.02–1.44)
NIHSS score >20	90/104 (87%)	37/58 (64%)	1.36 (1.10–1.67)
Type of treatment[b]			
Antithrombotics	38/51 (75%)	47/62 (76%)	0.98 (0.79–1.22)
IV tPA or IV tPA/IAT	28/35 (80%)	47/62 (76%)	1.06 (0.85–1.31)
No treatment	14/14 (100%)	47/62 (76%)	1.32 (1.15–1.52)
Time to treatment[c]			
4–6 h	35/50 (70%)	38/50 (76%)	0.92 (0.73–1.17)
7–9 h	13/17 (76%)	38/50 (76%)	1.01 (0.74–1.37)
≥10 h	27/31 (87%)	38/50 (76%)	1.15 (0.93–1.41)
Cause of stroke			
Embolism[d]	65/85 (76%)	38/47 (81%)	0.95 (0.79–1.14)
Symptomatic intracranial hemorrhage	14/15 (93%)	113/147 (77%)	1.21 (1.03–1.43)
Insufficient recanalization	18/20 (90%)	32/49 (65%)	1.38 (1.07–1.77)

[a] Distal occlusion was taken as reference and is recorded under "characteristic absent". [b] IAT only was taken as reference and is recorded under "characteristic absent". [c] 0–3 h was taken as reference and is recorded under "characteristic absent". [d] Atherosclerosis was taken as reference and is recorded under "characteristic absent".

CI 1.00–1.38), location of occlusion (middle third vs. distal third: RR 1.21, 95% CI 1.02–1.44), NIHSS score >20 on presentation (RR 1.36, 95% CI 1.10–1.67), type of treatment (no treatment vs. intra-arterial thrombolytic therapy (IAT) only: RR 1.32, 95% CI 1.15–1.52), SICH (RR 1.21, 95% CI 1.03–1.43), and insufficient recanalization (RR 1.38, 95% CI 1.07–1.77).

The proportion of patients with poor functional outcome in age subgroups ≥75 years was as follows: 64/82 (78%) in patients 75–79 years of age, 40/49 (82%) in patients

80–84 years, 16/23 (70%) in patients 85–89 years, and 7/8 (88%) in patients 90 years or older. The oldest patient with good functional outcome was 91 years of age, despite an NIHSS score of 21 on admission. This patient was treated with intravenous recombinant tissue plaminogen activator (rtPA) only, and had an mRS score of 2 at 1 month follow-up.

DISCUSSION

The BASICS study shows that patients ≥75 years with BAO have an increased risk of poor functional outcome and death compared with younger patients, despite comparable recanalization rates. In contrast with a small previous study,[6] our data show that a substantial group of patients ≥75 years survives with good functional outcome.

Previously, it has been suggested that the increased risk of poor functional outcome in elderly patients resulted from a higher prevalence of atherosclerotic occlusions and consequently lower recanalization rates.[3] However, in our study population patients ≥75 years were more likely to have an embolic rather than an atherosclerotic cause of BAO, mainly due to a higher prevalence of atrial fibrillation. Patients ≥75 years with an embolic cause of BAO had a similar risk of poor functional outcome compared with patients in this age group with an atherosclerotic cause of BAO. Sufficient recanalization was achieved in 71% of patients in this age group.

In patients ≥75 years, several baseline- and treatment-related characteristics were associated with an increased risk of poor functional outcome. A recent large case series of patients with BAO, in which only a minority of patients was ≥75 years, identified similar risk factors for poor functional outcome and death [7].

The strength of this study is that BASICS was a prospective registry of consecutive patients, and therefore our results are representative for daily practice. A limitation of this study is that this was a post hoc analysis of non-randomized data, and therefore the data regarding treatment-dependent outcomes are prone to bias. Due to the prospective collection of detailed data, we were able to perform Poisson regression analyses to adjust for important confounding baseline characteristics.

We conclude that a substantial group of elderly patients survives with a good functional outcome. This study cannot answer the question which treatment option is superior in elderly patients, nor can it define an upper age limit above which treatment is no longer effective. These and other questions may be answered in the recently started BASICS trial in which patients with BAO of up to 85 years of age are randomized between intravenous thrombolysis (IVT) alone vs. IVT followed by additional intra-arterial therapy (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2617; accessed February 1, 2012).

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9

Time is Brain(stem) in Basilar Artery Occlusion

Mervyn D.I. Vergouwen, Ale Algra, Thomas Pfefferkorn, Christian Weimar, Christina M. Rueckert, Vincent Thijs, L. Jaap Kappelle, Wouter J. Schonewille; on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose The frequent use of a longer time window for recanalization therapy in patients with basilar artery occlusion (BAO) in daily practice is not supported by any scientific evidence. We investigated the relationship between time to recanalization therapy and functional outcome in BAO with data from the Basilar Artery International Cooperation Study (BASICS).

Methods BASICS is a prospective multicenter registry of patients (n=619) with radiologically confirmed BAO. We analyzed patients receiving intravenous thrombolysis or intra-arterial treatment. Patients were divided into 4 groups based on the interval between estimated time of BAO and start of recanalization therapy: ≤3 hours (n=134), >3 to ≤6 hours (n=151), >6 to ≤9 hours (n=56), and >9 hours (n=68). Primary outcome measure was poor functional outcome (modified Rankin scale score 4–6) after 1 month. We calculated adjusted risk ratios with 95% CIs using Poisson regression analyses with the ≤3 hours group as the reference group.

Results Patients had an increased risk of poor functional outcome as time to recanalization therapy became longer (≤3 hours: 62%; >3 to ≤6 hours: 67% [adjusted risk ratio, 1.06; 0.91–1.25]; >6 to ≤9 hours: 77% [adjusted risk ratio, 1.26; 1.06–1.51]; >9 hours: 85% [adjusted risk ratio, 1.47; 1.26–1.72]).

Conclusions Early recanalization therapy in patients with BAO is associated with a more favorable outcome with a significant increased chance of a poor outcome when recanalization therapy is started >6 hours after estimated time of BAO.

INTRODUCTION

Patients with acute ischemic stroke in the anterior circulation benefit from intravenous thrombolysis (IVT) within 4.5 hours after symptom onset.[1] The earlier IVT can be administered, the more benefit can be expected. Intra-arterial thrombolysis might even be effective when patients are treated within 6 hours.[2] It remains unknown whether the time window for recanalization therapy in patients with basilar artery occlusion (BAO) can be longer than in patients with arterial occlusions in the anterior circulation.[3] White matter, which is relatively more present in the brain stem than in other parts of the brain, might be more resistant to ischemia than other brain tissue. Furthermore, penumbral tissue might be preserved for a longer period of time as a result of better collaterals in the posterior than in the anterior circulation. Case reports suggest that patients with BAO can recover from recanalization therapy beyond 8 hours after symptom onset.[4]

We aimed to study the relationship between time to recanalization therapy and functional outcome in patients with acute BAO who participated in the Basilar Artery International Cooperation Study (BASICS).

METHODS

BASICS is a prospective, observational registry of 619 consecutive patients ≥18 years with an acute symptomatic BAO (see online-only Data Supplement).[3] The protocol was approved by the ethics committee of the University Medical Center Utrecht, Utrecht, The Netherlands. For the purpose of the present study we excluded patients receiving no treatment and those who were treated with platelet aggregation inhibitors or heparin only. Recanalization therapy was defined as IVT or any intra-arterial treatment (intra-arterial thrombolysis, mechanical clot disruption, or both). Time to recanalization therapy was defined as the interval between estimated time of BAO and start of recanalization therapy. Estimated time of BAO was defined as time of onset of acute symptoms leading to clinical diagnosis of BAO or, if not known, last time the patient was seen normal before onset of these symptoms. Patients were divided into 4 groups based on time to recanalization therapy: ≤3 hours, >3 to ≤6 hours, >6 to ≤9 hours, and >9 hours.

Primary outcome was poor functional outcome (modified Rankin Scale score 4–6) after 1 month. We also investigated if our conclusions changed if poor functional outcome was defined as modified Rankin Scale 3 to 6. Secondary outcomes were death and insufficient vessel recanalization (defined as Thrombolysis In Myocardial Infarction score 0–1). A sensitivity analysis was performed to investigate if our primary outcome was similar if patients were excluded with unknown time of onset of acute symptoms leading to a clinical diagnosis of BAO (for example, patients with wake-up stroke). Furthermore, we analyzed time as a linear factor with the 4 time to recanalization therapy groups. In a subgroup analysis, we studied the incidence of poor functional outcome in patients with severe and mild to moderate strokes. Severe stroke was defined as patients in a coma, with tetraplegia, or in a locked-in state, whereas mild to moderate stroke was defined as any deficit that was less severe.[5]

Outcomes were compared among the 4 groups. Risk ratios with 95% CIs were calculated with the ≤3 hours group as the reference group. Variables associated with functional outcome in the BASICS registry (ie, age, National Institutes of Health Stroke Scale score, diabetes mellitus, prodromes, and location of occlusion)[5] were used simultaneously in Poisson regression analyses to calculate adjusted risk ratios (aRRs).

RESULTS

We included 409 patients (≤3 hours: n=134; >3 to ≤6 hours: n=151; >6 to ≤9 hours: n=56; and >9 hours: n=68). Baseline characteristics are listed in the Table. The risk of poor functional outcome increased when time to recanalization therapy was longer (≤3 hours: 62%; >3 to ≤6 hours: 67% [aRR, 1.06; 0.91–1.25]; >6 to ≤9 hours: 77% [aRR, 1.26; 1.06–1.51]; and >9 hours: 85% [aRR, 1.47; 1.26–1.72]; Table; and Figure 1). In a sensitivity analysis that excluded 24 patients in which time of symptom onset leading to a clinical diagnosis of BAO was unknown, the risk of poor functional outcome was similar (≤3 hours: 62%; >3 to ≤6 hours: 67% [aRR, 1.06; 0.91–1.25]; >6 to ≤9 hours: 76% [aRR, 1.25; 1.04–1.50]; and ≤9 hours: 87% [aRR, 1.48; 1.26–1.74]). If the 4 time to recanalization therapy categories were taken as a continuous variable (with ≤3 hours=0, >3 to ≤6 hours=1, >6 to ≤9 hours=2, and ≤9 hours=3), the risk ratio for increase to a later time to recanalization therapy class was

1.14 (95% CI, 1.09–1.20; p≤0.001; adjusted for National Institutes of Health Stroke Scale score, diabetes mellitus, prodromes, and location of occlusion) indicating a

Table 1 Baseline characteristics and poor functional outcome (mRS 4–6) according to time to treatment

	0 to 3 h* (n=134)	3 to 6h (n=151)	6 to 9h (n=56)	>9h (n=68)
Median age, y (IQR)	67 (57–75)	66 (55–75)	62 (50–73)	63 (50–72)
Median NIHSS (IQR)	25 (15–30)	24 (14–30)	25 (15–30)	19 (12–27)
Diabetes mellitus	23 (17%)	35 (23%)	11 (20%)	16 (24%)
Prodromes	55 (41%)	78 (52%)	33 (59%)	38 (56%)
Location of occlusion				
Distal third	48 (36%)	53 (35%)	19 (34%)	17 (25%)
Middle third	30 (22%)	41 (27%)	11 (20%)	15 (22%)
Proximal third	56 (42%)	57 (38%)	26 (46%)	36 (53%)
Poor functional outcome	83 (62%)	101 (67%)	43 (77%)	58 (85%)
Unadjusted risk ratio	1	1.08 (0.91–1.29)	1.24 (1.02–1.51)	1.38 (1.17–1.63)
Adjusted risk ratios				
Age	1	1.09 (0.92–1.29)	1.29 (1.06–1.57)	1.45 (1.23–1.70)
NIHSS	1	1.08 (0.91–1.27)	1.24 (1.03–1.49)	1.48 (1.27–1.72)
Diabetes mellitus	1	1.07 (0.90–1.27)	1.24 (1.02–1.50)	1.36 (1.16–1.61)
Prodromes	1	1.06 (0.89–1.27)	1.21 (0.99–1.47)	1.35 (1.14–1.59)
Location of occlusion	1	1.08 (0.91–1.29)	1.23 (1.02–1.49)	1.35 (1.14–1.59)
All 5 factors	1	1.06 (0.91–1.25)	1.26 (1.06–1.51)	1.47 (1.26–1.72)

Data are no. (%) or risk ratio (95% CI). mRS indicates modified Rankin Scale; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale. * Reference group.

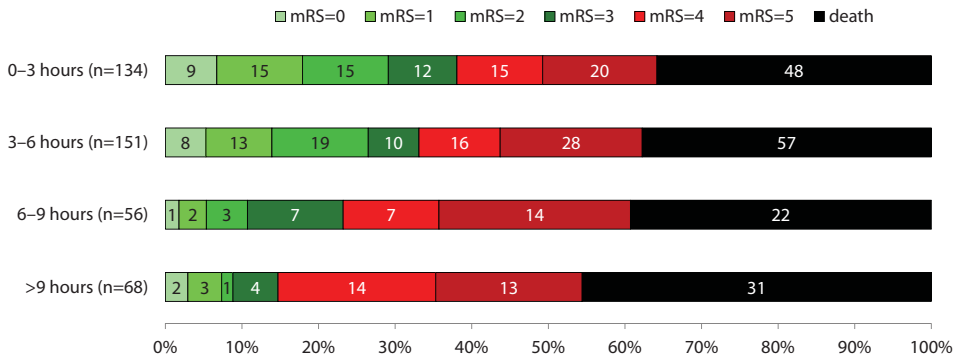

Figure 1 Functional outcome according to time to treatment. mRS = modified Rankin scale score.

strong, statistically significant relationship between time to recanalization therapy and poor outcome. Also when poor outcome was defined as a modified Rankin Scale of 3 to 6 instead of 4 to 6, risk of poor functional outcome increased when time to recanalization therapy was longer (≤3 hours: 71%; >3 to ≤6 hours: 74% [aRR, 1.02; 0.90–1.17]; >6 to ≤9 hours: 89% [aRR, 1.27; 1.10–1.45]; and ≤9 hours: 91% [aRR, 1.35; 1.18–1.53]).

A time-dependent relationship was observed between time to recanalization therapy and risk of death (≤3 hours: 36%; >3 to ≤6 hours: 38% [aRR, 1.05; 0.79–1.41]; >6 to ≤9 hours: 39% [aRR, 1.18; 0.82–1.71]; ≤9 hours: 46% [aRR, 1.44; 1.05–1.99]). Similarly, a time-dependent relationship was observed between time to recanalization therapy and risk of insufficient recanalization (≤3 hours: 15 of 89 [17%]; >3 to ≤6 hours: 26 of 116 [22%] [aRR, 1.32; 0.75–2.31]; >6 to ≤9 hours: 14 of 45 [31%] [aRR, 1.87; 0.99–3.50]; ≤9 hours: 14 of [48] [29%] [aRR, 2.00; 1.04–3.84]).

The incidence of poor functional outcome according to stroke severity is shown in Figures 2 and 3. In patients with severe strokes at presentation, all patients treated >9 hours after symptom onset had poor functional outcome (≤3 hours: 71%; >3 to ≤6 hours: 77% [aRR, 1.07; 0.91–1.25]; >6 to ≤9 hours: 88% [aRR, 1.28; 1.08–1.51]; and ≤9 hours: 100% [aRR, 1.43; 1.25–1.63]). In patients with mild to moderate strokes, the risk of poor functional outcome was as follows: ≤3 hours: 42%; >3 to ≤6 hours: 49% (aRR, 1.10; 0.71–1.70); >6 to ≤9 hours: 50% (aRR, 1.10; 0.63–1.90); and >9 hours: 63% (aRR, 1.61; 1.01–2.56).

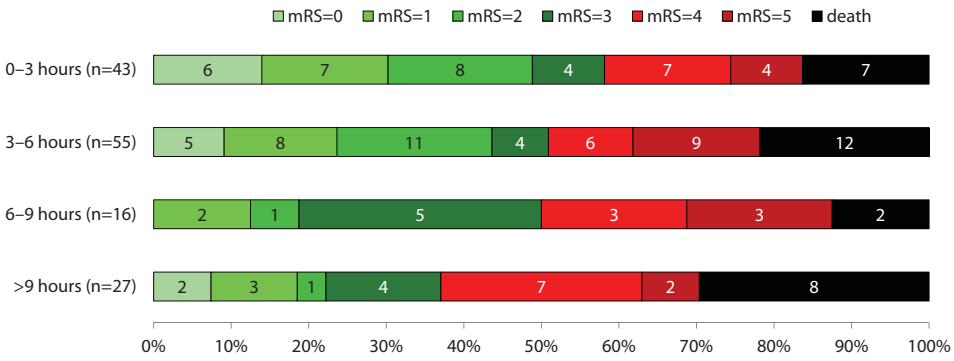

Figure 2 Functional outcome according to time to treatment in patients with mild to moderate strokes. mRS = modified Rankin scale score.

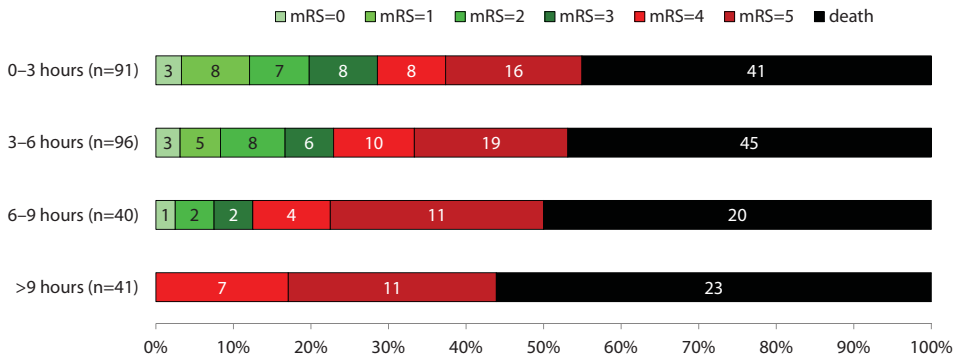

Figure 3 Functional outcome according to time to treatment in patients with severe strokes. mRS = modified Rankin scale score.

DISCUSSION

Our study shows that in patients with BAO the risk of poor functional outcome, death, and insufficient recanalization increases when time to recanalization therapy is longer. Absolute risks were highest for those treated >9 hours, also after multivariable adjustment. All patients with severe strokes at presentation treated >9 hours after symptom onset had poor functional outcome.

Previous studies that investigated predictors of recanalization and functional outcome after BAO often dichotomized time to treatment with a cutoff of 6 hours after symptom onset.[6,7] Some studies found no association between time to treatment and recanalization or outcome.[6,7] Others found that time to treatment was a predictor of functional outcome in univariable but not in multivariable analyses.[8]

Our results imply that patients with BAO should be treated as soon as possible after symptom onset, similar to patients with ischemic stroke in the anterior circulation. Because all patients with severe stroke treated >9 hours after symptom onset had poor functional outcome, there is probably no benefit of recanalization therapy in this group of patients.

Previous studies have shown that BAO is preceded by prodromal symptoms in >60% of patients.[9,10] Most of these patients would be excluded from a potential trial that has the time of onset of any symptom to treatment as an inclusion criterion. Therefore, we used an estimated time to treatment from the onset of symptoms

consistent with a clinical diagnosis of BAO rather than the more commonly used time of onset of any symptom to treatment. Our findings support the use of a more liberal definition of time of onset in patients with BAO.

Although patients treated at later time intervals tended to be younger and to have less severe stroke symptoms, these patients had a worse outcome, which was also true after correction for baseline imbalances. We did not make a distinction between patients treated with intra-arterial treatment or IVT. In a previous study we did not find significant differences between these treatment groups in various time to treatment subcategories, which might be caused by the small number of patients in each subgroup.[5] The question of which treatment option is superior in patients with BAO will be answered by the recently started BASICS trial, in which patients are randomized between IVT alone versus IVT followed by additional intra-arterial treatment (www.basicstrial.com). In the BASICS trial, patients will only be included if initiation of intra-arterial treatment is feasible within 6 hours of estimated time of BAO. The present study shows that only 23% of patients treated between 6 and 9 hours had good functional outcome compared with 35% of patients treated within 6 hours. Including patients beyond 6 hours after estimated time of BAO in a randomized trial would dilute a potential beneficial effect and require a larger sample size.

The strength of this study is that BASICS was a prospective registry of consecutive patients and therefore our results are representative for daily practice. A limitation is that it was a post hoc analysis of nonrandomized data, and therefore the data regarding treatment-dependent outcomes are prone to bias. However, the prospective collection of detailed data allowed us to adjust for important confounding baseline characteristics.

We conclude that early recanalization therapy in patients with BAO is associated with a more favorable outcome. This implies that these patients should be treated as soon as possible. Beyond 9 hours, the prognosis of patients with severe BAO is universally dismal despite recanalization therapy.

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Recanalization and outcome after basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS)

Wouter J. Schonewille, Christian Weimar, Heinrich Audebert,
Heinrich P. Mattle, Keith W. Muir, Jorge Pagola, Ale Algra, L. Jaap Kappelle;
on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose Recanalization has been shown to be a predictor of clinical outcome in patients with acute anterior circulation stroke. We investigated the relationship between recanalization and outcome in the Basilar Artery International Cooperation Study (BASICS).

Methods BASICS is a prospective multicenter registry of 619 patients with radiologically confirmed basilar artery occlusion (BAO). Patency on follow-up was assessed by computed tomography angiography (CTA), magnetic resonance angiography (MRA), transcranial Doppler (TCD) or digital substraction angiography, and scored as patent, severely stenotic or persistently occluded. End of procedure recanalization after intra-arterial therapy was defined as a thrombolysis in myocardial infarction (TIMI) score of 3. The primary outcome measure was good outcome at 1 month, defined as a modified Rankin Scale (mRS) score of 0-3 (independence). The association between recanalization and clinical outcomes was described as a risk ratio (RR) with 95% confidence intervals (CI).

Results Good outcome was predicted by end of procedure recanalization in patients who had intra-arterial treatment (IAT) (RR 2.64: 95% CI 1.66–4.21), by patency on follow-up (RR 1.72; 95% CI 1.28–2.33) and also by patency on follow-up in patients with persistent occlusion at end of procedure (RR 3.84; 95% CI 1.16–12.7).

Conclusions Our results confirm the strong association between recanalization and outcome in patients with BAO and suggest that patients who underwent IAT might benefit from post-procedural delayed recanalization.

INTRODUCTION

The main focus of current acute stroke therapy is on timely recanalization. Thanks to rapidly evolving endovascular techniques, recanalization rates have reached 80–90% in patients with anterior circulation stroke.[1-2] Recanalization has been shown to be a strong predictor of clinical outcome in patients with acute anterior circulation stroke.[3-5] Our aim was to assess the association of recanalization with clinical outcome in patients with basilar artery occlusion (BAO) in the Basilar Artery International Cooperation Study (BASICS).[6]

METHODS

The Basilar Artery International Cooperation Study (BASICS) was a prospective, observational, international registry of consecutive patients aged 18 years or older who presented with clinical features of an acute symptomatic and radiologically confirmed BAO.[6,7] Treatment was left to the discretion of the treating physician.

Patency of the basilar artery on follow-up was assessed at least 24 hours after onset of clinical features using computed tomography angiography (CTA), magnetic resonance imaging angiography (MRA), transcranial Doppler (TCD) or digital substraction angiography. Vessel status on follow-up was scored as patent, severely stenotic or persistently occluded. End of procedure recanalization after intra-arterial treatment (IAT) was scored by the local interventionalist, using the thrombolysis in myocardial infarction (TIMI) score. Recanalization was defined as a TIMI score of 3 (complete recanalization). There was no central reading of images.

Clinical outcome was assessed at 1 month using the modified Rankin scale (mRS). Good outcome was defined as an mRS of 0 to 3 (independence) after one month. The association between recanalization and clinical outcomes was described as a risk ratio (RR) with 95% confidence intervals (CI).

RESULTS

Of the 619 patients included in the registry, 184 were treated only with antiplatelet agents or anticoagulants (AT), 120 with intravenous thrombolysis (IVT) (79 with IVT only, 41 with IVT followed by additional IAT) and 288 with IAT only. Twenty-seven patients were excluded from further analysis, because they did not receive any antithrombotic or recanalization therapy.

As shown in the flow chart (Figure 1), patency on follow-up (median follow-up 2 days) was assessed in 303 out of 592 treated patients (51%). Patients in whom patency was not assessed tended to be older (mean age 65 vs 62), were more likely to be female (41 vs 33%), more often had a severe deficit (60 vs 46%) and were less likely to be treated with IVT (16 vs 25%). None of these differences reached significance (Table 1). A good outcome was seen in 92 out of 177 patients (52%) with a patent basilar artery on follow up and in 38 out of 126 patients (30%) with a severe residual stenosis or persistent occlusion (RR 1.72; 95% CI 1.28–2.33).

End of procedure recanalization was assessed in 252 (88%) patients treated with IAT (Figure 2). A good outcome was seen in 51 out of 127 patients (40%) with an end of procedure recanalization (TIMI 3) and in 19 out of 125 patients (15%) with a TIMI 0-2 (RR 2.64: 95% CI 1.66–4.21).

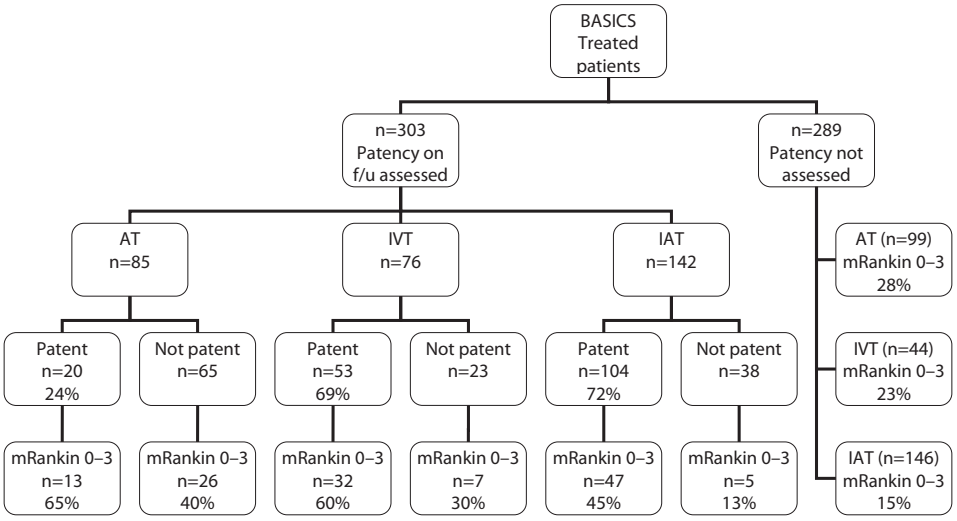

Figure 1 Flow chart; patency on follow-up and outcome. AT = anti-thrombotic therapy, IVT = IV thrombolysis with or without additional IAT, IAT = IA therapy only.

Both end of procedure recanalization and patency on follow-up were assessed in 125 patients. Among patients with a persistent end of procedure occlusion (TIMI 0–2) a good outcome was seen in 9 out of 25 patients (36%) with a patent basilar artery on follow-up and in 3 out of 32 (9%) patients with a non-patent basilar on follow-up (RR 3.84: 95% CI 1.16–12.7).

Table 1 Characteristics of patients in whom patency was and wasn't assessed

Characteristic	Patentency	
	Assessed n=303 (%)	Not assessed n=289 (%)
Age (Mean)	61.7	65.2
Female sex	100 (33)	118 (41)
Hypertension	184 (61)	181 (63)
Diabetes mellitus	72 (24)	56 (19)
Atrial fibrillation	68 (22)	58 (20)
Time to treatment (hours)		
0–3	89 (29)	90 (31)
4–6	104 (34)	86 (30)
≥7	110 (37)	113 (39)
NIHSS >20	138 (46)	172 (60)
Type of treatment		
Asa/hep	85 (28)	98 (34)
IVT	76 (25)	45 (16)
IAT	142 (47)	146 (51)
Type of presentation		
Fluctuating symptoms	48 (16)	34 (12)
Maximum from onset	109 (36)	109 (38)
Progressive stroke	139 (46)	131 (45)
Location occlusion		
Proximal	125 (41)	131 (45)
Middle	75 (25)	64 (22)
Distal	103 (34)	94 (33)
CT prior to treatment		
Normal	109 (41)	104 (42)
Dense basilar	91 (30)	68 (24)
Early ischemic changes	70 (23)	80 (28)
Embolic stroke	115 (38)	99 (35)
Atherosclerotic stroke	102 (34)	108 (38)

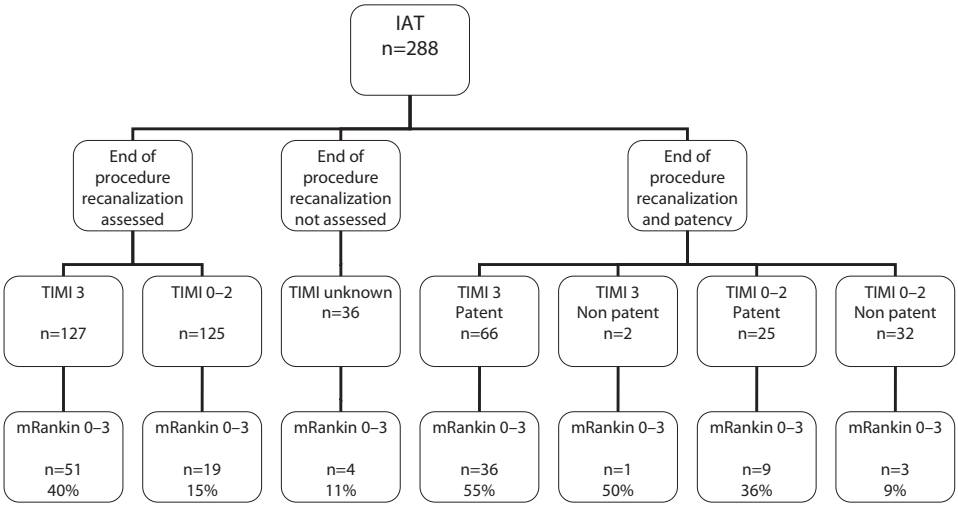

Figure 2 Flow chart; recanalization, patency on follow-up and outcome IAT patients.

DISCUSSION

In the BASICS registry population both end of procedure recanalization after IAT and a patent basilar artery on follow-up imaging were statistically significant predictors of good outcome after one month.

The end of procedure recanalization rate after IAT in our registry was comparable to the rates found in large case series of patients with BAO treated with IAT (37–52%).[8,9] Case series of patients with BAO treated with IVT have shown early recanalization in only 4 to 33%.[10-12]

Our patency rate on follow-up is similar to the one described in a previous case series of patients with BAO treated with IVT.[13] There was no statistically significant difference in patency rate on follow-up between patients treated with IVT (69%) or with IAT (72%; Figure 1). To the best of our knowledge there are no published series about patency at 24 hours or beyond in patients with BAO treated with IAT.

Due to selection bias we do not have reliable data about the true patency rate on follow up. For the same reason a comparison of patency rates on follow-up and the effect of patency on outcome with series of anterior circulation occlusion is not very meaningful. Patients who have a persistent occlusion or re-occlusion after initial early

recanalization may be in too poor a clinical condition to have follow-up imaging, a category of patients which is likely to be considerably larger in series with BAO than in series with anterior circulation occlusion. Besides this clinical selection bias we did not find mayor differences in baseline characteristics of patients in whom patency was and was not assessed.

A considerable number of patients with an absent or incomplete end of procedure recanalization directly after IAT showed patency at follow up. The good outcome rate in these patients was comparable to the rate that was found in patients with end of procedure recanalization. These findings support the notion that there is a subgroup of patients with BAO who benefits from late recanalization.

In conclusion: our results confirm the strong association between recanalization and outcome in patients with basilar artery occlusion. Further studies are needed to assess the frequency and clinical relevance of post procedural re-occlusion and delayed recanalization after IAT in patients with basilar artery occlusion.

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Vertebral artery stenosis in the Basilar Artery International Cooperation Study (BASICS); prevalence and outcome

Annette Compter, Erik J.R.J van der Hoeven, H. Bart van der Worp, Jan Albert Vos, Christian Weimar, Christina M. Rueckert, L. Jaap Kappelle, Ale Algra, Wouter J. Schonewille; on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose We assessed the prevalence of vertebral artery (VA) stenosis or occlusion and its influence on outcome in patients with acute basilar artery occlusion (BAO).

Methods We studied patients with acute BAO enrolled in the Basilar Artery International Cooperation Study (BASICS) registry of whom baseline CT angiography (CTA) of the VAs was available (n=141). CTA was limited to the intracranial circulation in 69 patients. Adjusted risk ratios (aRRs) for death and poor outcome, defined as a modified Rankin Scale score ≥ 4, were calculated with Poisson regression in relation to VA occlusion, VA occlusion or stenosis ≥50%, and bilateral VA occlusion.

Results Sixty six (47%) patients had an intracranial VA occlusion or stenosis ≥50%. Of the 72 patients with intra- and extracranial CTA, 46 (64%) had a VA occlusion or stenosis ≥50%. VA occlusion or stenosis ≥50% was not associated with the risk of poor outcome. Only patients with bilateral VA occlusion had a higher risk of poor outcome (100%; aRR, 1.23; 95% CI, 1.02–1.50) than patients without bilateral VA occlusion (73%). The risk of death did not depend on the presence of unilateral or bilateral VA occlusion or stenosis.

Conclusions In patients with acute BAO, unilateral VA occlusion or stenosis ≥50% is frequent but not associated with an increased risk of poor outcome or death. Patients with BAO and bilateral VA occlusion have a slightly increased risk of poor outcome.

Basilar artery occlusion (BAO) is associated with a high mortality rate and poor functional outcome among survivors.[1,2] The most frequent underlying etiology is either atherosclerotic stenosis of the basilar artery (BA) or vertebral artery (VA), or embolism from the heart.[3,4]

Patients with a symptomatic BA stenosis or occlusion and extensive atherosclerotic disease of both the VA and BA have been reported to have a better outcome than patients with BAO and normal VAs.[5] This might be explained by a better developed collateral circulation in patients with generalized atherosclerosis as opposed to patients with a sudden occlusion caused by embolism from the heart or a large artery. VA stenosis, particularly if intracranial, is a strong predictor of future stroke in patients with a recent TIA in the posterior circulation.[6] Little systematic research has been performed into the prevalence of VA occlusion or stenosis in patients with acute BAO, and its relation with their prognosis. In addition, it is unknown whether VA hypoplasia influences outcome in BAO.

The aim of the current study was to investigate the prevalence of VA occlusion or stenosis ≥50% in patients with acute BAO and its relation with outcome at one month. Furthermore, we assessed the influence of VA hypoplasia and a continuous thrombus in one or both VAs and the BA.

SUBJECTS AND METHODS

Study population

The present study is a post-hoc analysis of the Basilar Artery International Cooperation Study (BASICS), a prospective, observational, international registry of consecutive patients aged 18 years or older who presented with an acute symptomatic and radiologically confirmed BAO.[7] The methods of BASICS have been described previously.[2] The BASICS registry was approved by the ethics committee of the University Medical Center Utrecht in the Netherlands and all patients or patient's representatives provided written informed consent.

A total of 619 patients were included in the BASICS registry. For the present study we included patients who were recruited at sites that had performed a CTA in at least 10 of the included patients (Figure 1). In addition we required a CTA of good

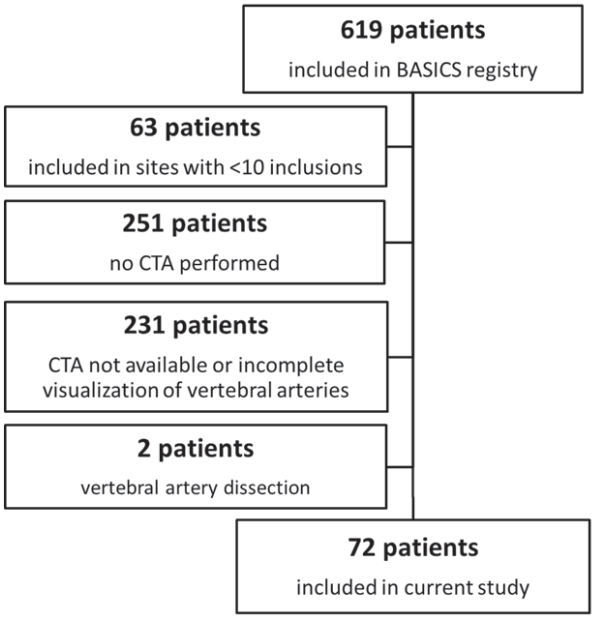

Figure 1 Flow chart. CTA = CT angiography.

quality, available in Digital Imaging and Communications in Medicine (DICOM) format, and confirming the BAO. Patients with previous surgical or endovascular treatment of the VA and patients with a dissection of the VA resulting in a BAO were excluded.

Outcome measures

Outcome measures were poor outcome at one month (modified Rankin scale (mRs) score 4 or 5, or death), and death at one month.

Intra- and extracranial CTAs were independently reviewed by two investigators (AC and EH), who were blinded to all clinical information. When the assessment of the two readers was inconsistent, a consensus meeting took place. The degree of stenosis in the VA on CTA was calculated by dividing the residual lumen (N) by vessel diameter at a point distal to the stenosis where the normal vessel calibre has been restored (D), and applying the formula: (1 – N/D) x 100% = degree of stenosis.[8] Atherosclerotic narrowing of the VA was divided in three groups: stenosis <50%, stenosis 50–99%, and occlusion. For the location of the stenosis the VA was

structurally divided in four parts: V1-V3 for the extracranial vertebral artery and V4 for the intracranial vertebral artery.[9] Hypoplasia of an extracranial vertebral artery was defined by a diameter of ≤2 mm in both the V1 and V2-segment.[10] The larger (contralateral) VA was then defined as the dominant vertebral artery. We classified the VAs as symmetric if both VAs had a diameter greater than 2 mm. The presence of a continuous thrombus in one or both VAs and the BA was assessed separately.

Data analysis

The frequency of baseline characteristics between patients with and without VA occlusion or stenosis ≥50%–99% in the intracranial or extra- and intracranial VAs were compared by Poisson regression analysis and described as prevalence ratios with corresponding 95% confidence intervals (CIs).

Risk ratios (RRs) and corresponding 95% CIs were calculated for poor outcome and death according to the presence of VA occlusion, bilateral VA occlusion, VA occlusion or stenosis ≥50%, and VA occlusion or stenosis ≥50% in a dominant VA. In multivariable analysis adjustments were made for the three factors affecting the crude risk ratio the most. In addition, the RR for poor outcome and death at one month was calculated for extracranial VA hypoplasia and a continuous thrombus in one or both VAs and the BA. Missing baseline data (<5% for each variable) were imputed with regression imputation for optimal adjustment for baseline differences between the groups of interest.[11]

The inter-observer variability for VA occlusion or stenosis ≥50% was calculated with kappa statistics.

RESULTS

Of the 619 patients included in the BASICS registry, 141 patients with a CTA of the intracranial VA were included in the present study, of whom 72 also had a CTA of the extracranial VAs (Figure 1). The inter-observer agreement on the presence of VA occlusion or stenosis ≥50% was good (κ, 0.84). Of the 141 patients, 48 (34%) had an occlusion of at least one VA and 21 (15%) of both VAs (Table 1). VA occlusion

or stenosis ≥50% was found in 66 patients (47%); this occlusion or stenosis affected the dominant VA in 27 patients (19%). In 37 patients (26%) a continuous thrombus in one or both VAs and the BA was found.

Of the 72 patients with a CTA of the intra- and extracranial VAs, 32 (44%) had a VA occlusion, and 46 (64%) a VA occlusion or stenosis ≥50% (Table 1). VA hypoplasia was found in 6 patients (8%).

Baseline characteristics of patients with and without VA occlusion or stenosis ≥50% are presented in Table 2. Patients with VA occlusion or stenosis ≥50% more frequently were male, more often had an occlusion of the proximal or middle BA, and less often had atrial fibrillation compared with patients without VA occlusion or stenosis ≥50%. Patients with intracranial VA stenosis or occlusion more often had diabetes mellitus or hyperlipidemia. In 22 patients (16%) stenting or percutaneous

Table 1 Presence of occlusion or stenosis >50% in vertebral artery

	Presence of occlusion or stenosis >50% in intracranial VA (n=141)	Presence of occlusion or stenosis >50% in extra- or intracranial VA (n=72)
Occlusion VA	48 (34%)	32 (44%)
Bilateral occlusion VA	21 (15%)	9 (12%)
Occlusion V1		13 (18%)
Occlusion V2		10 (14%)
Occlusion V3		9 (13%)
Occlusion V4	48 (34%)	26 (36%)
Stenosis VA	23 (16%)	21 (29%)
Bilateral stenosis VA	6 (4%)	8 (11%)
Stenosis V1		13 (18%)
Stenosis V2		4 (6%)
Stenosis V3		0 (0%)
Stenosis V4	23 (16%)	12 (17%)
Occlusion/ stenosis in at least one VA	66 (47%)	46 (64%)
Occlusion/ stenosis in dominant VA	27 (19%)	14 (19%)
Occlusion/ stenosis in both VAs	32 (23%)	20 (28%)
Thrombus in BA and VA	37 (26%)	20 (28%)
Hypoplasia VA		6 (8%)

VA = vertebral artery; BA = basilar artery.

Table 2 Baseline characteristics in relation to presence of vertebral artery occlusion or stenosis ≥50%

	CTA of intracranial VA n=141			CTA of extra- and intracranial VA n=72		
	Occlusion or stenosis ≥50% (n=66)	No occlusion or stenosis ≥50% (n=75)	Prevalence ratio (95% CI)	Occlusion or stenosis ≥50% (n=46)	No occlusion or stenosis ≥50% (n=26)	Prevalence ratio (95% CI)
Male sex	50 (76%)	41 (55%)	1.4 (1.1–1.8)	32 (70%)	10 (39%)	1.8 (1.1–3.1)
Age (years)*	65 (13)	65 (17)	1.0 (0.9–1.1)	63 (14)	67 (21)	0.9 (0.8–1.1)
Hypertension	44 (67%)	43 (57%)	1.2 (0.9–1.5)	29 (63%)	13 (50%)	1.3 (0.8–2.0)
Diabetes mellitus	18 (27%)	9 (12%)	2.3 (1.1–4.7)	8 (17%)	3 (12%)	1.5 (0.4–5.2)
Hyperlipidemia	24 (36%)	13 (17%)	2.1 (1.2–3.8)	16 (35%)	6 (23%)	1.5 (0.7–3.4)
Atrial fibrillation	4 (6%)	21 (28%)	0.2 (0.1–0.6)	2 (4%)	7 (27%)	0.2 (<0.1–0.7)
Coronary artery disease	9 (14%)	8 (11%)	1.3 (0.5–3.1)	5 (11%)	4 (15%)	0.7 (0.2–2.4)
Smoking	10 (15%)	16 (21%)	0.7 (0.4–1.5)	8 (17%)	4 (15%)	1.1 (0.4–3.4)
Prodromal minor stroke	30 (45%)	27 (36%)	1.3 (0.8–1.9)	17 (37%)	5 (19%)	1.9 (0.8–4.6)
Treatment						
No treatment	9 (14%)	4 (5%)	2.6 (0.8–7.9)	4 (9%)	2 (8%)	1.1 (0.2–5.8)
AT	21 (32%)	22 (29%)	1.1 (0.7–1.8)	9 (20%)	13 (50%)	0.4 (0.2–0.8)
IVT	8 (12%)	5 (7%)	1.8 (0.6–5.3)	6 (13%)	1 (4%)	3.4 (0.4–26.7)
IVT-IAT	4 (6%)	6 (8%)	0.8 (0.2–2.6)	4 (9%)	4 (15%)	0.6 (0.2–2.1)
IAT	24 (36%)	38 (51%)	0.8 (0.5–1.1)	23 (50%)	6 (23%)	2.2 (1.0–4.6)
PTA or stenting	9 (14%)	13 (17%)	0.8 (0.4–1.7)	16 (35%)	2 (8%)	4.5 (1.1–18.1)
Time to treatment						
0–3h	19 (29%)	21 (28%)	†	12 (26%)	7 (27%)	‡
4–6h	9 (14%)	28 (37%)	†	13 (28%)	6 (23%)	‡
7–9h	13 (20%)	5 (7%)	†	7 (15%)	2 (8%)	‡
>9h	16 (24%)	17 (23%)	†	10 (22%)	9 (35%)	‡
Severe deficit at time of treatment§	39 (59%)	54 (72%)	0.7 (0.5–1.0)	26 (57%)	16 (62%)	0.9 (0.6–1.4)
NIHSS score*	23 (12–33)	25 (16-30)	0.9 (0.8–1.1)	20 (12–30)	22 (11–30)	1.0 (0.8–1.3)
NIHSS score >20	34 (52%)	52 (69%)	0.7 (0.6–1.0)	21 (46%)	14 (54%)	0.8 (0.5–1.4)
Occlusion proximal or middle BA	54 (82%)	35 (47%)	1.8 (1.3–2.3)	38 (83%)	7 (27%)	3.1 (5.6–5.9)

Data are mean (SD), number (%), or median (IQR). CTA = CT angiography; CI = confidence interval; TIA = transient ischemic attack; AT = antithrombotic treatment with aspirin or heparin; IVT = intravenous thrombolysis; IVT-IAT = combined treatment with intravenous thrombolysis and intra-arterial therapy; IAT = intra-arterial therapy; PTA = percutaneous transluminal angioplasty; NIHSS=National institutes of Health Stroke Scale score. * Prevalence ratio is expressed as the ratio per additional year of age or point at NIHSS. † p=0.01, overall chi square test. ‡ p=0.58, overall chi square test. § Severe deficit at time of treatment indicates coma, locked-in state, or tetraplegia.

transluminal angioplasty of the BA or VA had been performed during IA treatment, this treatment was more often performed in patients with CTA of the intra- and extracranial VAs and occlusion or stenosis ≥50%.

At one month 107 patients (76%) had a poor outcome, of whom 64 (60%) had died. Figure 2 shows the outcomes according to the presence of VA occlusion, and VA occlusion or stenosis ≥50%.

No differences were found for unadjusted and adjusted risks of poor outcome in patients with and without VA occlusion (Table 3). In patients with a CTA of the intra- and extracranial VAs, the presence of bilateral VA occlusion resulted in a higher risk of poor outcome (aRR, 1.23; 95% CI 1.02–1.50) compared with patients without a

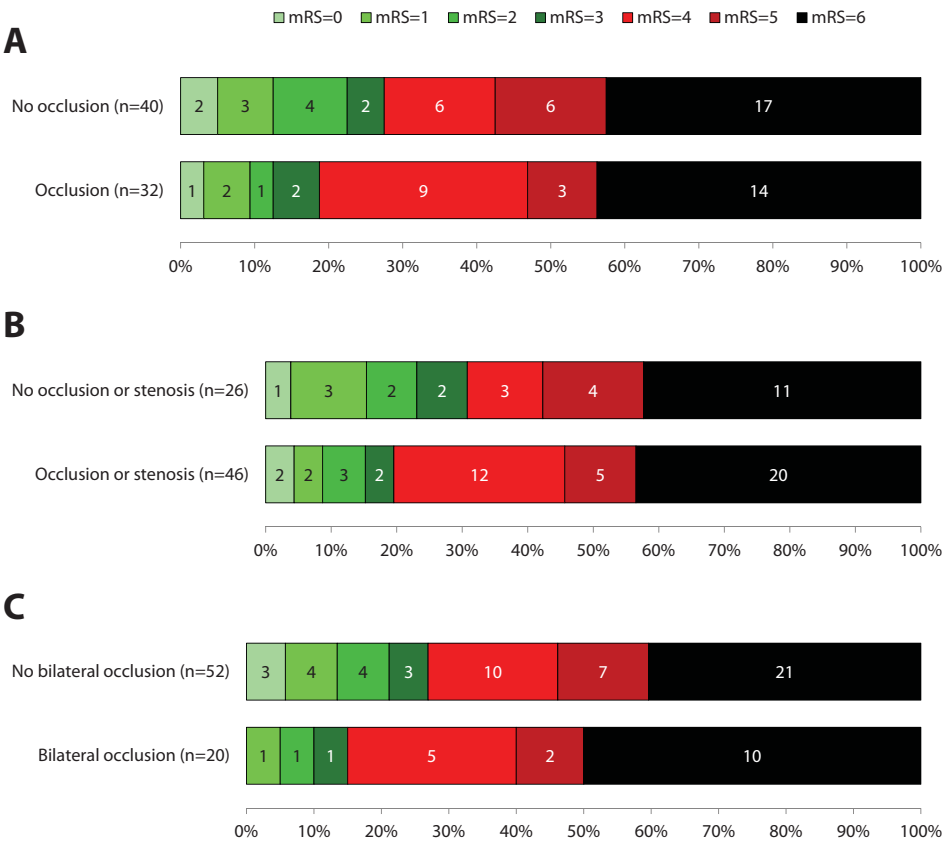

Figure 2 Outcome at 1 month according to presence of vertebral artery occlusion or stenosis ≥50%. **(A)** CTA of intracranial vertebral artery (n=141). **(B)** CTA of intra- and extra cranial vertebral artery (n=72). CTA = CT angiography; mRS = modified Rankin scale score.

bilateral VA occlusion. The presence of VA occlusion or stenosis ≥50% in any VA or the dominant VA was not associated with poor outcome or death. Patients who had had an intracranial CTA and had a continuous thrombus in one or both VAs and the BA had a higher risk of death (aRR, 1.44; 95% CI, 1.02–2.02). The presence of extracranial VA hypoplasia did not affect the risk of poor outcome or death.

DISCUSSION

We found that almost half of the patients with acute BAO had a concomitant intracranial VA stenosis ≥50% or occlusion and more than 60% had a stenosis in the intra- or extracranial VA. The presence of VA occlusion and VA stenosis ≥50% or unilateral occlusion did not influence clinical outcome. However, patients with BAO and bilateral intra- and extracranial VA occlusion had a higher risk of a poor clinical outcome.

About half of the patients with a symptomatic BA stenosis or occlusion had concomitant VA atherosclerosis in two previous registries, in line with the current study.[5,12] Embolism from the heart or extracranial vertebral artery was associated with poor outcome in a previous registry of patients with BA stenosis or occlusion not treated with thrombolysis.[5] It was hypothesized that patients without atherosclerosis, but with an embolic occlusion of the BA, have less time to develop collateral circulation than patients with atherosclerosis and consequently tolerate ischemic symptoms for a shorter period of time. This theory was supported by the finding that patients with widespread atherosclerotic posterior circulation disease had the best prognosis in the previous registry.[5] In the current study, patients with occlusion or stenosis ≥50% in the extra- or intracranial VA did not have a better outcome than patients without occlusion or stenosis. The difference with the previous registries is probably explained by the important fact that in the present study only patients with acute, symptomatic BAO were included, whereas in the previous registries also patients with a TIA or ischemic stroke due to BA stenosis and chronic BA occlusion had been included.

In the current study patients with BAO and bilateral VA occlusion had a higher risk of poor clinical outcome. Bilateral VA occlusion is associated with a decreased ability to develop adequate collateral supply and a lower recanalization rate due to

Table 3 Poisson regression analysis: unadjusted and adjusted risk ratios for poor outcome and death

	Total	Unadjusted RR	Adjusted RR
CTA of intracranial VA n=141			
Occlusion *vs* no occlusion			
Poor outcome	37/48 (77%) *vs* 70/93 (75%)	1.02 (0.84–1.24)	1.02 (0.84–1.25)*
Death	25/48 (52%) *vs* 39/93 (42%)	1.24 (0.87–1.78)	1.20 (0.84–1.71)*
Bilateral occlusion *vs* no bilateral occlusion			
Poor outcome	19/21 (91%) *vs* 88/120 (73%)	1.23 (1.04–1.47)	1.18 (0.99–1.40)*
Death	14/21 (67%) *vs* 50/120 (42%)	1.60 (1.11–2.31)	1.30 (0.90–1.86)*
Occlusion or stenosis ≥50 *vs* no occlusion or stenosis ≥50%			
Poor outcome	51/66 (77%) *vs* 56/75 (75%)	1.04 (0.86–1.25)	1.08 (0.89–1.30)*
Death	30/66 (45%) *vs* 34/75 (45%)	1.00 (0.70–1.44)	1.04 (0.73–1.49*
Occlusion or stenosis ≥50% in dominant VA *vs* no occlusion or stenosis ≥50%			
Poor outcome	23/27 (85%) *vs* 56/75 (75%)	1.14 (0.93–1.40)	1.18 (0.97–1.44)*
Death	15/27 (56%) *vs* 34/75 (45%)	1.23 (0.81–1.86)	1.19 (0.80–1.76)*
Continuous thrombus in VA and BA present *vs* thrombus absent			
Poor outcome	31/37 (84%) *vs* 76/104 (73%)	1.15 (0.95–1.38)	1.16 (0.96–1.41)*
Death	22/37 (59%) *vs* 42/104 (40%)	1.47 (1.03–2.10)	1.44 (1.02–2.02)*
CTA of extra- and intracranial VA n=72			
Occlusion *vs* no occlusion			
Poor outcome	26/32 (81%) *vs* 29/40 (73%)	1.12 (0.87–1.44)	1.03 (0.81–1.32)†
Death	14/32 (44%) *vs* 17/40 (43%)	1.03 (0.60–1.75)	0.97 (0.60–1.55)*
Bilateral occlusion *vs* no bilateral occlusion			
Poor outcome	9/9 (100%) *vs* 46/63 (73%)	1.37 (1.18–1.59)	1.23 (1.02–1.50)†
Death	7/9 (78%) *vs* 24/63 (38%)	2.04 (1.28–3.27)	1.34 (0.77–2.32)*
Occlusion or stenosis ≥50% *vs* no occlusion or stenosis ≥50%			
Poor outcome	37/46 (80%) *vs* 18/26 (69%)	1.16 (0.87–1.56)	1.08 (0.79–1.47)†
Death	20/46 (44%) *vs* 11/26 (42%)	1.03 (0.59–1.79)	1.01 (0.61–1.67)*
Occlusion or stenosis ≥50% in dominant VA *vs* no occlusion or stenosis ≥50%			
Poor outcome	12/14 (86%) *vs* 18/26 (69%)	1.24 (0.89–1.73)	1.09 (0.73–1.61)†
Death	10/14 (71%) *vs* 11/26 (42%)	1.69 (0.97–2.95)	1.70 (0.93–3.12)*
Continuous thrombus in VA and BA present *vs* thrombus absent			
Poor outcome	18/20 (90%) *vs* 37/52 (71%)	1.27 (1.01–1.59)	1.19 (0.91–1.55)†
Death	11/20 (55%) *vs* 20/52 (39%)	1.43 (0.85–2.42)	1.34 (0.83–2.17)*
Hypoplasia extracranial VA *vs* no hypoplasia			
Poor outcome	4/6 (67%) *vs* 51/66 (77%)	0.86 (0.48–1.54)	0.91 (0.51–1.63)†
Death	2/6 (33%) *vs* 29/66 (44%)	0.76 (0.24–2.43)	0.79 (0.22–2.89)*

Data are number (%) or risk ratio (95% CI). CTA = CT angiography; RR = risk ratio; poor outcome = modified Rankin scale score of 4, 5, or death; VA = vertebral artery; BA = basilar artery. * Adjustment for age, sex, and treatment. † Adjustment for sex, treatment, and atrial fibrillation.

a higher clot burden. In a previous study mortality in BAO was associated with the length of BA occlusion.[13] In anterior circulation stroke the size of the intracranial thrombus, as quantified with the clot burden score, predicted poor functional outcome and larger final infarct size.[14]

Occlusion of the VA in patients with BAO can result from either atherosclerosis, an embolus, or retrograde thrombus growth after BAO in case of distal vertebral artery occlusion. Differentiation of the underlying pathophysiology will not always be possible in the acute phase of BAO when urgent treatment is required. Consequently, in the current study we focused on CTA findings of the VA instead of the underlying pathophysiology, which is in line with clinical practice.

The design of BASICS as a prospective, observational registry inherently has limitations in comparison with randomized trials. The choice of treatment was left to the discretion of the clinicians, and was inevitably influenced by the suspected prognosis and effect of treatment. In univariable analysis patients with VA occlusion or stenosis were more frequently treated with percutaneous angioplasty or stenting. Nevertheless, after adjustments for treatment in multivariable analysis the risk of poor clinical outcome and death remained essentially the same. Selection bias may also have influenced our results, because not all patients had had visualization of the VAs by CTA in the acute phase of BAO.

In the last decade endovascular treatment options have evolved rapidly, both for acute ischemic stroke and secondary prevention in patients with large vessel stenosis. Currently, two trials are investigating the role of stenting in symptomatic VA stenosis[15,16] and one trial compares IV and IV/IA treatment in acute BAO.[17] Arguments for stenting of the VA directly during intra-arterial treatment for BAO are optimization of the intra-arterial entrance to the BA, prevention of recurrent embolism from the VA and recruitment of collaterals during intervention. Whether these interventions for VA stenosis influence outcome in patients with BAO should be assessed in a future study.

In conclusion, our study shows that in patients with acute BAO, VA occlusion and stenosis ≥50% are frequently present and are not related to poor outcome at one month. Consequently, accompanying VA occlusion or stenosis should not be a reason to withhold any treatment in BAO.

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Prodromal transient ischemic attack or minor stroke and outcome in basilar artery occlusion

Adriana B. Conforto, Gabriel R. de Freitas, Wouter J. Schonewille,
L. Jaap Kappelle, Ale Algra; on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose The presence of prodromal transient ischemic attacks (TIAs) has been associated with a favorable outcome in anterior circulation stroke. We aimed to determine the association between prodromal TIAs or minor stroke and outcomes at one month, in the Basilar Artery International Cooperation Study (BASICS), a registry of patients presenting with an acute symptomatic and radiologically confirmed basilar artery occlusion.

Methods 619 patients were enrolled in the registry. Information on prodromal TIAs was available for 517 patients and on prodromal stroke, for 487 patients. We calculated risk ratios and corresponding 95% CIs for poor clinical outcome (modified Rankin scale score ≥4) according to the variables of interest.

Results Prodromal minor stroke was associated with poor outcome (crude risk ratio, cRR, 1.26, 95% CI 1.12–1.42), but TIAs were not (cRR 0.93, 95% CI 0.79–1.09). These associations remained essentially the same after adjustment for confounding variables.

Conclusions Prodromal minor stroke was associated with an unfavorable outcome in patients with basilar artery occlusion, whereas prodromal TIA was not.

INTRODUCTION

Induction of ischemic tolerance during the prodromes and enhanced patency of collateral circulation have been considered potential mechanisms underlying better outcomes when transient ischemia heralds a full-blown ischemic stroke. Further support for this idea came from the finding of smaller lesions in diffusion-weighted MRI within 12 hours from stroke, in patients with history of transient ischemic attack (TIA) compared with those without, despite similar perfusion deficits.[1]

Case series looking at the association between prodromal TIA and outcome in anterior circulation infarcts have shown conflicting results.[2-6] Series of patients with infarcts caused by either basilar stenosis or occlusion have suggested an association between prior TIAs and good outcome.[7-9] However, these studies were retrospective with a limited number of patients.

The aim of this study was to determine the association between prodromal TIAs or minor stroke and outcome at one month in patients with symptomatic basilar artery occlusion.

METHODS

We used data of the Basilar Artery International Cooperation Study (BASICS) registry; details have been published previously.[10] Members of the BASICS Study Group are listed in the Appendix. Patients were eligible for entry if they presented with symptoms or signs attributable to the posterior circulation, and had a basilar artery occlusion as confirmed by CT angiography, magnetic resonance angiography, or conventional contrast angiography.

The primary outcome was poor clinical outcome at one month (modified Rankin scale score 4, 5 or death). The two variables of interest were prodromal TIA and prodromal minor stroke (defined as a stroke that did not lead to coma, locked-in syndrome or tetraplegia), prior to basilar artery occlusion. We calculated risk ratios and corresponding 95% confidence intervals (CIs) with Poisson regression according to our two variables of interest. Ratios were adjusted for factors that affected the crude risk ratio more than 5%. Missing values were imputed with regression methods for baseline variables except the two variables of interest.

The BASICS protocol was approved by the Ethics committee of the University Medical Center Utrecht, Netherlands. The requirement for additional local ethical approval differed between participating countries and was obtained if needed. Verbal or written informed consent was obtained from the patient or patient's representative, as required by national and local guidelines. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

We enrolled 619 patients in 48 centres in Europe (41), South America (3), North America (2), Australia (1), and the Middle East (1) from November 1, 2002 to October 1, 2007. Information about prodromal TIA was available for 507 patients (83.5%) and about prodromal stroke for 487 patients (78.7%). Baseline data are shown in Table 1. Prodromal TIAs were reported in 21.9% of patients and prodromal minor strokes in 18.9% patients.

Poor outcome was observed in 71/113 (68%) patients with prodromal TIAs and in 76/92 (83%) patients with prodromal minor strokes. Prodromal minor stroke was associated with poor outcome (RR 1.26; 95% CI 1.12–1.42) but history of TIAs was not (RR 0.93; 95% CI 0.79–1.09) (Figure 1, Table 2). The associations remained essentially the same after adjustment for variables that affected crude risk ratio more than 5% (hyperlipidemia, NIHSS, location of occlusion and treatment).

DISCUSSION

Our secondary analyses of the BASICS registry data do not confirm the association of prodromal TIAs with a favorable outcome described in earlier series of patients with posterior circulation stroke. However, we did find a statistically significant association between the presence of prodromal minor stroke and worse outcome after basilar artery occlusion.

Whether or not TIAs trigger mechanisms of ischemic tolerance is still a matter of debate. Despite findings of possible protective effects of TIA in smaller series of patients with anterior or posterior circulation infarcts, no relation was found

Table 1 Baseline characteristics according to presence of prodromal transient ischemic attacks (TIAs) or minor strokes

	Prodromal TIAs		Prodromal minor strokes	
	Yes	No	Yes	No
	n=113	n=404	n=92	n=395
Mean age (SD)	61 (14)	64 (16)	63 (14)	63 (15)
Age ≤50 years	27 (24%)	81 (20%)	16 (17%)	85 (22%)
Age ≥70 years	30 (27%)	160 (40%)	32 (35%)	139 (35%)
Women	29 (26%)	160 (40%)	29 (32%)	143 (36%)
Hypertension	71 (63%)	248 (61%)	64 (70%)	227 (56%)
Diabetes mellitus	25 (22%)	86 (21%)	32 (35%)	77 (20%)
Hyperlipidemia	40 (35%)	110 (27%)	22 (36%)	106 (27%)
Atrial fibrillation	13 (12%)	88 (22%)	14 (15%)	83 (21%)
Coronary artery disease	21 (19%)	73 (18%)	17 (19%)	73 (19%)
Prodromal TIA			20/74 (27%)	81/367 (22%)
Prodromal stroke	20/101 (20%)	54/340 (16%)		
Deficit at time of treatment				
Mild to moderate	52 (46%)	165 (41%)	40 (44%)	157 (40%)
Severe	61 (54%)	239 (59%)	52 (56%)	238 (60%)
NIHSS score#	18 (9–28)	21 (12–30)	20 (11–28)	23 (12–30)
NIHSS score >20	51 (45%)	211 (52%)	43 (47%)	219 (55%)
Location occlusion				
Distal third	20 (18%)	143 (35%)	17 (19%)	129 (33%)
Middle third	30 (27%)	92 (23%)	25 (27%)	95 (24%)
Proximal third	63 (56%)	169 (42%)	50 (54%)	171 (43%)
Treatment				
None	2 (2%)	13 (3%)	4 (4%)	12 (3%)
Antithrombotic	36 (32%)	126 (31%)	33 (36%)	114 (29%)
Primary IVT ± IAT	18 (16%)	87 (22%)	11 (12%)	89 (23%)
Primary IAT	57 (50%)	178 (44%)	44 (48%)	180 (46%)
Time to treatment*				
0–3 h	29 (26%)	127 (33%)	29 (33%)	111 (29%)
3–6 h	34 (31%)	128 (33%)	28 (32%)	126 (33%)
7–9 h	17 (15%)	52 (13%)	10 (11%)	60 (16%)
>9 h	31 (28%)	84 (22%)	21 (24%)	86 (23%)

IVT = intravenous thrombolysis; IAT = primary intra-arterial therapy. * For treated patients. # Interquartile ranges in parentheses.

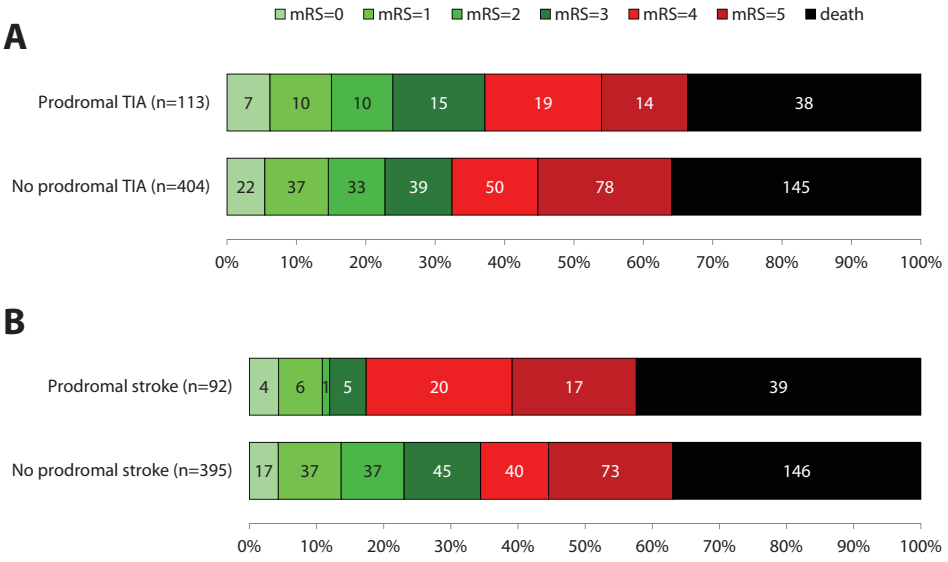

Figure 1 Modified Rankin scores in patients with prodromal transient ischemic attacks **(A)** and prodromal minor strokes **(B)**.

Table 2 Crude and adjusted risk ratios for poor outcome according to history of prodromal transient ischemic attack (TIA) or prodromal stroke

	Prodromal TIA	Prodromal stroke
Poor outcome	71/113 (63%) *vs.* 273/404 (68%)	76/92 (83%) *vs.* 259/395 (66%)
Crude risk ratio	0.93 (0.79–1.09)	1.26 (1.12–1.42)
Adjusted for		
Age	0.95 (0.81–1.11)	1.26 (1.12–1.42)
Sex	0.92 (0.79–1.08)	1.26 (1.12–1.41)
Hypertension	0.93 (0.79–1.09)	1.26 (1.12–1.42)
Diabetes mellitus	0.93 (0.80–1.09)	1.25 (1.11–1.41)
Hyperlipidemia	0.95 (0.81–1.10)	1.29 (1.15–1.45)
Atrial fibrillation	0.93 (0.79–1.08)	1.26 (1.12–1.41)
Severe deficit	0.96 (0.83–1.11)	1.29 (1.15–1.43)
NIHSS score	0.98 (0.84–1.13)	1.34 (1.20–1.50)
Location of occlusion	0.89 (0.76–1.04)	1.22 (1.09–1.38)
Treatment	0.93 (0.79–1.08)	1.24 (1.10–1.39)
Five variables*	0.96 (0.83–1.10)	
Four variables#		1.30 (1.16–1.45)

* Adjusted for age, sex, hyperlipidemia, NIHSS score and location of occlusion. # Adjusted for hyperlipidemia, NIHSS, location of occlusion and treatment.

between history of TIA and disability from stroke in the retrospective Northern California TIA study.[4] Likewise, and consistent with the results from BASICS, no association between history of TIA and outcome was reported in a retrospective series of patients older than 65 years with first-ever ischemic strokes,[5] and no relation was found between history of TIAs and mortality.[11]

The complexity of mechanisms involved in ischemic tolerance likely contributes to discrepancies between studies that include different patient populations. Candidate factors that likely influence these results are TIA duration, intervals between TIAs and stroke, as well as stroke etiology (lacunar vs. nonlacunar; atherosclerosis vs. other etiologies), timing of ischemia and development of collateral circulation.[11-14] A dose-dependent neuroprotective effect of chronic intermittent hypoxia on the ischemic brain has been reported.[15] Our findings do not discard a potential influence of prior TIAs on the induction of ischemic tolerance. It is possible that the number of prior TIAs was too limited to trigger enhancement of collateral flow. Also, in a large study as BASICS, heterogeneity of mechanisms involved across patients may have clouded net effects of TIAs on prognosis.

The worse outcome associated with a prodromal minor stroke could be explained by it being a marker of inadequate collateral flow and/or inability to enhance collateral flow. This failure would then predispose patients to worse stroke outcomes.[11] An alternative explanation is that minor stroke itself may be associated with increased disability, as indicated by smaller prospective studies that used milder definitions of minor stroke than BASICS.[16-23] In SPOTRIAS (Specialized Program of Translational Research in Acute Stroke), 20–43% of patients admitted with minor strokes (NIHSS scores, 0–3) were not discharged home.[23] In ASAP (Acute Stroke Accurate Prediction Study), 29% of patients with NIHSS scores from 0 to 5 had MRS scores from 2–6 at 90 days. Cognitive deficits, early worsening or medical complications may explain these results.[22]

In BASICS, the information of prodromal minor stroke was collected retrospectively and hence, there are no data available about severity of prodromal minor stroke. The definition of minor stroke was "a stroke that did not lead to coma, locked-in syndrome or tetraplegia". This definition likely classified as prodromal minor strokes, infarcts that were more severe than those reported in SPOTRIAS and ASAP. The definition of poor outcome of index strokes in BASICS was also more stringent (MRS

>3) and prognosis was evaluated at 1-month post-stroke instead of at 3 months as in ASAP. Neurological improvement can occur over several months after stroke, and worse outcomes can be obtained at shorter follow-ups. All variables considered, it is possible that residual neurological impairment and disability from the prodromal minor stroke may have contributed to worse outcomes after index strokes in BASICS.

The strength of this study is its prospective design with a large number of patients. A limitation might be recall bias as this may influence reporting the history of TIA or minor stroke, particularly in patients who present with severe neurological deficits. Under this condition, history is often obtained from family members who may not provide accurate information. Unfortunately, we were unable to obtain sufficient data on the number and duration of TIAs, and on the time interval between prodromal minor stroke and index event, although these variables were incorporated in the registry questionnaire. These factors could influence the predictive value of TIAs on outcome.

In order to clarify the association between prodromal ischemia and outcome, ongoing or future stroke registries should collect more detailed clinical and imaging data.

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Extent of hypoattenuation on CT angiography source images in basilar artery occlusion: Prognostic value in the Basilar Artery International Cooperation Study

Volker Puetz, Andrei Khomenko, Michael D. Hill, Imanuel Dzialowski, Patrik Michel, Christian Weimar, Christine A.C. Wijman, Heinrich P. Mattle, Stefan T. Engelter, Keith W. Muir, Thomas Pfefferkorn, David Tanne, Kristina Szabo, L. Jaap Kappelle, Ale Algra, Ruediger von Kummer, Andrew M. Demchuk, Wouter J. Schonewille; on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose The posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) quantifies the extent of early ischemic changes in the posterior circulation with a 10-point grading system. We hypothesized that pc-ASPECTS applied to CT angiography source images predicts functional outcome of patients in the Basilar Artery International Cooperation Study (BASICS).

Methods BASICS was a prospective, observational registry of consecutive patients with acute symptomatic basilar artery occlusion. Functional outcome was assessed at 1 month. We applied pc-ASPECTS to CT angiography source images of patients with CT angiography for confirmation of basilar artery occlusion. We calculated unadjusted and adjusted risk ratios (RRs) of pc-ASPECTS dichotomized at ≥8 versus <8. Primary outcome measure was favorable outcome (modified Rankin Scale scores 0–3). Secondary outcome measures were mortality and functional independence (modified Rankin Scale scores 0–2).

Results Of 158 patients included, 78 patients had a CT angiography source images pc-ASPECTS ≥8. Patients with a pc-ASPECTS ≥8 more often had a favorable outcome than patients with a pc-ASPECTS <8 (crude RR 1.7; 95% CI 0.98–3.0). After adjustment for age, baseline National Institutes of Health Stroke Scale score, and thrombolysis, pc-ASPECTS ≥8 was not related to favorable outcome (RR 1.3; 95% CI 0.8–2.2), but it was related to reduced mortality (RR 0.7; 95% CI 0.5–0.98) and functional independence (RR 2.0; 95% CI 1.1–3.8). In post hoc analysis, pc-ASPECTS dichotomized at ≥6 versus <6 predicted a favorable outcome (adjusted RR 3.1; 95% CI 1.2–7.5).

Conclusions pc-ASPECTS on CT angiography source images independently predicted death and functional independence at 1 month in the CT angiography subgroup of patients in the BASICS registry.

INTRODUCTION

Despite recent advances in the treatment of patients with acute ischemic stroke, the rate of death or disability associated with basilar artery occlusion (BAO) remains high.[1] If treated conventionally, nearly 80% of patients die or survive with severe disability.[2] Because of this poor prognosis, treating physicians are tempted to use the most aggressive treatment approach available. Intravenous (IV) thrombolysis, IV thrombolysis followed by intra-arterial (IA) therapy, or IA therapy alone are the most frequently used recanalization strategies. However, predicting a treatment benefit from such therapies is difficult. Up to 75% of patients with BAO have a poor functional outcome despite the use of recanalization therapies.[1,3]

In patients with an acute ischemic stroke in the anterior circulation, the extent of early ischemic changes on pretreatment noncontrast CT or diffusion-weighted MRI predicts functional outcome and treatment response to IV and IA thrombolysis.[4-7] Compared with noncontrast CT, CT angiography (CTA) source images (CTA-SI) are more accurate in predicting the final extent of infarction and clinical outcome.[8-11] Recent studies have suggested that the extent of hypoattenuation on CTA-SI, quantified with the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) or the Pons–midbrain-index, predicts functional outcome of patients with BAO.[12,13] Patients with extensive CTA-SI hypoattenuation (pc-ASPECTS <8 or Pons-midbrain-index ≥3) were unlikely to achieve a favorable outcome despite IA thrombolysis or recanalization of the basilar artery, respectively.

The Basilar Artery International Cooperative Study (BASICS) was a prospective international observational registry of consecutive patients with radiologically confirmed acute symptomatic BAO.[1] We hypothesized that the extent of hypoattenuation on CTA-SI predicts functional outcome of patients in the BASICS registry.

METHODS

Patients

The BASICS registry opened in November 2002 and closed in October 2007. Patients were eligible if they presented with symptoms or signs attributable to posterior circulation ischemia and had BAO confirmed by CTA, MR angiography,

or conventional digital subtraction angiography. Treatments were allocated at the discretion of the treating physician. Details of the registry protocol have been described previously.[1,14]

Inclusion criterion for the present study was confirmation of BAO by CTA. To ensure CTA experience, we limited participation to BASICS centers who used CTA in ≥10 patients in the registry. Patients who had been treated with IV thrombolysis in peripheral hospitals in a "drip and ship" approach were included if they had persistent BAO on CTA on arrival at the BASICS center.[15] We excluded patients in whom CTA images were not available electronically, were of inadequate technical quality, or if additional imaging findings (eg, tumor, hemorrhage) with influence on functional outcome were present.

For the BASICS registry, detailed data were recorded with a web-based data entry form that included information on baseline characteristics, stroke risk factors, estimated time of BAO, prodromal minor stroke, location of occlusion, type and timing of treatment, neurological deficits at the time of treatment as assessed with the National Institutes of Health Stroke Scale (NIHSS) score, and functional outcome at 1 month as assessed with the modified Rankin Scale (mRS) score.[1]

The BASICS protocol was approved by the ethics committee of the University Medical Center Utrecht, Utrecht, The Netherlands. The requirement for additional local ethical approval differed between participating countries and was obtained if required. Verbal or written informed consent was obtained from the patient or patient's representative as required by national and local guidelines.

Image collection

We requested all available CTA images of patients who fulfilled the inclusion criteria from the BASICS sites. Digital Imaging and Communications in Medicine format images were transferred to Dresden University Stroke Center for central interpretation. CTAs were performed according to the local protocols of the participating BASICS sites.

Image analysis

We reviewed axial Digital Imaging and Communications in Medicine format CTA images with 0.8-mm to 6.0-mm slice thickness on a high-resolution monitor. We adjusted window and level individually to allow maximum contrast differentiation on CTA-SI. Regions of relatively diminished contrast enhancement were scored as abnormal. Images were analyzed in a 3-readers consensus setting by stroke neurologists experienced in the interpretation of CTA-SI in acute ischemic stroke (A.M.D., I.D., V.P.).[12,16] Readers were blinded to clinical information. We graded hypoattenuating areas in posterior circulation territories with the pc-ASPECTS score and the Pons-midbrain-index as described before (Figure 1).[12,13]

Pc-ASPECTS allots the posterior circulation 10 points. One point each is subtracted for hypoattenuation on CTA-SI in the left or right thalamus, cerebellum, or posterior cerebral artery territory, respectively, and 2 points each are subtracted for hypoattenuation on CTA-SI in any part of the midbrain or pons. A pc-ASPECTS of 10 indicates absence of visible posterior circulation ischemia, and a score of 0 indicates hypoattenuation in all pc-ASPECTS territories.

For the Pons-midbrain-index, CTA-SIs were analyzed for hypoattenuation bilaterally in the pons and midbrain. Each side was graded as: 0, no hypoattenuation; 1, ≤50% hypoattenuation; or 2, >50% hypoattenuation. A Pons-midbrain-index of 0 indicates absence of CTA-SI hypoattenuation in the midbrain and pons, and a score of 8 indicates >50% hypoattenuation bilaterally in these brain stem territories.

Outcome measures

The primary outcome measure was favorable outcome, defined as an mRS score of 0 to 3, at 1 month. Secondary outcome measures were functional independence (mRS score of 0–2) and death.

Hypothesis

Our primary hypothesis was that the CTA-SI pc-ASPECTS score, dichotomized at ≥8 versus <8, predicted primary and secondary outcome measures of patients in the BASICS registry.[12] As a secondary hypothesis we assessed whether the Pons-midbrain-index dichotomized at <3 versus ≥3 predicted these outcome measures.[13]

Statistical analysis

Data are reported using standard descriptive statistics. We calculated unadjusted and adjusted risk ratios (RRs) of the imaging variables (pc-ASPECTS and Pons-

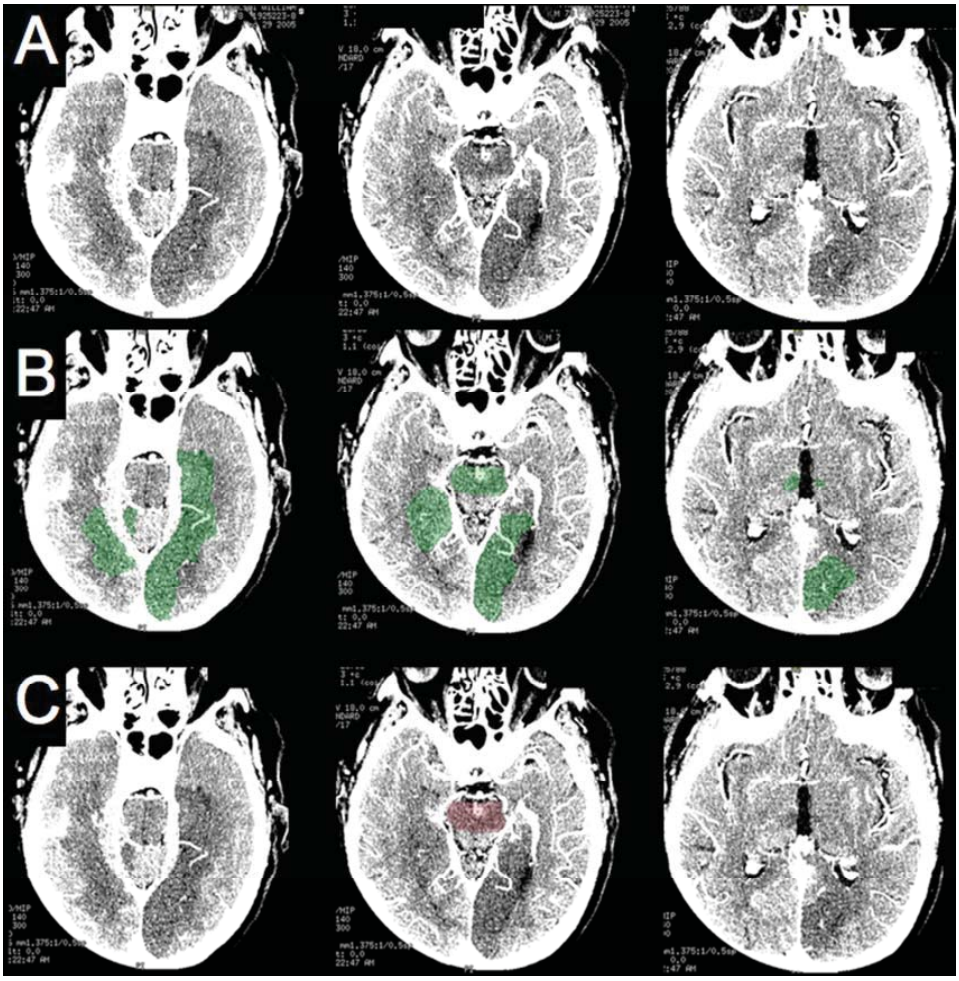

Figure 1 Example of a patient from the BASICS registry. CT angiography source images **(A)** demonstrate hypoattenuation in the posterior circulation. For pc-ASPECTS **(B)**, hypoattenuation (marked green) in both posterior cerebral artery territories (1 point each), the right cerebellum (1 point), both thalami (1 point each), and the midbrain (2 points) resulted in a pc-ASPECTS score of 3. For the Pons-midbrain-index **(C)**, >50% hypoattenuation (marked red) bilaterally in the midbrain (2 points each) resulted in a Pons-midbrain-index of 4. (Note that pc-ASPECTS ranges from 0 to 10 in which 10 is best and the Pons-midbrain-index ranges from 0 to 8 in which 0 is best.) BASICS indicates Basilar Artery International Cooperation Study; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score.

midbrain-index) for primary and secondary outcome measures. Adjusted models were initially derived to account for age, gender, baseline NIHSS score, prodromal minor stroke, diabetes mellitus, onset-to-CTA time, location of occlusion, and thrombolytic treatment as reported in the primary analysis of the BASIC registry.[1] However, due to the smaller numbers of outcomes in this subset of the BASICS cohort, we could adjust for a maximum of 3 variables simultaneously only. The variables that had the strongest influence on crude RR in univariable adjustment were selected for adjustment.

For the analysis, we combined the IV, IA and IV–IA treatment groups to a thrombolysis group and used thrombolysis as a binary variable. We considered main effects only. Because we were specifically interested in the role that imaging played in predicting outcome, imaging variables (pc-ASPECTS or Pons-midbrain-index) were considered forced variables in these models. We used a generalized linear modeling approach with log link to directly derive RRs.

To assess differences in the relation between pc-ASPECTS and outcome between patients who received thrombolysis and those who did not, we did an interaction test using a Wald test within a multivariable model. In some cases, we were missing potential predictor variables (eg, NIHSS score) for a small number of patients (n=11). Where this occurred, we imputed the median NIHSS score for these patients to allow us to derive adjusted models for the entire data set.

RESULTS

Patients

Of 619 patients who were registered in the BASICS registry, 27 patients were excluded from the analysis because they did not receive any antithrombotic or thrombolytic therapy. Of the remaining 592 patients who were analyzed in the BASICS registry, 259 patients were registered by centers with ≥10 patients in the registry and had CTA confirmation of BAO (Figure 2). Of these, Digital Imaging and Communications in Medicine format CTA images were available from 161 patients. Three further patients were excluded because CTA images did not cover sufficient brain structures to determine pc-ASPECTS (n=2) or showed subdural hematoma (n=1).

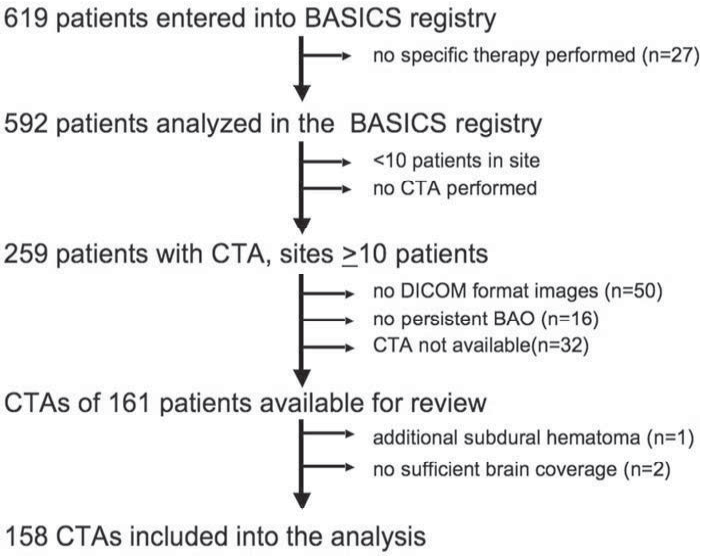

Figure 2 Patient selection. Inclusion and exclusion criteria are specified in the text. CTA indicates CT angiography.

The final analysis included 158 patients from 12 BASICS centers. The mean age was 65_15 years, 64% were men, and the median baseline NIHSS score was 25 (interquartile range, 24). CTAs were performed after a median time of 234 minutes (interquartile range, 349) since the estimated time of BAO. Overall, 62 patients (39%) were treated with antithrombotic therapies, 15 patients (9%) with IV thrombolysis, 53 patients (34%) with chemical or mechanical IA thrombolysis, and 28 patients (18%) with combined IV–IA treatment regimens. Three patients had been treated with IV thrombolysis before confirmation of BAO.

At 1 month, 40 patients (25%) had a favorable outcome (mRS scores 0–3), 49 patients (31%) survived with an unfavourable outcome (mRS scores 4–5), and 69 patients (44%) had died. The overall median pc-ASPECTS on CTA-SI was 7 (interquartile range, 4) and the median Pons-midbrain-index on CTA-SI was 2 (interquartile range, 4).

Association of imaging findings with functional outcome

Primary hypothesis: pc-ASPECTS dichotomized at >8 versus <8

Seventy-eight patients had a CTA-SI pc-ASPECTS ≥8. Baseline clinical data according to categorized CTA-SI pc-ASPECTS groups are summarized in Table 1. Compared with patients with a CTA-SI pc-ASPECTS ≥8, patients with a score <8 were less likely to receive IV or IA thrombolysis.

Compared with patients with a CTA-SI pc-ASPECTS <8, patients with a CTA-SI pc-ASPECTS ≥8 tended to have more often a favorable outcome (RR 1.7; 95% CI 0.98–3.0), were more likely to be functionally independent (RR 2.1; 95% CI 0.98–4.3), and less likely to die (RR 0.6; 95% CI 0.4–0.9; Table 2; Figure 3). After adjustment for age, baseline NIHSS score, and thrombolysis, pc-ASPECTS ≥8 was not related

Table 1 Baseline characteristics according to categorized CTA-SI pc-ASPECTS groups

	pc-ASPECTS	
Parameter	8–10	0–7
Number, n	78	80
Age (years), median (iqr)	66.5 (20)	64.5 (21)
Male sex, n (%)	49 (63)	52 (65)
Baseline NIHSS score, median (iqr)	25 (18)	26.5 (16)
Onset-to-CTA time (min), median (iqr)	232 (314)	234 (432)
Prodromal minor stroke, n (%)	13 (17)	12 (15)
Treatment category, n (%)		
Antithrombotics	23 (29)	39 (49)
IV thrombolysis	9 (12)	6 (8)
IA therapy	31 (40)	22 (28)
IV-IA	15 (19)	13 (16)
Any thrombolysis, n (%)	55 (71)	41 (51)
Time to thrombolysis (min), median (iqr)	290 (240)	300 (360)
Vascular risk factors, n (%)		
Diabetes mellitus	16 (21)	15 (19)
Arterial hypertension	49 (63)	47 (59)
Atrial fibrillation	17 (22)	11 (14)
Coronary artery disease	11 (14)	11 (14)
Current smoking	19 (24)	12 (15)
Hypercholesterolemia	22 (28)	21 (26)
Peripheral vascular disease	8 (10)	2 (3)

Table 2 Relation of pc-ASPECTS on CTA-SI (>8 versus <8) with functional outcome

	pc-ASPECTS		Risk ratio (95% CI)	
Outcome	8–10	0–7	Unadjusted	Adjusted*
Number, n	78	80	-	-
Primary outcome measure				
mRS ≤3, % (n)	32 (25)	19 (15)	1.7 (0.98–3.0)	1.3 (0.8–2.2)
Secondary outcome measures				
mRS ≤2, % (n)	23 (18)	11 (9)	2.1 (0.98–4.3)	2 (1.1–3.8)
Death, % (n)	32 (25)	55 (44)	0.6 (0.4–0.9)	0.7 (0.5–0.98)

* Models were adjusted for baseline NIHSS score, age and thrombolytic therapy.

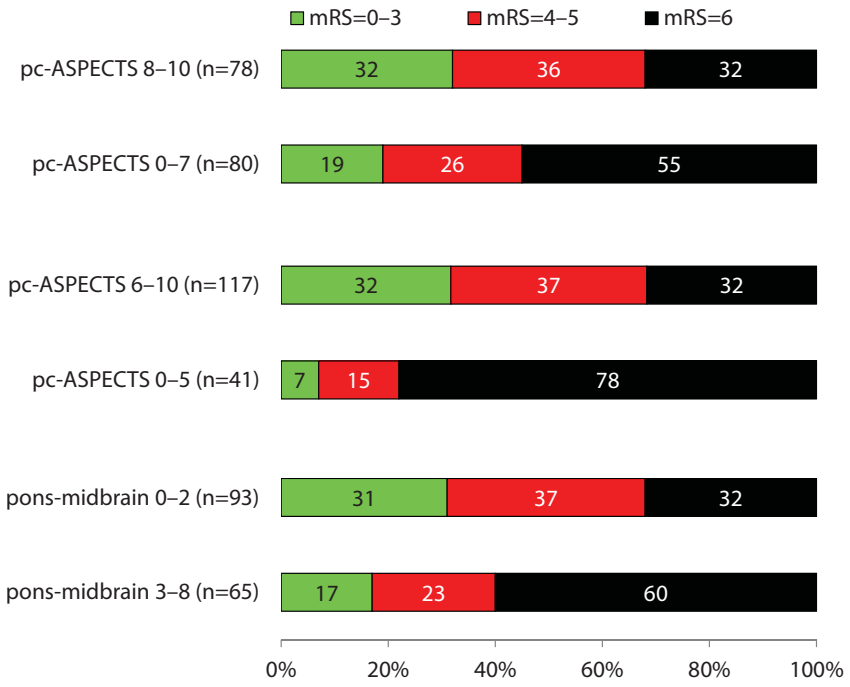

Figure 3 Distribution of functional outcomes according to dichotomized pc-ASPECTS and Pons-midbrain-index, respectively.

to favorable outcome (RR 1.3; 95% CI 0.8–2.2), but it was related to functional independence (RR 2.0; 95% CI 1.1–3.8) and reduced risk of death (RR 0.7; 95% CI 0.5–0.98; Table 2). The relationship of pc-ASPECTS (≥8 and <8) and the primary and secondary outcome measures was not different between patients who did or did not receive thrombolysis (P interaction >0.05, Wald test).

Secondary hypothesis: Pons-midbrain-index dichotomized at <3 versus ≥3

The Pons-midbrain-index, dichotomized at <3 versus ≥3, was associated with a favorable outcome (RR 1.8; 95% CI 0.99–3.4; Table 3), functional independence (RR 2.0; 95% CI 0.9–4.4), and a reduced risk of death (RR 0.5; 95% CI 0.3–0.8; Figure 3). After adjustment for age, baseline NIHSS score, and thrombolysis, the magnitude of the effect was slightly attenuated for death (RR 0.6; 95% CI 0.4–0.8) and not statistically significant for favorable outcome (RR 1.5; 95% CI 0.8–2.6) or functional independence (RR 1.7; 95% CI 0.9–3.4).

Post hoc analysis: pc-ASPECTS dichotomized at ≥6 versus <6

A review of the distribution of the mRS scores according to the CTA-SI pc-ASPECTS scores in the present study suggested that pc-ASPECTS values in 2 categories (≥6 and <6) best discriminated a favorable outcome from an unfavorable outcome and death. We performed a post hoc analysis to assess whether the CTA-SI pc-ASPECTS score dichotomized at ≥6 versus <6 predicted favorable outcome.

Thirty-seven of 117 patients (32%) with a CTA-SI pc-ASPECTS ≥6 compared with 3 of 41 patients (7%) with a CTA-SI pc-ASPECTS <6 had a favorable outcome (RR 4.3; 95% CI 1.4–13.3; Table 3; Figure 3). After adjustment for age, baseline NIHSS score, and thrombolysis, pc-ASPECTS dichotomized at ≥6 versus <6 was an independent predictor of favorable outcome (RR 3.1; 95% CI 1.2–7.5).

Table 3 Relation of Pons-midbrain-index (<3 versus >3) and pc-ASPECTS (>6 versus <6) on CTA-SI with favourable outcome

	Pons-midbrain-index		Risk ratio (95% CI)		pc-ASPECTS		Risk ratio (95% CI)	
Outcome	0–2	3–8	Unadjusted	Adjusted*	6–10	0–5	Unadjusted	Adjusted*
Number, n	93	65	-	-	117	41	-	-
mRS ≤3, % (n)	31 (29)	17 (11)	1.8 (0.99–3.4)	1.5 (0.8–2.6)	32 (37)	7 (3)	4.3 (1.4–13.3)	3.1 (1.2–7.5)

* Models were adjusted for baseline NIHSS score, age and thrombolytic therapy.

DISCUSSION

Our study demonstrates that pc-ASPECTS on CTA-SI, dichotomized at ≥8 versus <8, predicts functional independence (mRS scores 0–2) and death at 1 month in the CTA subgroup of the BASICS registry population. Furthermore, pc-ASPECTS dichotomized at ≥6 versus <6 was an independent predictor of favorable outcome (mRS scores 0–3) in this population.

In BASICS, nearly 70% of patients had a poor functional outcome despite the initiation of IV or IA recanalization therapies.[1] The present study confirms that the extent of hypoattenuation on CTA-SI is independently related to the functional outcome of patients with BAO. Whereas dichotomization of the pc-ASPECTS score at ≥8 versus <8 predicted a favorable outcome (mRS scores 0–3) in the pc-ASPECTS study, dichotomization at lower pc-ASPECTS scores (≥6 versus <6) predicted favorable outcome in the present study.[12] Potential explanations for the lower pc-ASPECTS threshold in the BASICS registry are the absence of time window exclusion criteria and the inclusion of patients with prodromal minor stroke.

MRI with diffusion-weighted imaging sequences is the diagnostic "gold standard" in patients with posterior circulation stroke.[17] A recent study has confirmed the prognostic value of pc-ASPECTS if applied to diffusion-weighted imaging of patients with posterior circulation stroke.[18] However, the feasibility of MRI acquisition is limited in these frequently unstable patients.[19,20] We have recently demonstrated that CTA-SIs increase the sensitivity for early ischemic changes in the posterior circulation compared with noncontrast CT.[12,16] Compared with CTA-SI, perfusion CT techniques may provide additional diagnostic and prognostic information in patients with acute posterior circulation stroke.[21,22] The comparison of CTA, perfusion CT, and multimodal MRI to predict functional outcome and treatment response in patients with BAO could be the subject of future studies.

We have applied 2 semiquantitative scores to assess the extent of CTA-SI hypoattenuation: the pc-ASPECTS score and the Pons-midbrain-index.[12,13] Both scores were related with functional outcome in our study. Although both scores emphasize ischemic changes in the brain stem, pc-ASPECTS assesses ischemic changes in additional posterior circulation territories with prognostic relevance. Future studies should assess whether 1 score provides superior prognostic information in a subgroup of patients with BAO.

The optimal treatment regimen for patients with BAO is unknown. A recent meta-analysis has demonstrated that IA compared with IV thrombolysis is not associated with improved functional outcome in patients with BAO.[3] In line with these results, the BASICS registry did not identify an overall treatment benefit of IA therapies compared with IV thrombolysis or antithrombotic treatment regimens.[1] We could not demonstrate a pc-ASPECTS by thrombolysis interaction in our study. Our data therefore do not support withholding thrombolytic therapies in patients with basilar artery occlusion and extensive CTA-SI hypoattenuation. However, this analysis has low power due to small numbers. Therefore, failure to show a statistical interaction effect could be due to a Type 2 error. The BASICS trial will randomize patients with BAO to IV thrombolysis or a combined IV–IA treatment approach. We plan to test for a pc-ASPECTS by treatment–category interaction as a prespecified imaging substudy in the BASICS trial. The demonstration of such an interaction may have implications for the clinical management of patients with BAO.

We were not able to collect all CTAs of patients in the BASICS registry. Our results may therefore be influenced by selection bias. Because BASICS had no time window exclusion criteria, we may have misinterpreted subacute ischemic changes as early ischemic changes in our study. Because follow-up images were not available, we cannot comment on the accuracy of CTA-SI to predict infarction in the present study. Patients in the BASICS registry were not treated under a treatment protocol and different treatment regimens may have influenced the importance of imaging findings on functional outcomes in our study. Because the functional status of patients with BAO may still improve after 1 month, the assessment of functional outcomes after a longer rehabilitation period may have caused different results. Moreover, this imaging substudy was not prospectively designed as part of the BASICS registry. However, images were prospectively and blindly analyzed with prespecified imaging criteria and prespecified imaging hypotheses based on the results of published literature.[12,13]

In summary, our study confirms the prognostic relevance of early ischemic changes on CTA-SI in patients with acute symptomatic BAO. Patients with BAO and extensive hypoattenuation on CTA-SI were unlikely to achieve a favorable functional outcome. A potential pc-ASPECTS-by-treatment-category interaction will be prospectively analyzed as an imaging substudy in the BASICS trial.

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14

Diagnostic and prognostic impact of pc-ASPECTS applied to perfusion CT in the Basilar Artery International Cooperation Study

Lars-Peder Pallesen, Johannes Gerber, Imanuel Dzialowski, Erik J.R.J. van der Hoeven, Patrik Michel, Thomas Pfefferkorn, Christoph Ozdoba, L. Jaap Kappelle, Baerbel Wiedemann, Andrei Khomenko, Ale Algra, Michael D. Hill, Ruediger von Kummer, Andrew M. Demchuk, Wouter J. Schonewille, Volker Puetz; on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose The posterior circulation Acute Stroke Prognosis Early CT Score (pc-APECTS) applied to CT angiography source images (CTA-SI) predicts the functional outcome of patients in the Basilar Artery International Cooperation Study (BASICS). We assessed the diagnostic and prognostic impact of pc-ASPECTS applied to perfusion CT (CTP) in the BASICS registry population.

Methods We applied pc-ASPECTS to CTA-SI and cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) parameter maps of BASICS patients with CTA and CTP studies performed. Hypoattenuation on CTA-SI, relative reduction in CBV or CBF, or relative increase in MTT were rated as abnormal.

Results CTA and CTP were available in 27/592 BASICS patients (4.6%). The proportion of patients with any perfusion abnormality was highest for MTT (93%; 95% confidence interval [CI], 76%–99%), compared with 78% (58%–91%) for CTA-SI and CBF, and 46% (27%–67%) for CBV ($p<.001$). All 3 patients with a CBV pc-ASPECTS <8 compared to 6/23 patients with a CBV pc-ASPECTS ≥8 had died at 1 month (RR 3.8; 95% CI 1.9–7.6).

Conclusion CTP was performed in a minority of the BASICS registry population. Perfusion disturbances in the posterior circulation were most pronounced on MTT parameter maps. CBV pc-ASPECTS <8 may indicate patients with high case fatality.

INTRODUCTION

Although there has been progress in the management of patients with acute ischemic stroke, acute symptomatic basilar artery occlusion is associated with a high risk for death or survival with severe disability.[1] Due to absence of data from randomized controlled trials, treatment decision-making in individual patients remains challenging.[2] In the Basilar Artery International Cooperation Study (BASICS), intra-arterial (IA) thrombolysis alone was not associated with improved functional outcome compared to intravenous (IV) thrombolysis with or without additional IA thrombolysis.[3]

We have recently shown that the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) applied to CT angiography source images (CTA-SI) predicts independent functional outcome and death of patients with acute symptomatic basilar artery occlusion in the BASICS registry population.[4] Patients with extensive ischemic changes on CTA-SI, defined by CTA-SI pc-ASPECTS <8, were unlikely to achieve an independent functional outcome and had a high risk to die. A recent study has validated the prognostic value of pc-ASPECTS applied to magnetic resonance imaging (MRI) with diffusion-weighted images (DWIs) in patients with basilar artery occlusion who were treated with IV and IA thrombolysis.[5] However, the feasibility of MRI is limited in these frequently unstable patients.[6]

Perfusion CT (CTP) delineates the ischemic core and the ischemic penumbra and may identify patients with improved benefit from recanalizing therapies.[7] The benefit from CTP in patients with posterior circulation stroke and particularly basilar artery occlusion has not been systematically analyzed. We sought to assess the diagnostic and prognostic impact of pc-ASPECTS applied to perfusion CT of patients with acute symptomatic basilar artery occlusion from the BASICS registry population.

MATERIALS AND METHODS

Patients

BASICS was a prospective observational multicenter registry, which opened in November 2002 and closed in October 2007. The detailed study protocol has been described previously.[8] Basilar artery occlusion was confirmed with either

CTA, MRA (magnetic resonance angiography), or digital DSA (digital subtraction angiography).

The patient population of this study is a subgroup of those BASICS patients who have been analyzed in the recently published BASICS-CTA study.[4] The BASICS-CTA study included patients with confirmation of BAO by CTA from BASICS centers who used CTA in 10 or more patients in the registry. The latter criterion was applied to ensure CTA experience of centers. Patients who had been treated with IV thrombolysis in peripheral hospitals in a "drip and ship" approach were included if they had persistent BAO on CTA on arrival at the BASICS center.[9] For this study we included the subgroup of patients from the BASICS-CTA study who underwent additional CTP at baseline. The decision to perform additional CTP was at the discretion of the treating stroke neurologist and neuroradiologist. The reasons to perform additional CTP were not prospectively collected as part of the BASICS registry.

As part of the BASICS registry, detailed clinical information was prospectively recorded including the baseline NIHSS score, stroke risk factors, and the acute treatment modality. Diagnostic concerning recanalization was not mandatory for the BASICS registry but was recorded in individual cases with CTA, MRI, transcranial Doppler, and DSA. All data were collected in a central web-based data entry form. The primary clinical outcome measure was favorable functional outcome defined as mRS scores of 0–3 at 1 month. Secondary outcome measure was death.

The BASICS study protocol was approved by the ethics committee of the University Medical Center Utrecht, The Netherlands. Further ethics approval was obtained by local ethics committees of participating centers if required by local authorities.

Images

CTA and CTP studies were performed according to local protocols of the participating BASICS sites. Acquisition times were 40 seconds in 18 patients, 60 seconds in 7 patients, and 45 seconds in 2 patients, respectively. Slice thicknesses were 10 mm in 20 patients, 5 mm in 6 patients, and 8 mm in 1 patient, respectively. The choice of the arterial input function was performed via manually chosen region of interest in the anterior circulation. For all patients simple deconvolution

technique was used. For the analysis, we used CTP parameter maps for cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) that had been generated at the individual BASICS sites according to local protocols. Digital Imaging and Communications in Medicine (DICOM) format CTP parameter maps were transferred to Dresden University Stroke Center for central interpretation.

Image analysis

We reviewed CTA-SI and CTP parameter maps on a high-resolution monitor in a 3-reader-consensus setting. CTA-SI were analyzed by stroke neurologists experienced in the interpretation of CTA-SI in patients with acute ischemic stroke (AMD, VP, ID).[4] CTP parameter maps were analyzed by one neuroradiologist (JCG) and two stroke neurologists (VP, LPP) in a different reading session more than 6 months after interpretation of CTA-SI. All readers were blinded to clinical information, treatment modality, and functional outcome.

We assigned pc-ASPECTS to CTA-SI and CTP parameter maps (Figure 1). pc-ASPECTS allots the posterior circulation territories 10 points.[10] One point each is subtracted for presence of perfusion changes on CTP parameter maps in the left or right thalamus, cerebellum, and posterior cerebral artery (PCA) territory; two points each are subtracted for hypoattenuation or perfusion deficits in any part of the pons and midbrain. A pc-ASPECTS score of 10 indicates absence of ischemic changes in the posterior circulation; a pc-ASPECTS score of 0 indicates presence of ischemic changes in all pc-ASPECTS regions.

For CTA-SI, we reviewed axial DICOM-format CTA images with 0.8- to 6.0-mm slice thickness. We adjusted window and level individually to allow maximum contrast differentiation on CTA-SI. Regions with relatively diminished contrast enhancement compared to nonaffected regions (ie, contralateral side, different vascular territories) were scored as abnormal.

For CTP, we applied pc-ASPECTS to color-coded CBV, CBF, and MTT parameter maps. As time-to-peak (TTP) parameter maps were only available in a small (n=10) number of BASICS patients with CTP studies performed, we did not include analysis of TTP parameter maps in our study. We rated regions with visible qualitative changes on color-coded maps compared to nonaffected regions (ie, contralateral

side, different vascular territories) as abnormal. A visible qualitative reduction in CBV or CBF, or visible qualitative increase in MTT on color-coded maps was rated as abnormal (Figure 1).[7]

The primary target of our study was to analyze whether perfusion disturbances in patients with basilar artery occlusion could be detected on CTP parameter maps and whether more extensive ischemic changes were associated with poor functional outcome. For this purpose we wanted to avoid any overestimation of ischemic changes.

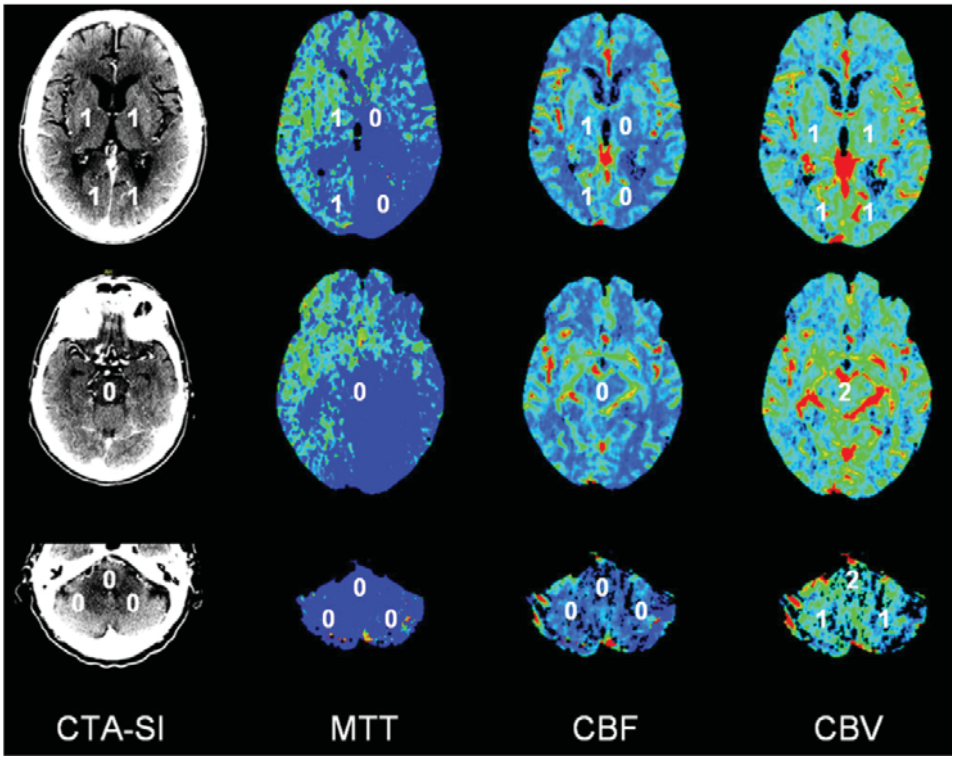

Figure 1 Example of the application of pc-ASPECTS to CTA-SI and CTP parameter maps in a 73-year-old male from the BASICS registry (baseline NIHSS score 7, acute treatment with IV heparin only; complete recanalization of the basilar artery on follow-up CTA after 24 hours; mRS score of 1 at 1 month). The first column shows CTA-SI with hypoattenuation in the pons, midbrain, and cerebellum with a resulting pc-ASPECTS score of 6. The second column (MTT) demonstrates MTT delay in the left thalamus, left PCA territory, midbrain, pons and cerebellum resulting in a pc-ASPECTS score of 2. MTT is also mildly increased in the left middle cerebral artery territory due to pre-existing carotid artery stenosis. The third column (CBF) displays CBF delay in the same pattern as MTT (pc-ASPECTS score 2). CBV parameter maps demonstrate no decreased CBV, thus resulting in a pc-ASPECTS score of 10.

For the analysis, we therefore rated pc-ASPECTS regions that were not represented on the available CTP parameter maps as normal (ie, no presence of ischemic changes).

Statistical analysis

Standard descriptive and explorative statistical analysis was performed using SPSS (version 19.0; Chicago, IL, USA). We calculated the percentages of patients with presence of any ischemic changes (ie, pc-ASPCETS <10) on CTA-SI and CTP parameter maps and used the Cochran's Q test for comparison. The median pc-ASPECTS values for the different imaging modalities were compared with the Friedman test. Based on prior analysis we calculated risk ratios to test whether pc-ASPECTS dichotomized at ≥8 versus <8 was associated with favorable functional outcome and death.[4,10] Multivariable analyses regarding the association between pc-ASPECTS scores and outcome were calculated using binary logistic regression analysis adjusting for age and stroke severity.

RESULTS

Patients

Of 592 patients in the BASICS registry, basilar artery occlusion was confirmed with CTA in 259 patients of whom CTA-SI from BASICS sites with 10 or more patients were available for review in 158 patients.[4] Among these 158 patients, an additional baseline CTP study was performed in 27 patients from 4 BASICS sites (4.6% of the BASICS registry population). These were 18 men (67%) and 9 women (33%) with an overall median age of 62 years (interquartile range [IQR] 49–77). Clinical baseline characteristics and vascular risk factors are summarized in Table 1.

Fifteen patients (56%) were treated with antithrombotics only, 7 patients (26%) were treated with IA thrombolysis, 3 patients (11%) were treated with IV thrombolysis, and 2 patients (7%) were treated with combined IV-IA treatment regimens (Table 1). The median (IQR) time from the estimated time of basilar artery occlusion to initiation of thrombolysis was 6 (2.5-9.5) hours. Overall at 1 month, 9 patients (33%) had a favorable functional outcome (mRS scores 0–3), 8 patients (30%) survived with an unfavorable outcome (mRS scores 4–5), and 10 patients (37%) had died.

Table 1 Clinical baseline characteristics and treatment category

Characteristic	BASICS registry population	CTP subgroup
Number of patients, n	592	27
Male gender, n (%)	374 (63)	18 (67)
Baseline NIHSS score, median (IQR)	22 (11–30)	19 (7–31)
Age (years), median (IQR)	63 (55–75)	62 (49–77)
Onset-to-CTA time (min), median (IQR)	–	145 (103–389)
Vascular risk factors, n (%)		
Diabetes	128 (22)	5 (19)
Arterial hypertension	365 (62)	17 (63)
Atrial fibrillation	126 (21)	3 (11)
Hyperlipidemia	163 (28)	11 (41)
Peripheral vascular disease	30 (5)	1 (4)
Coronary artery disease	106 (18)	2 (7)
Current smoking	105 (18)	5 (19)
Treatment modality, n (%)		
Antithrombotics	183 (31)	15 (56)
Intravenous	80 (14)	3 (11)
Intraarterial	288 (49)	7 (26)
Intravenous/intraarterial	41 (7)	

IQR = interquartile range; GCS = Glasgow coma scale.

Imaging data

Images were available in 27 patients (100%) for CTA-SI and CBF and MTT parameter maps, and in 26 patients (96%) for CBV parameter maps. CTP parameter maps consisted of 2 axial cuts in 2 patients (7%), 4 axial cuts in 15 patients (56%), 8 axial cuts in 4 patients (15%), and 16 axial cuts in 6 patients (22%). On CTP parameter maps, the individual pc-ASPECTS regions were represented in all 27 patients (100%) for the PCA-territory, 26 patients (96%) for the thalami, 15 patients (56%) for the cerebellum, 19 patients (70%) for the midbrain, and 5 patients (19%) for the pons, respectively. On CTA-SI, the individual pc-ASPECTS regions were represented in all patients (100%). All individual pc-ASPECTS regions were represented on CTA-SI and all CTP parameters maps in 4 of the 27 patients.

The proportion of patients with any perfusion abnormality in the posterior circulation (ie, pc-ASPECTS <10) was 93% (95% confidence interval [CI], 76%–99%) for MTT parameter maps, 78% (95% CI 58%–91%) for both CTA-SI and CBF parameter

Table 2 Percentage of patients with any ischemic changes and median pc-ASPECTS values for the different imaging modalities

Imaging modality	Any ischemic changes % (95% CI)	p-value	pc-ASPECTS value median (IQR)	p-value
MTT	93 (76–99)	<0.001*	6 (5–8)	<0.001†
CTA-SI	78 (58–91)		7 (5–9)	
CBF	78 (58–91)		8 (6–9)	
CBV	46 (27–67)		10 (9–10)	

* Cochran's Q test. † Friedman test.

maps, and 46% (95% CI 27%–67%) for CBV parameter maps (Table 2; Cochran's Q test, p<.001). The median pc-ASPECTS value was lowest (ie, more extended ischemic changes) for MTT parameter maps (median 6; IQR 5–8), followed by CTA-SI (7; IQR 5–9), CBF parameter maps (8; IQR 6–9), and CBV parameter maps (10; IQR 9–10) (Table 2; Friedman test, p<.001).

Recanalization status within 24 hours was assessed in 9 of 27 patients demonstrating recanalization of the basilar artery in 6 patients. The pc-ASPECTS for all CTP modalities and the CTA-SI was not associated with recanalization (p>.05). Moreover, pc-ASPECTS was not associated with location of occlusion for all imaging modalities (p>.05).

Association of imaging findings with functional outcome

Pc-ASPECTS dichotomized at ≥8 versus <8 was not associated with favorable functional outcome (mRS scores 0–3) for all imaging modalities. All 3 patients (100%; 95% CI 29%–100%) with a CBV pc-ASPECTS <8 compared to 6 of 23 patients (26%; 95% CI 10%–48%) with a CBV pc-ASPECTS ≥8 had died at 1 month (RR, 3.8; 95% CI 1.9%–7.6%). pc-ASPECTS dichotomized at ≥8 versus <8 was not associated with death for further imaging modalities in this population. Using multivariable analysis adjusting for age and stroke severity, no association between pc-ASPECTS scores and Functional outcome was found for all imaging modalities.

DISCUSSION

CTP was performed in a minority of patients in the BASICS registry. Among these, CTP parameter maps did not cover the entire pc-ASPECTS regions in the most patients. With these limitations, perfusion disturbances in the posterior circulation were most frequent and most pronounced on MTT parameter maps. An extensive lesion on CBV parameter maps (pc-ASPECTS <8) was associated with high case fatality; however, the precision of this association was low.

MRI with DWI is considered the diagnostic "gold standard" for the detection of ischemic changes in patients with posterior circulation stroke.[11] A recently introduced DWI score was an independent predictor for favorable outcome following IA thrombolysis in patients with vertebrobasilar occlusion.[12] Moreover, two small case series have described an MRI-based mismatch model in patients with basilar artery occlusion who underwent IA thrombolysis.[13,14] However, CT is the most commonly applied imaging modality in the local general hospital where most patients with acute ischemic stroke present.[6,15] In the BASICS registry population, about 60% of patients with acute basilar artery occlusion initially presented to a local general hospital.[1] Moreover, the feasibility of MRI is limited in these frequently unstable patients.[6,16]

In patients with anterior circulation stroke, CTP seems to allow an estimation of the final infarct size similarly to stroke MRI.[17-19] Areas with increased MTT include potentially reversible ischemic lesions, whereas almost all areas with relatively reduced CBV or hypoattenuation on CTA-SI may lead to irreversible ischemia.[17,20] For patients with posterior circulation stroke, the data on the prognostic impact of CTP is limited to case reports.[21] In a recent study that analyzed the diagnostic impact of CTP, patients with posterior circulation were excluded for technical issues.[22] Reasons include that the standard axial CTP plains represent the ganglionic and supraganglionic levels, and do not routinely cover the entire infratentorial structures, which are supplied by the basilar artery.[7] Consequently, our study has demonstrated that CTP was only performed in a minority (4.6%) of the BASICS registry population and that the individual pc-ASPECTS regions were completely represented in a minority of these patients only. Particularly the brainstem areas, which are highly relevant for the functional outcome of patients with basilar artery occlusion, were only covered in 70% (midbrain) and 19% (pons), respectively.

An extensive lesion on CBV parameter maps (pc-ASPECTS <8) was associated with high case fatality in our study. Our finding indicates that the detection of the ischemic core is most relevant for the prediction of the functional outcome of patients with basilar artery occlusion similarly to patients with middle cerebral artery stroke.[23] However, the precision of this association in our study was low due to small numbers and does therefore not allow valid conclusions. In line with our finding, pc-ASPECTS applied to DWI was an independent predictor for the functional outcome of patients with acute basilar artery occlusion who were treated with IA thrombolysis in a recent study.[5]

In contrast to a study that showed an association between ischemic changes in the anterior circulation and vessel recanalization after application of intravenous rt-PA, our study failed to reveal such an association, although the small sample size and lack of data regarding early recanalization limit the validity of this finding.[24]

Although the lesion extent on CBF parameter maps may better delineate the ischemic core compared with CBV, we did not identify a significant association of CBF parameter maps with favorable functional outcome or death in our study.[25] This finding is limited as no prospective imaging protocol and standardized thresholds for the identification of a CBF lesion were applied in the BASICS registry.

The lack of a standardized prospective imaging protocol, standardized algorithms for the creation of CTP parameter maps, incomplete coverage of the areas of interest in most patients, and the small number of patients, limit the value of the study. Furthermore, no quantitative analysis was possible since we have analyzed the parameter maps that were generated by the individual centers without access to the raw imaging data. Our study is further limited by its retrospective study design and the small number of patients with CTP images available. The reasons to perform an additional CTP study were not prospectively recorded, thus resulting in potential selection bias. The BASICS registry population represents a "real world" population of consecutive patients with acute basilar artery occlusion. A high percentage of patients were not treated with recanalizing treatment regimens, which may further influence our findings on the association of imaging findings with functional outcome. Due to the lack of a prospective imaging protocol and standardized algorithm for the creation of CTP parameter maps we could only perform a qualitative analysis of CTP parameter maps in our study. We can therefore

not comment on quantitative CTP thresholds, which may predict reversibly or irreversibly injured tissue in the posterior circulation. Moreover, we cannot judge whether CTP parameter maps predicted the final infarct extent in patients with basilar artery occlusion in our study as follow-up images were not routinely available.

CONCLUSION

The main conclusion that can be drawn from our data is that—during the study period of the BASICS registry—very few patients with an acute basilar artery occlusion had a CTP study performed of which very few were performed adequately to determine ischemic changes in the entire posterior circulation territories. As expected, MTT parameter maps seem most sensitive for perfusion disturbances in the posterior circulation and may add diagnostic information in patients with suspected basilar artery occlusion and inconclusive CTA. Our observation that an extensive reduction of CBV was associated with high case fatality is not valid for the time being because of the small number of patients, however suggests validation in larger datasets with a standardized imaging protocol. Newer generation CT scanners provide whole brain perfusion imaging and may overcome the problem that the brain stem areas were not represented in the majority of our patients.[26] Alternatively, optimized CTP protocols for the evaluation of posterior circulation ischemia due to acute symptomatic occlusion of the basilar artery should be established. We plan to prospectively analyze the prognostic impact of CTP as an imaging substudy in the randomized controlled BASICS trial.[27]

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The Basilar Artery International Cooperation Study (BASICS): Study protocol for a randomised controlled trial

Erik J.R.J. van der Hoeven, Wouter J. Schonewille, Jan Albert Vos, Ale Algra, Heinrich J. Audebert, Eivind Berge, Alfonso Ciccone, Mikael Mazighi, Patrik Michel, Keith W. Muir, Víctor Obach, Volker Puetz, Cristanne A.C. Wijman, Andrea Zini, Jaap L. Kappelle; on behalf of the BASICS Study Group

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ABSTRACT

Background and purpose Despite recent advances in acute stroke treatment, basilar artery occlusion (BAO) is associated with a death or disability rate of close to 70%. Randomised trials have shown the safety and efficacy of intravenous thrombolysis (IVT) given within 4.5 h and have shown promising results of intra-arterial thrombolysis given within 6 h of symptom onset of acute ischaemic stroke, but these results do not directly apply to patients with an acute BAO because only few, if any, of these patients were included in randomised acute stroke trials.

Recently the results of the Basilar Artery International Cooperation Study (BASICS), a prospective registry of patients with acute symptomatic BAO challenged the often-held assumption that intra-arterial treatment (IAT) is superior to IVT. Our observations in the BASICS registry underscore that we continue to lack a proven treatment modality for patients with an acute BAO and that current clinical practice varies widely.

Design BASICS is a randomised controlled, multicentre, open label, phase III intervention trial with blinded outcome assessment, investigating the efficacy and safety of additional IAT after IVT in patients with BAO. The trial targets to include 750 patients, aged 18 to 85 years, with CT angiography or MR angiography confirmed BAO treated with IVT. Patients will be randomised between additional IAT followed by optimal medical care versus optimal medical care alone. IVT has to be initiated within 4.5 h from estimated time of BAO and IAT within 6 h. The primary outcome parameter will be favourable outcome at day 90 defined as a modified Rankin Scale score of 0–3.

Discussion The BASICS registry was observational and has all the limitations of a non-randomised study. As the IAT approach becomes increasingly available and frequently utilised an adequately powered randomised controlled phase III trial investigating the added value of this therapy in patients with an acute symptomatic BAO is needed (clinicaltrials.gov: NCT01717755).

BACKGROUND

Stroke is the leading cause of disability in developed countries.[1] Posterior circulation stroke accounts for about 20% of all ischaemic strokes. The basilar artery is the main vessel of the posterior circulation that supplies most of the brainstem and occipital lobes, and part of the cerebellum and thalami. Basilar artery occlusion (BAO) can cause many symptoms such as isolated cranial nerve palsies or hemiplegia, but also a locked-in state or coma. Despite recent advances in acute stroke treatment BAO is associated with death or disability rate of close to 70%.[2]

Randomised trials have shown the safety and efficacy of intravenous thrombolysis given within 4.5 h and promising results of intra-arterial thrombolysis given within 6 h of symptom onset of acute ischaemic stroke.[3-8] Unfortunately these results do not directly apply to patients with an acute BAO because only few, if any, of these patients were included in randomised acute stroke trials. As yet, BAO has not been studied in isolation in randomised clinical trials. Patients with BAO only represent about 5% of all thrombolysed stroke patients.[9,10] We are aware of only one attempt to perform a randomised treatment trial in patients with an acute BAO, which was terminated prematurely because of poor recruitment.[11] Case series of patients with BAO found similar outcomes in patients treated with antithrombotic therapy, intravenous thrombolysis (IVT) or intra-arterial treatment (IAT).[11,12]

Recently our study group reported the results of the BASICS registry, a prospective registry of patients with an acute BAO.[2] We were not able to identify a statistically significant superior treatment strategy. However the inclusion of >600 patients in the registry over a 5-year period suggests that the performance of a randomised trial in patients with BAO is feasible.

Our observations in the BASICS registry underscore that we continue to lack a proven treatment modality for patients with an acute BAO and that current clinical practice varies widely. Furthermore, the often-held assumption that IAT is superior to IVT in patients with an acute symptomatic BAO is challenged by our data. Although recanalisation rates are consistently higher after IAT as compared to IVT in observational studies, this was not consistently accompanied by improved outcome.[13,14]

The BASICS registry was observational and has all the limitations of a non-randomised study. Reasons for clinicians to select a specific treatment option are more

complex than can be captured in the scope of a prospective registry. Multivariable analyses can never adjust completely for systematic differences between treatment groups. A bias towards a more aggressive treatment approach in patients who were thought to have a worse prognosis may have influenced the outcome in the IAT group and relinquishing both IVT and IAT in patients with a severe deficit may have been an expression of a more palliative approach. Crossover to another treatment group because of clinical worsening or lack of treatment response was not taken into account. There may have been unmeasured variables relevant to outcome that were imbalanced between groups.

As the IAT approach becomes increasingly available and frequently utilized an adequately powered large randomised controlled phase III trial investigating the added value of this therapy in patients with an acute symptomatic BAO is needed.

METHODS

BASICS is a multicentre, open label, randomised, controlled, phase III trial comparing optimal medical care with best intra-arterial therapy in patients with BAO who were treated with intravenous thrombolysis. A total of 750 patients will be included. Follow-up will continue until 1 year after inclusion of the last patient.

Enrollment criteria

Patients can be enrolled in the study if the following criteria have been met:

1. symptoms and signs compatible with ischaemia in the basilar artery territory and an National Institutes of Health Stroke Scale (NIHSS) ≥10 at time of randomisation;
2. BAO confirmed by CTA or MRA;
3. aged 18 to 85 years;
4. initiation of IV rt-PA within 4.5 h of estimated time of BAO. Estimated time of BAO is defined as time of onset of acute symptoms consistent with the clinical diagnosis of basilar artery occlusion or if not known last time patient was seen normal prior to onset of these symptoms, hence time from symptom onset can be considerably longer than 4.5 h;

5. initiation of IA therapy should be feasible within 6 h of estimated time of BAO;
6. informed consent.

Patients will be excluded from the study in case of:

1. pre-existing dependency with a modified Rankin scale (mRS) ≥3;
2. female of childbearing potential who is known to be pregnant or lactating or who has a positive pregnancy test on admission;
3. need for haemodialysis or peritoneal dialysis;
4. other serious, advanced or terminal illness;
5. any other condition that the investigator feels would pose a significant hazard to the patient if IA therapy is initiated;
6. current participation in another research drug treatment protocol (patient cannot start another experimental agent until after 90 days);
7. lesion consistent with haemorrhage of any degree on neuroimaging;
8. significant cerebellar mass effect or acute hydrocephalus on neuroimaging;
9. bilateral extended brainstem ischaemia on neuroimaging.

Study procedures

Based on the experience in the BASICS registry an estimated 40% to 50% of patients will present in community hospitals with subsequent referral to an intervention centre. Community hospitals should be encouraged to initiate IVT prior to transfer according to the 'drip and ship' principle. Intubation prior to transfer should be strongly encouraged in any subject deemed unstable or at high risk of aspiration. If sedation is needed, short acting drugs, like propofol (di-isopropylfenol) should be given to avoid interference with the neurological examination upon arrival at the intervention centre. A diagnostic neuroimaging screening with CT/CTA or MRI/MRA confirming the presence of BAO and the absence of imaging exclusion criteria, and a NIHSS of 10 or more will be used to identify patients eligible for the trial.

In case of an increase in NIHSS by ≥5 points during transfer and in any comatose subject a repeat CT scan of the brain should be performed prior to randomisation

to exclude intracranial hemorrhage. In those patients in whom BAO is assessed prior to transfer a repeat CTA should be performed prior to randomisation in the intervention centre to reassess basilar artery patency in case of an improvement in NIHSS by ≥5 points during transfer or a time delay beyond 2 h after initial confirmation of BAO and in any comatose subject.

Randomisation

After obtaining informed consent patients will be randomised into one of the two treatment arms. Patients are randomised by a secure link to a central randomisation database. Randomisation will be stratified for stroke severity (NIHSS score <20 versus ≥20), for centre and for time of symptom onset (within 4.5 h of symptom onset versus beyond 4.5 h of symptom onset, but within 4.5 h of estimated time of BAO).

Registry of patients with BAO who are not randomised

To evaluate a possible selection bias of patients included in the trial, participating centres are obliged to enter all patients with acute symptomatic BAO presenting at their centre who are treated with IVT or IAT but who are not randomised, in a registry. Data are collected on patient characteristics, time to treatment, eligibility, reason for non-inclusion and type of treatment.

Treatment

One of the guiding principles of the BASICS trial is rapid initiation of thrombolytic therapy to an eligible subject to provide maximal benefit. To minimize any delay in the administration of a proven effective therapy (that is, IV rt-PA), the standard dose of open-label IV rt-PA (0.9 mg/kg; 90 mg maximum) is initiated prior to enrolment and randomisation in the trial if standard eligibility criteria are met.

Patients treated with IVT within 4.5 h of first symptom onset, and those who are treated beyond 4.5 h of first symptom onset, but within 4.5 h of estimated time of BAO, will be regarded as two pre-specified subgroups for secondary analysis. In patients treated beyond 4.5 h of symptom onset, informed consent needs to be obtained prior to initiation of IVT.

IA therapy has to be initiated within 6 h of estimated time of BAO. Endovascular treatment will be performed by an experienced interventional radiologist with a track record of at least 10 intra-arterial interventions both in the middle cerebral and basilar artery in the last 2 years. If an appropriate thrombus or residual stenosis is identified, the choice of IA strategy will be made by the treating neurointerventionalist.

Objectives

The primary objective of the trial is to evaluate the efficacy of additional IAT in patients with BAO treated with IVT, in terms of favourable outcome at 90 days, defined as a modified Rankin score of 0–3.

Secondary analysis will compare outcome in the following pre-defined subgroups: patients with a baseline NIHSS of 10–19, and those with a baseline NIHSS of ≥20.

Patients treated with IVT within 4.5 h of first symptom onset, and those treated beyond 4.5 h of first symptom onset within 4.5 h of estimated time of BAO.

Secondary objectives are safety evaluation of a combined IV/IA approach compared with IV rt-PA alone, evaluation of the safety and efficacy of mechanical devices as part of a combined IV/IA approach and evaluation of efficacy of a combined IV/IA approach compared with IV rt-PA alone in terms of a favourable outcome on other clinical and radiological measures. Other clinical and radiological measures for evaluation of efficacy will be: (1) Excellent outcome defined as a mRS of 0–2 at day 90 and 1 year; (2) mRS – not dichotomized at day 90 and 1 year; (3) EQ-5D at day 90 and 1 year; (4) an improved early response to treatment as determined by a reduction in NIHSS by 5 points or more at 24 h; (5) a CT or MR angiography assessment of basilar artery patency at 24 h, and (6) the extent of cerebral infarction as measured by the pc-ASPECTS score on NCCT (non-contrast CT) or MRI at 24 h. The primary measures for evaluation of safety will be symptomatic intracranial haemorrhage or intracranial haemorrhage contributing to patients' death as determined by the study safety committee confirmed on neuroimaging within 3 days of treatment initiation (CT or MRI), or overall mortality at 90 days.

Follow-up

Length of follow-up will be 1 year with a blinded exam at day 90 (mRS, EQ-5D) and telephone surveys at 30 days (mRS) and 1 year (mRS, EQ-5D).

Statistical considerations

Power calculation

Assuming an absolute increase of 10% of favourable outcome at 90 days by additional IA therapy compared to optimal medical care alone, we calculated that 712 patients would be needed. This calculation was based on a type 1 error of 5%, a type 2 error of 20%, and a presumed incidence of the primary outcome event of 30% in the group treated with optimal medical care. This latter incidence was based on data of the BASICS registry study [2]. Based on these assumptions the trial would yield a risk ratio of 1.33 with a 95% confidence interval of 1.09 to 1.63, that is, a relative increase of 33% more patients with a favourable outcome with additional IA therapy. The sample size formula used originated from the standard work on clinical trials by SJ Pocock.[15] To account for potential dropout a target of 750 patients was set.

Data analysis

Continuous data will be summarised with means and standard deviations. For count data percentages will be given.

The primary aim of the univariable analysis is to compare the proportion of patients with a favourable outcome at 90 days between the two treatment groups. For this purpose a risk ratio with corresponding 95% CI will be calculated. The analyses will be based on the intention-to-treat principle.

Multivariable analyses will only be carried out if important incomparability is detected between the two treatment groups. In that case risk ratios will be calculated that are adjusted for the variables that show baseline imbalance. To this end Poisson regression will be used, similar to that used in the BASICS registry study.[2]

Safety reporting

An adverse event (AE) is any unfavourable and unintended sign, symptom, or disease occurring during the follow-up period of the study. Adverse events occurring after randomisation will be recorded on the adverse event page of the CRF. A serious adverse event (SAE) is defined as any adverse event that results in: (1) death; (2) a life-threatening condition; (3) inpatient hospitalisation or prolongation of existing hospitalisation; or (4) persistent or significant disability/incapacity.

Adverse reactions are all untoward and unintended responses to the investigational treatment related to any dose or device used.

Serious unexpected adverse reactions (SUSARs) are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information.

All SAEs and SUSARS will be reported to and collected by the data coordination unit. An Internal Safety Committee will review safety data on an ongoing basis, including monitoring the trend in serious adverse outcome events and submitting reports to regulatory agencies and the data safety monitoring board (DSMB).

Monitoring

An independent DSMB will monitor the trial. For efficacy a symmetrical two-sided stopping rule will be used. The size of the trial is based on the assumption of a 10% absolute increase of the proportion of patients with a favourable outcome treated with additional IA therapy as compared with optimal medical care alone. If the observed benefit is 'clearly' larger or if optimal medical care appears to be better than additional IA therapy early termination of the trial may be recommended. A restricted procedure will be used with alpha equal to 0.05 and a power of 0.80.[16]

Safety will be monitored as follows. The BASICS registry observed that the risk of symptomatic intracranial haemorrhage (sICH) in patients treated with IA therapy was 14% (95% CI 10–18%) and 7% (95% CI 3–11%) in those treated with IVT only.[2] A more than two-fold excess of symptomatic intracranial haemorrhage in the group treated with additional IA therapy as compared with maximum supportive treatment may therefore be considered as problematic. However, symptomatic intracranial haemorrhage is a contributing component of the primary outcome and hence is weighed during monitoring of this outcome. A higher than expected sICH rate in

the absence of a significant difference in functional outcome may therefore lead to a decision to put the trial on hold to analyse the reason for this higher sICH rate and the need to change treatment recommendations such a adjustments in the dose of thrombolytics used or the use of specific devises.

The BASICS Trial Office will put an active follow-up system into effect, such that for each patient 90-day follow-up data and those on the occurrence of symptomatic intracranial haemorrhage are obtained without delay. The first interim analysis will be performed at the moment the 3-month follow-up data are available on the first 10 patients randomised. Every 4 months thereafter the DSMB will be given the latest follow-up data and will advise the steering committee about the continuation of the trial based on these data. Thus a sequential monitoring process is installed based on the procedures described by Whitehead in 1997.[16] For this purpose the program PEST 4 will be used. The recommendation on the continuation will be based on: (1) stopping rules as described above; and (2) the most recent information from medical literature or congresses in the field of cerebrovascular disease.

Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (http://www.wma.net21-10-2008 website) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The BASICS trial was approved by the ethics committee of the St. Antonius Hospital on 20 January 2011 and is registered under number R-10.39A. National ethical approval was given by the Central Commission of Human Research (CCMO) on 21 December 2010 and is registered under number NL33550.100.10. Approval by the local medical ethical review board is required for each participating centre before start of patient inclusion.

Patients or their legal representatives will be informed about the trial by their treating neurologist or neurology resident who will also obtain informed consent. In acute situations or if the patient is incapable to give written informed consent oral informed consent may be obtained. In case of oral informed consent a witness (for example, family or nurse) should be present when the information is presented to the patient or patient representative. A written summary that describes the essential information will be presented to the patient or patient representative. The witness, and responsible neurologist or neurology resident will sign this document.

In case of a subject with severe decrease of consciousness (along with national legislations), informed consent can be obtained from the patient's proxy in person or by telephone as long as the identity of the proxy can be confirmed. If approved by the local ethical review board an independent physician can sign informed consent. Community hospitals are encouraged to obtain informed preliminary consent for trial participation of the subject or his proxy prior to transfer.

In patients who are not eligible for standard IVT because IVT cannot be initiated within 4.5 h of symptom onset but who are treated within 4.5 h of estimated time of BAO informed consent has to be obtained prior to IVT. In those centres where CTA or MRA is not part of the standard acute stroke work-up informed consent has to be obtained prior to CTA or MRA.

Publication of the trial results

The trial results will be published by the members of the Executive and Steering Committee, on behalf of the investigators.

DISCUSSION

There are several factors that distinguish patients with BAO from those with middle cerebral artery (MCA) occlusion that may warrant a different treatment approach:

Severity of deficit: previous studies have suggested a greater benefit of IA therapy in patients with a severe deficit.

High poor outcome rate: because of a higher poor outcome rate, patients with BAO have more to gain.

Collateral flow: the basilar artery not only receives collateral flow through cortical cerebellar branches, comparable to the cortical hemispheric branches of the MCA, but also by retrograde filling by the anterior circulation through the posterior communicating arteries as part of the circle of Willis. IVT may be more effective in the presence of good collateral flow, by attacking the thrombus from both sides.

Time window for treatment: the BASICS registry data suggest the presence of a longer time window from symptom onset to time of treatment. The PROACT studies used

a limit of time from symptom onset to time of treatment of 6 h.[4,17] The IMS III study used a 5-h time window from symptom onset to initiation of IAT.[18] The BASICS trial uses a 6-h time window from estimated time of BAO to initiation of IA treatment. The BASICS registry used the estimated time of symptom onset consistent with the clinical diagnosis of BAO to treatment rather than the more commonly used time of onset of any symptoms to treatment. Previous studies have shown that BAO is preceded by prodromal symptoms in >60% of patients.[19,20] Most of these patients would be excluded from a potential trial using the time of onset of first symptom <4.5 h to treatment as an inclusion criterion. We believe that the results from the BASICS registry support the use of the estimated time of BAO rather than using the time of onset of any symptom to treatment as an inclusion criterion for the BASICS trial.

IVT versus *IVT/IAT comparison:* IV thrombolysis is the current standard of care in patients presenting with acute ischaemic stroke with a proven safety and efficacy and therefore should be regarded as the current 'Gold Standard' with which potential new treatment strategies should be compared.

The use of an IVT only arm in a trial of patients with acute symptomatic BAO is supported by the results of the BASICS registry in which no significant difference was found between IVT or IAT treated patients with a severe deficit.[2]

The performance of a trial comparing IVT alone vs. IAT alone in patients with BAO does not seem feasible nor ethical. Referral of a patient to an intervention centre for randomisation between IVT vs. IAT alone would mean delaying the initiation of a treatment which is of proven benefit – whereas there is convincing evidence for the principle of 'time is brain', also in patients with BAO.[21,22] The number of patients with BAO presenting directly to an intervention centre will be too limited. Patients with BAO only represent an approximate 5% of all IVT eligible patients, and only 40% of patients in the BASICS registry where admitted directly (without referral) to an intervention centre.

In order to include a sufficient number of patients the BASICS trial will therefore mainly depend on the inclusion of patients referred from non-intervention community hospitals. The non-intervention hospitals are encouraged to start IVT without delay before sending the patient with the clinical diagnosis of BAO to the intervention centre.

A combined IV and IA approach to acute ischaemic stroke therapy was designed to offer rapid initiation of IV rt-PA, followed by additional titrated local IA therapy, to patients with moderate-to-severe strokes (NIHSS ≥10). The goal was to achieve higher rates of early, successful reperfusion in a widely accessible manner. This approach has been tested in clinical trials of >200 patients, starting with the Emergency Management of Stroke (EMS) pilot trial from 1995 to 1996, followed by the Interventional Management of Stroke (IMS) I trial in 2001, the IMS II trial from 2003 to 2006, and several additional cohorts.[23-25] The data from EMS and IMS show that the combined approach to recanalisation may be more effective than standard IV rt-PA alone for moderate-to-severe (NIHSS ≥10) strokes, while maintaining a similar safety profile. The recently published IMS III trial data did not show a significant difference in outcome comparing IV rt-PA with IV rt-PA followed by IAT in patients with a NIHSS of 8 or greater treated within 3 h.[26] Few patients with BAO were included, about 2% in both treatment arms. Furthermore, few patients had radiologic confirmation of occlusion and most patients in the IA arm were treated with IA thrombolysis or first generation thrombectomy devices, much less effective than the currently used stentretrievers.[27,28]

IVT arm

The 4.5-h time window is based on the results of the ECASS III study.[7] A time window of 0–4.5 h from symptom onset to treatment in patients with acute ischaemic stroke is widely accepted. The BASICS registry results show the safety of using a 0 to 4.5-h time window from estimated time of occlusion to treatment in patients with acute BAO.[2]

IVT + IAT arm

Based on the results of the PROACT studies the 6-h time window for IA thrombolysis in patients with MCA occlusion is widely accepted.[4,17]

A case series of 69 patients treated with IA thrombolysis (urokinase, reteplase or alteplase) following full dose IVT showed the safety of full dose IVT followed by IA thrombolysis. Symptomatic haemorrhage occurred in four out of 69 (5.8%) patients.[29]

The MERCI studies suggested safety of mechanical thrombectomy up to 8 h from symptom onset.[30] The BASICS study shows that a time window of 0 to 6 h from estimated time of occlusion to IA treatment is safe in patients with a severe deficit while little can be gained in both IVT and IAT treated patients beyond the 6-h time window.[2]

The main theoretical advantage of an IA approach is the variety of treatment options, which can be tailored to the individual patient. Because of the variety in approved IA treatment options and the limited number of patients, the experience with specific devices or thrombolytics varies considerably among stroke centres both within and between countries. Limiting the use of treatment options would exclude centres from participation because of lack of experience with the selected device or thrombolytic despite ample experience in the use of alternative devices or thrombolytics. New devices or thrombolytics that become available during the study may be used in the IAT arm depending on national and local approval and experience. Prior approval by the steering committee needs to be obtained.

TRIAL ORGANISATION

Steering Committee

The Steering Committee carries the ultimate responsibility for the trial. Specific tasks of the Steering Committee are: (1) approval of the study protocol; (2) approval of amendments to the study protocol; (3) deciding whether or not to continue the trial based on the recommendation of the DMSB; (4) reviewing protocols for satellite studies; and (5) approval of reports and publication of the trial.

As of 18-10-2012, members of the Steering Committee are (in alphabetical order): A. Algra*, clinical epidemiologist, University Medical Center Utrecht, Utrecht, the Netherlands; H.J. Audebert*, neurologist, Charité Berlin, Berlin, Germany; E. Berge, neurologist, Oslo University Hospital Ullevål, Oslo, Norway; A. Ciccone, neurologist, Carlo Poma Hospital, Mantua, Italy; L.J. Kappelle*, neurologist, University Medical Center Utrecht, Utrecht, the Netherlands; M. Mazighi, interventional neurologist, Bichat University Hospital, Paris, France; P. Michel*, neurologist, University Medical Centre Vaudois, Lausanne, Switzerland; K.W. Muir, neurologist, University Medical

Centre Glasgow, Glasgow, United Kingdom; V. Obach, neurologist, Clinic Hospital Barcelona, Barcelona, Spain; V. Puetz, neurologist, Dresden Stroke Centre, Dresden, Germany; W.J. Schonewille*, neurologist, St. Antonius Hospital, Nieuwegein, the Netherlands, principal investigator; J.A. Vos*, interventional radiologist, St. Antonius Hospital, Nieuwegein, the Netherlands, co-principal investigator; C.A.C. Wijman†, neurologist, Stanford University Medical Centre, Palo Alto, CA, USA; A. Zini, neurologist, St. Agostino-Estense Hospital, Modena, Italy.

* Also member of the Executive Committee
† Deceased

Executive Committee

As of 18 October 2012, members of the Executive Committee, who are responsible for the trial on a day-to-day basis, are all members of the Steering Committee indicated with an * and E.J.R.J. van der Hoeven, radiology resident, St. Antonius Hospital, Nieuwegein, the Netherlands, coordinating investigator.

Trial Coordination Centre

The Trial Coordination Centre is located at the Neurology department in the St. Antonius Hospital Nieuwegein in the Netherlands.

Data Safety and Monitoring Board

An independent Data Safety and Monitoring Board, consisting of clinicians familiar with the treatment of stroke, a biostatistician and a neuro-interventionalist, has been established to monitor the progress of the trial. Details on the advice(s) of the DSMB will be notified to the Steering Committee and the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed.

As of 15 April 2011, members of the Data Safety and Monitoring Board, are (in alphabetical order): K.T. Hoffmann, interventional radiologist, University of Leipzig, Leipzig, Germany; P. Lyden, neurologist, Cedars-Sinai MC, Los Angeles, CA, USA (Chair); R. Raman, Biostatistician, University California, San Diego, CA, USA; D. Toni, neurologist, University 'La Sapienza', Rome, Italy.

Trial status

The trial started in October 2011 in the coordinating centre, the St Antonius Hospital Nieuwegein with the inclusion of the first patient. Eleven other centres in the Netherlands, Switzerland, Czech Republic and Italy have joined since then. As of July 2013 21 patients have been randomised. In Germany, France and Spain the protocol is awaiting national ethical approval. Several other Dutch, German, French, Czech, Swiss, Italian, Spanish and Norwegian centres have indicated that they are interested in participating (http://www.basicstrial.com website).

Acknowledgements

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General discussion

Despite important advances in acute stroke therapy, reported outcomes after basilar artery occlusion (BAO) have not improved over the last 40 years.[1-3] In the BASICS registry, the main subject of this thesis, almost 70% of patients had a poor outcome, independent of type of treatment.[3] The wide variety of treatment strategies among dedicated stroke centres participating in the BASICS registry shows that there is great uncertainty about the most effective treatment approach.

Prior to the BASICS registry the belief in the efficacy of IA therapy (IAT) in patients with basilar artery occlusion was comparable to the conviction that planet Earth was flat.

Figure 1 The Flammarion engraving (1888) depicts a traveler who arrives at the edge of a flat Earth and sticks his head through the firmament.

Scientific evidence of the contrary was ignored until a few brave men dared to challenge the concept and did not fell of the face of the earth.

Evidence of the contrary with regard to the efficacy of IAT as compared with conventional therapy and IV thrombolysis (IVT) in patients with BAO was ignored. Arguments in favour of IAT were hard to contradict because of lack of sound data. Thanks to the detailed prospectively collected data from the BASICS registry, the discussion has changed. The argument that the lack of a difference in outcome can be explained by patient selection has been weakened considerably, thanks to the possibility to adjust for other important predictors of outcome. The only possible explanation left for the true IA believer is the power of clinical judgement: "*Clinical judgement is based on more factors than can be adjusted for on statistical analysis*". This

final argument can only be challenged in a randomised trial in which the decision of which treatment to use is not influenced by the treating physician.

The most important prerequisite for a randomised controlled trial is the presence of equipoise. Prior to the BASICS registry the general opinion among stroke physicians was that there was insufficient doubt of superiority of IA over IV thrombolysis in patients with BAO to warrant a trial. The BASICS registry results do not support this opinion.

BASICS TRIAL

The BASICS trial protocol was designed to show a difference of efficacy favouring IAT over the current standard of care IVT in patients with BAO, based on the presumption that the lack of a significant difference in outcome between these two treatment strategies in the meta-analysis of case series[2] and BASICS registry was indeed mainly due to patient selection. Furthermore, the IV/IA approach used in the trial is far more advanced than IA therapy in the BASICS registry.

In an era of ″negative″ or ″futile″ acute stroke trials the main question is if the difference in treatment effect favouring IAT will be large enough to show up in a randomised trial.

The best way to increase the chance of a positive trial is to use the most effective treatment approach in a population that is most likely to benefit. Unfortunately, the willingness of treating physicians to randomise patients in a trial is inversely proportional with the perceived benefit of the treatment approach tested. The main challenge of all acute stroke trials is to randomise as many eligible patients as possible.

Eligibility criteria should aim to describe a patient population which is not only most likely to benefit from the treatment approach tested but also most likely to be randomised. To avoid selection bias, participants should be discouraged from selecting patients other than by the eligibility criteria. Currently there is no evidence of efficacy of any specific recanalization therapy, in any subgroup of patients with BAO. In the presence of a so called “grey-zone” or a perceived lack of equipoise in a subgroup of trial eligible patients a predetermined subgroup analysis should be agreed on.

Patient population

The BASICS trial population will consist of patients with an NIHSS of ≥10. Although the BASICS registry suggests a superiority of IVT over IAT in patients with BAO and a mild to moderate deficit, there is still reasonable uncertainty as to the balance of benefit and harm of IAT over IVT in patients with a NIHSS of 10–19 (hemiparalysis and cranial nerve palsy). In a secondary analysis we will compare outcome in patients with a baseline NIHSS of 10–19 and those with a baseline NIHSS of ≥20 (tetraplegia or coma).

The BASICS registry used the estimated time of symptom onset consistent with the clinical diagnosis of BAO to treatment rather than the more commonly used time of onset of any symptoms to treatment. Previous studies have shown that BAO is preceded by prodromal symptoms in over 60% of patients. Most of these patients would be excluded from a trial using the time of onset of any symptom to treatment as an inclusion criterion. The results from the registry support the use of the estimated time of BAO (<4.5 hours for IVT, <6 hours for IAT) rather than using the time of onset of any symptom to treatment as an inclusion criterion for the BASICS trial. In a secondary analysis we will compare outcome in patients treated with IVT within 4.5 hours of symptom onset, and those treated beyond 4.5 hours of symptom onset within 4.5 hours of estimated time of basilar artery occlusion.

Treatment arms

IVT

IVT with alteplase is the current standard of care in acute stroke therapy worldwide and has been shown to be safe and effective both in randomised trials and in clinical practice when initiated within 4.5 hours of symptom onset.[4-6] Treatment with IVT only requires a proper clinical diagnosis of stroke and the ability to rule out intracranial hemorrhage by computed tomography (CT) imaging and is currently offered by almost all general hospitals in developed countries. As with other recanalization therapies the efficacy of IVT is strongly dependent on time to treatment. After the implementation of IVT as a standard therapy, time to treatment initiation has decreased considerably thanks to the increased awareness of the importance of rapid initiation of acute stroke therapy among the general

public and all those involved in acute stroke care. The likelihood of an excellent clinical outcome (mRankin score 0–1) in acute stroke patients after treatment initiation within 1.5 hours is twice as high as after initiation within 1.5 to 3 hours, and three times as high as after 3 to 4.5 hours.[7] Simple measures to decrease time to treatment, such as initiation of IVT in the CT room in stead of on arrival at the stroke unit, have therefore been more effective in the last decades than any technical improvement in acute stroke therapy itself. With a current average door-to-needle time approaching 30 minutes in many hospitals, little potential gain is left to increase time to treatment in the hospital setting. A recent trial has shown the safety and feasibility of initiating IVT in a prehospital setting using an ambulance equipped with a CT scanner, point-of-care laboratory, and a telemedicine connection with a stroke team.[8] Furthermore other thrombolytics, such as tenecteplase which requires only a single bolus, show the potential of further improving the efficacy of IVT by decreasing time to recanalization and increasing recanalization rates, without an increase of intracranial hemorrhage.[9] In other words, IVT is not only the current standard of care in acute stroke therapy, but also has the potential of further improving efficacy in the near future.

As pointed out in the introduction of this thesis, the efficacy of IVT in BAO has not been tested in randomised trials. As suggested for patients with intracranial carotid-T occlusion (occlusion of the distal carotid artery with extension into both the anterior and middle cerebral artery),[10,11] the thrombus load in patients with BAO might be too extensive to be dissolved by IV or IA thrombolysis alone.

The combined IV/IA approach

As compared with IVT, IAT is a completely different treatment approach which can only be performed in a tertiary care intervention centre because of its complexity. The use of IAT requires the 24 hours, 7 days a week availability of a treatment team consisting of a stroke neurologist, interventional radiologist and intensive care facilities.

The main disadvantage of IAT, besides the complexity of the treatment, is the time delay to treatment initiation as compared with IVT. As the majority of patients currently present in non intervention centres, treatment with IAT usually requires transfer to an intervention centre. Furthermore, CT imaging prior to IAT

is not only done to exclude hemorrhage, but also to confirm the presence of an intracranial occlusion by CT angiography (CTA) and to assess accessibility of the lesion for endovascular therapy. While IVT can be initiated in the CT room, IAT requires transfer to the angiography suite. Gaining intra-arterial access requires time consuming sterile conditions. Once IA access has been obtained it still takes considerable time to advance the catheter from the groin to the occlusion site, especially in case of BAO. It is often quite difficult to manoeuvre the catheter into the vertebral artery and to advance the catheter through the tortuous vessel. In many centres endovascular therapy is only performed under general anaesthesia for fear of complications caused by sudden unexpected movement caused by agitation. Due to all these factors the door to treatment initiation time of IAT, even under ideal circumstances, is much longer than with IVT. This difference in time to treatment is the main argument against a direct comparison of IAT versus IVT. In the "negative" SYNTHESIS trial,[12] a trial of IVT versus IAT in patients with acute ischemic stroke, the hypothesis was that the disadvantage of delayed treatment initiation of IAT as compared with IVT, would be offset by more rapid and effective recanalization after IAT.

During the BASICS registry most IA patients were not pre-treated with IVT. This was probably mostly due to the strong belief in efficacy of IAT and the fear of hemorrhagic complications with the combination of IV and IA thrombolysis. Currently the large majority of IA patients are pre-treated with IVT. The time delay to initiation of IAT caused by prior treatment with IVT is, at most, negligible. Groin puncture and endovascular treatment initiation can be done while IVT is still ongoing. Furthermore, the combination of IVT and IA therapy has shown to be safe.[13] In other words, there is really no good reason not to start IVT prior to IAT, unless contra-indicated. The combined IV/IA approach takes advantage of the rapid initiation of IVT, an evidence based effective treatment approach, with an estimated 20–30% early recanalization rate[14-16] and subsequent local therapy if needed. From personal experience, I have seen many patients who have been transferred with an occlusion of the basilar artery who had recanalized on arrival after initiation of IVT in the local hospital or in whom the thrombus load had decreased considerably as compared with CTA prior to transfer. If anything, the BASICS registry results have shown us that the effect of IVT in BAO should not be underestimated.

The lack of superiority of IAT over IVT in the BASICS registry does not mean that there is no role for IAT alone in patients with BAO. IAT is as effective as IVT in patients with a severe deficit and should be considered as an option in patients with a contra indication for IVT. There is an ongoing debate among BASICS investigators if patients with a contra-indication for IVT, such as recent surgery or an INR of >1.7, should be randomised in the BASICS trial. At the start of the trial the general opinion was that few centres would be willing to randomise patients between IAT and maximum medical care without IVT.

Except for the costs and efforts involved, there are no strong arguments to withhold IAT to an individual patient treated with IVT and a persistent occlusion as there is convincing evidence that recanalization is a strong predictor of outcome (chapter 10 of this thesis). Unfortunately, we do not know if patients with a persistent occlusion after IVT benefit from additional IAT. In the IMS III trial, the only trial with an IV/IA arm, early recanalization status on angiography was only assessed in the IV/IA arm.[13]

The main advantage of IAT is the high recanalization rate. Mechanical thrombectomy devices can remove large volume and complex thrombi which are not affected by thrombolytics. The techniques used in IAT have evolved rapidly over the last decades. Especially the use of retrievable stents as mechanical thrombectomy device has markedly improved the time to recanalization and the technical success rate of recanalization.[17,18] The disadvantage of mechanical thrombectomy is that it only removes the clot from the main vessel, without affecting perforating or collateral arteries other than by increasing perfusion pressure after recanalization. For this reason mechanical thrombectomy is frequently combined with a low dose of local thrombolytics.

Timing of randomisation

A trial of patients with a persistent BAO on angiogram and lack of clinical improvement after completion of IVT, which from a scientific standpoint would probably be the best way to prove efficacy of additional IAT, would be extremely hard to complete as these patients would be unlikely to be randomised because of a lack of perceived equipoise.

For the BASICS trial we choose to randomise patients after confirmation of basilar artery occlusion on non-invasive imaging. Only patients randomised to the combined IV/IA arm will have a conventional angiogram. This way patients randomised to IVT alone will not be exposed to the discomfort and risks of conventional angiography and interventionalists will not be tempted to commit a serious protocol violation by pursuing IAT after visualization of a persistent occlusion after IVT on conventional angiography. Almost all patients randomised after transfer from other hospitals will be IV failures as they were treated with IVT in the transferring hospital and were randomised after confirmation of persistent occlusion on CTA on arrival in the intervention centre, causing a bias in favour of the IV/IA arm.

CURRENT EVERYDAY CLINICAL PRACTISE

The individual patient

In 2011, a 40 year old male with a past medical history significant for a brief spell of atrial fibrillation 5 years ago, presented to the emergency room.

Two days prior to admission he had noticed a "heavy head" upon awakening after a good night sleep. Upon his way to the bathroom he noted that he could not move his right arm and he had to drag his right leg over the floor. He stumbled against the bathroom door. This whole episode lasted 10–15 seconds. He felt a light headache coming up for which he took a mild analgesic with a good response. Like every morning he took his car to work and worked as usual. Later that day while parking his car he suddenly noticed tingling in part of his left hand en leg. He could not focus well and noticed double vision during a few seconds. He thought the double vision was caused by the bright sun light. The double vision disappeared after putting on his sunglasses. Being worried about these symptoms he made an appointment to see his general practitioner (GP). While at his GPs office he noticed a sudden numbness in his left arm and leg which lasted less than a minute. His GP arranged an outpatient appointment with a neurologist for the next week. The next morning he experienced a brief moment of vertigo upon awakening followed by an unsteady gate which lasted the whole day. Driving his car to work he became nauseated and vomited. The nausea continued throughout the day and was accompanied by headache. After work he decided to go to the emergency room.

His father had a myocardial infarction at age 45 needing coronary bypass surgery. His neurological examination did not show any focal deficit except for a slight unsteadiness of gate. There were no laboratory abnormalities. He had sinus rhythm on his ECG. There were signs of recent infarction on computed tomography (CT) in his right occipital lobe and in his left cerebellum. On duplex ultrasound he had an occlusion of his proximal left vertebral artery, which was later confirmed by CT angiography. The distal left vertebral artery filled through collaterals. Although no atrial fibrillation could be documented, he was started on oral anticoagulation.

Four days after admission, on the afternoon of his planned discharge he developed progressive vertigo, double vision, dysarthria and a right sided hemiparesis at 15:00 hours. Basilar artery occlusion was confirmed on CTA at 15:30. His INR was 1.4. IV thrombolysis was initiated at 16:00 after obtaining informed consent from the patient. A repeat CT performed because of a decreased level of consciousness showed a small amount of hemorrhagic transformation in his left cerebellum and subtle subarachnoid hemorrhage. Any amount of cerebral hemorrhage being a contra indication for participation in the BASICS trial he was transferred to the angio suite for IA therapy after informed consent of his family. The procedure was initiated at 17:00. Due to access problems (occluded left vertebral artery and a hypoplastic distal segment of the right intracranial vertebral artery) it took two hours to deploy a detachable retrievable stent in his basilar artery. A few seconds after deployment he regained consciousness and exclaimed "I can move again". At 20:30 he was admitted to the intensive care unit for observation with a severe headache, with only a mild residual dysarthria and diplopia without any residual hemiparesis. He recovered completely and continued to do well and is again enjoying his work as a pastry chef.

This case is a dramatic example of the impact a new treatment approach can have on the life of an individual patient. Most of all, it is an example of the complicated nature of the disorder. Like 40% of patients with BAO, he had prodromal symptoms. Although alarming enough to visit his GP, his initial symptoms at first were not recognised by himself or by his GP to warrant an emergency evaluation.

Once diagnosed as symptomatic vertebral artery disease it is hard to distinguish the exact cause and to choose the appropriate treatment. If he would have had a stenosis of his left vertebral and not an occlusion, would it have been possible to prevent the occurrence of BAO by stenting? Surgical desobstruction (carotid endarterectomy) or

if contra indicated stenting of symptomatic carotid stenosis is part of routine clinical practise. Treatment of vertebral artery stenosis is still controversial. He was treated with IVT while he had a recent cerebral infarction which is considered an absolute contra indication in most stroke protocols. Despite evidence of intracerebral and subarachnoid hemorrhage he was treated with additional IAT on the presumption that he had very little to loose. Did we safe his life or would the outcome have been the same without IAT and/or without IVT? Was the proximal occlusion of the left vertebral artery caused by a cardiac embolism or by local atherosclerosis?

Few of these uncertainties, controversies and questions would have been raised in patients with anterior circulation ischemia. Treatment options in posterior circulation stroke are based on only a fraction of the evidence that is available for patients with anterior circulation ischemia.

CONCLUSION

Basilar artery occlusion is a disorder that distinguishes itself from anterior circulation occlusions by its severity and complexity. The results of the BASICS registry show that there is no evidence of a superior treatment approach. If not contra-indicated, all patients with basilar artery occlusion should be treated with IVT. Eligible patients with a basilar artery occlusion should be randomised in the BASICS trial.

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Summary
Non-scientific summary

SUMMARY

REVIEW

Chapter 2 summarizes our current knowledge on basilar artery occlusion (BAO) including anatomy, pathophysiology, clinical presentation, imaging techniques and treatment options.

CONVENTIONAL TREATMENT

We retrospectively collected data, from three dedicated stroke centers, on 82 patients with BAO who did not receive any treatment or were treated with antiplatelets, anticoagulation or both, between 1991 and 2002. Overall 80% of patients had a poor outcome (mRankin 4–6), with a case fatality rate of 40%. The poor outcome rate did not improve in more recent years (82% in 1997 to 2002 and 74% in 1991 to 1996), despite more patients being diagnosed with a minor stroke. (**Chapter 3**)

RATIONALE AND DESIGN OF THE BASICS REGISTRY

The main purpose of the registry was to collect data that would help direct the design of a future clinical treatment trial. The target number of patients included was 500. BASICS was a prospective, observational, multi-center, international registry of consecutive patients presenting with a symptomatic and radiologically confirmed basilar artery occlusion. The advantages of the BASICS registry over data derived from case series is the large number of patients included, the prospective and detailed data collection and the inclusion of consecutive patients treated with different treatment strategies. The detailed data available on a large number of patients enables the evaluation of several predictors of outcome. Patients are divided into three treatment groups for analysis: antithrombotic treatment alone (AT), intravenous thrombolysis (IVT) and intra-arterial therapy (IAT). Predictors of outcome are identified comparing patients with a poor clinical outcome (mRankin 4–6) at 1 month with patients with good clinical outcome (mRankin 0–3). Data was collected electronically using the BRAINS database of the University Medical Center Utrecht. (**Chapter 4**)

BASICS REGISTRY RESULTS

Chapter 5 is the main paper of this thesis and describes the results from the BASICS registry. Although we were not able to identify a statistically significant superior treatment approach, the willingness to include more than 600 patients with basilar artery occlusion, within 5 years, from over 50 centers, from 5 continents, shows that our research question is shared by many dedicated stroke centers worldwide.

Most patients were treated with intra-arterial therapy (IAT; 49%), followed by antithrombotic therapy (AT; 30%) and intravenous thrombolysis (IVT; 20%). Only 41 patients (7%) were treated with both IVT and IAT.

Patients treated with IVT or IAT were more likely to have a severe deficit than patients treated with AT. Patients treated with IVT were more commonly treated within 3 hours of estimated time of basilar artery occlusion as compared to IAT patients.

After adjustment for five factors, patients with a severe deficit (NIHSS≥20) had a significantly worse outcome when treated with AT compared with those treated with IAT or IVT.

In a direct comparison of IAT with IVT, patients with a mild-to-moderate deficit (NIHSS<20) had a higher risk of a poor outcome after adjustment for six factors when treated with IAT, whereas patients with a severe deficit had similar outcomes when treated with either IAT or IVT.

There was no statistically significant difference in outcome between IVT and IAT at any time window. None of the 41 patients with a severe deficit had a good outcome when treatment was started beyond 9 hours after the estimated time of occlusion.

Symptomatic intracranial haemorrhage was more commonly reported in patients treated with IAT (14%) than in those treated with IVT (6%), and by fewer than 1% of patients in the AT group.

These results challenge the often-held assumption that IAT is superior over IVT in patients with BAO and support the need for a randomised trial.

Gender

Men and women with acute BAO do not show any significant difference in clinical outcome and vessel recanalization regardless of treatment modalities. (**Chapter 6**)

Prediction model

Poor outcome after BAO can be reliably predicted by a simple model that includes older age, absence of hyperlipidemia, presence of prodromal minor stroke, higher NIHSS score, and longer time to treatment. There is no or limited added value of CT imaging findings or type of treatment for the prediction of poor outcome. Prediction models could be used to exclude patients with a very good or very poor prognosis, independent of treatment, from high risk interventions or inclusion in randomised trials. (**Chapter 7**)

Age

Although patients ≥75 years with BAO have an increased risk of poor outcome compared with younger patients, still more than 1 out of 5 have a good outcome. The oldest patient with a good functional outcome was 91 years of age, despite an NIHSS of 21 on admission. This patient was treated with IVT. (**Chapter 8**)

Time is brain(stem)

Like patients with an anterior circulation occlusion, patients with BAO have an increased risk of poor functional outcome as time to recanalization therapy becomes longer. Only 23% of patients treated beyond 6 hours of estimated time of BAO had good functional outcome compared with 35% of patients treated within 6 hours. Including patients beyond 6 hours after estimated time of BAO in a randomized clinical trial would dilute a potential beneficial effect and require a larger sample size. Beyond 9 hours, the prognosis of patients with a BAO and a severe deficit is universally dismal with or without therapy. (**Chapter 9**)

Recanalization and outcome

Both end of procedure recanalization after IAT and a patent basilar artery on follow-up imaging were statistically significant predictors of good outcome after one month. A good outcome was seen in 52% of patients with a patent basilar artery on follow up and 30% of patients with a severe residual stenosis or persistent occlusion. A good outcome was seen in 40% of patients with an end-of-procedure recanalization (TIMI 3) and in 15% of patients with a persistent partial recanalization or occlusion (TIMI 0-2). A considerable number of patients with an absent or incomplete end of procedure recanalization directly after IAT show patency at follow up. The good outcome rate in these patients is comparable to the rate in patients with end of procedure recanalization. These findings support the notion that there is a subgroup of patients with BAO who benefits from late recanalization. Further studies are needed to assess the frequency and clinical relevance of post procedural re-occlusion and delayed recanalization after IAT in patients with basilar artery occlusion. (**Chapter 10**)

Vertebral artery disease

Almost half of the patients with acute BAO have a concomitant significant intracranial vertebral artery (VA) stenosis or occlusion and more than 60% have a stenosis in the intra- or extracranial VA. The presence of VA occlusion and significant VA stenosis or unilateral occlusion did not influence clinical outcome. However, patients with BAO and bilateral intra- and extracranial VA occlusion have a higher risk of a poor clinical outcome. (**Chapter 11**)

Prodromal TIA or minor stroke

Prodromal minor stroke seems to be associated with an unfavorable outcome in patients with basilar artery occlusion. The worse outcome associated with a prodromal minor stroke can be explained by it being a marker of inadequate collateral flow and/or inability to enhance collateral flow. We could not confirm the association of prodromal TIAs with a favorable outcome described in earlier series of patients with posterior circulation stroke, thought to be caused by induction of ischemic tolerance and enhancement of collateral circulation. Unfortunately, we

were unable to obtain sufficient data on the number and duration of TIAs, and on the time interval between prodromal minor stroke and index event. These factors could influence the predictive value of TIAs on outcome. In order to clarify the association between prodromal ischemia and outcome, ongoing or future stroke registries should collect more detailed clinical and imaging data. (**Chapter 12**)

PC-ASPECTS applied to CTA source images

In patients with an acute ischemic stroke in the anterior circulation, the extent of early ischemic changes on pretreatment noncontrast CT predicts functional outcome and treatment response to IV and IA thrombolysis. CT angiography (CTA) source images (CTA-SI) are more accurate in predicting the final extent of infarction and clinical outcome. Earlier studies have suggested that the extent of hypoattenuation on CTA-SI, quantified with the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) with a 10-point grading system, predicts functional outcome of patients with BAO. Patients with extensive CTA-SI hypoattenuation (pc-ASPECTS <8) were unlikely to achieve a favorable outcome.

We analysed the pc-ASPECTS score on CTA-SI in 158 patients from the BASICS registry. After adjusting for other predictors of outcome a pc-ASPECTS ≥8 was not related to favorable outcome in our study. In post hoc analysis, pc-ASPECTS dichotomized at ≥6 versus <6 did predict a favourable outcome. A potential pc-ASPECTS-by-treatment-category interaction will be prospectively analyzed as an imaging substudy in the BASICS trial. (**Chapter 13**)

PC-ASPECTS applied to Perfusion CT

Perfusion CT (CTP) delineates the ischemic core and the ischemic penumbra and may further improve the identification of patients that may benefit from recanalization therapy. We assessed the diagnostic and prognostic impact of pc-ASPECTS applied to perfusion CT in the BASICS registry population. The main conclusion that can be drawn from our data is, that during the study period of the BASICS registry, very few patients with an acute basilar artery occlusion had a CTP study performed of which very few were performed adequately to determine ischemic changes in the entire posterior circulation territories. Our observation that

an extensive reduction of cerebral blood volume (CBV) was associated with a high case fatality is not valid for the time being because of the small number of patients assessed. Newer generation CT scanners provide whole brain perfusion imaging and may overcome the problem that the brain stem areas were not represented in the majority of our patients. Alternatively, optimized CTP protocols for the evaluation of posterior circulation ischemia due to acute symptomatic occlusion of the basilar artery should be established. We plan to prospectively analyze the prognostic impact of CTP as an imaging substudy in the BASICS trial. (**Chapter 14**)

BASICS trial: study protocol

BASICS is a randomised controlled, multicentre, open label, phase III intervention trial with blinded outcome assessment, investigating the efficacy and safety of additional IAT after IVT in patients with BAO. The trial targets to include 750 patients, aged 18 to 85 years, with CT angiography or MR angiography confirmed BAO treated with IVT. Patients will be randomised between additional IAT followed by optimal medical care versus optimal medical care alone. IVT has to be initiated within 4.5 h from estimated time of BAO and IAT within 6 h. The primary outcome parameter will be favourable outcome at day 90 defined as a modified Rankin Scale score of 0–3. The complete updated trial protocol can be found at the BASICS trial website; www.basicstrial.com. (**Chapter 15**)

NON-SCIENTIFIC SUMMARY

A brain attack, or stroke, is similar to a heart attack. Brain cells need oxygen and nutrients such as sugar to survive, which are supplied through blood vessels. When the blood supply to the brain is blocked during a brief moment of time a temporary dysfunction of the brain occurs called a transient ischemic attack or TIA. During prolonged periods of diminished blood supply brain cells can be damaged causing a longer time to recovery. If the period of diminished blood supply is too long permanent damage of brain cells can occur. In case of a stroke, brain function does not recover within 24 hours. The severity of dysfunction depends on the specific function and size of the section of the brain involved.

The primary goal of acute stroke treatment is to re-establish blood supply to the affected section of the brain as soon as possible to avoid permanent damage to brain cells. Acute treatment options involved are quite similar to ordinary plumbing techniques. There are two mayor options. You can try to dissolve the blockage by injecting a dissolving fluid or blood thinner into the veins, the so called intravenous thrombolysis (IVT) or you try to remove the clot by injecting the blood thinner straight into the blood clot using a hollow tube or mechanically by entering a removing device into the bloodstream, the so called intra-arterial treatment (IAT). The first technique can be applied by anyone. If it doesn't work, you call a plumber or in case of a stroke an interventional radiologist. Using the first option you have to be careful not to spill any liquid on clothing or bare skin. The second option can cause the pipes to brake. The first option is easy to use and sometimes effective. The second option is more effective but requires an expert.

The main subject of this thesis is the search for the most effective way of treating the blockage of the blood vessel supplying the brainstem, the so called basilar artery. The brainstem is situated at the base of the brain. All nerve connections between body and brain pass through the brainstem. The brainstem can therefore be considered the central computer of the brain. Even minor damage to the brainstem can cause a severe dysfunction or even death. Because patients with a brainstem stroke have a high risk of a bad outcome, many doctors believe that everything possible should be done to open a blocked basilar artery.

The first part of this thesis shows that indeed most patients with blockage of the basilar artery are treated with the more aggressive second option. Probably to the

surprise of professional plumbers, in only few of these patients doctors had tried the easy to use, widely available, first option. Looking at the outcome in over 600 patients treated in 50 stroke centres world wide, we did not find a difference in outcome between patients treated with the simple to use first option as compared to the complicated second option, even if we considered the unequal distribution of risk factors for a poor outcome among the treatment groups. It could very wel be that reasons for clinicians to select a specific treatment option are more complex than can be adjusted for in our analysis.

The only way to find out if both treatment options are indeed as effective is not to allow doctors to choose which treatment to use, but let chance decide. This way, with the help of a computer program, you can make sure that the patient group treated with the first option have the same risk of a poor outcome as the patients treated with the second option.

Chapter 15 describes the details of the design of such a study. All patients are treated with the first, easy to use, treatment option, IVT. Outcomes are compared between two patient groups; those who are treated with IVT alone versus those who are treated with both IVT and IAT.

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Samenvatting
Niet-wetenschappelijke samenvatting

SAMENVATTING

OVERZICHTARTIKEL

Hoofdstuk 2 betreft een samenvatting van onze huidige kennis van de anatomie, pathophysiologie, en klinische presentatie bij patiënten met een basilarisafsluiting. Daarnaast worden de diagnostische en therapeutische mogelijkheden besproken.

CONVENTIONELE BEHANDELING

Wij hebben retrospectief data verzameld, uit 3 ervaren strokecentra, van 82 patiënten met een basilarisafsluiting, die niet medicamenteus behandeld waren of uitsluitend behandeld waren met bloedplaatjesaggregatieremmers, anticoagulantia of met beide, in de periode 1991 tot en met 2002. In totaal had 80% van de patiënten een slechte uitkomst (mRankin 4-6), met een mortaliteit van 40%. Het percentage van patiënten met een slechte uitkomst verbeterde de afgelopen jaren niet (82% tussen 1997 en 2002 en 74% tussen 1991 en 1996), dit ondanks een toename van het aantal diagnoses bij patiënten met een minder ernstige uitval. (**Hoofdstuk 3**)

ACHTERGROND EN OPZET VAN DE BASICS REGISTRATIE

Het belangrijkste doel van de BASICS registratie was het verzamelen van data, van ten minste 500 patiënten, die ons zouden kunnen helpen bij het opzetten van een toekomstige gerandomiseerde behandel-trial. BASICS was een prospectieve, observationele, multi-centrum, internationale registratie van consecutieve patiënten met een symptomatische en radiologisch bevestigde basilarisafsluiting. Het voordeel van de BASICS registratie ten opzichte van de data verzameld uit eerder beschreven patiëntengroepen bestaat vooral uit het prospectief verzamelen van gedetailleerde data van een groot aantal consecutieve patiënten, die op verschillende manieren behandeld zijn. De beschikbaarheid van gedetailleerde data maakt het mogelijk de invloed van meerdere prognostische factoren te onderzoeken. Voor verdere analyse werden patiënten onderverdeeld in drie groepen: uitsluitend behandeld met antithrombotica (AT), intraveneuze trombolyse (IVT) en intra-arteriële behandeling (IAT). Voorspellers van uitkomst worden geïdentificeerd door middel van de vergelijking van patiënten

met een slechte uitkomst (mRankin 4-6) na 1 maand, met patiënten met een goede uitkomst (mRankin 0-3). Data werden elektronisch verzameld gebruikmakend van de BRAINS database van het Universitair Medisch Centrum Utrecht. (**Hoofdstuk 4**)

RESULTATEN BASICS REGISTRATIE

Hoofdstuk 5 betreft het hoofdartikel van dit proefschrift en beschrijft de uitkomsten van de BASICS registratie. Ondanks dat we geen statistisch significant betere behandelstrategie hebben kunnen aantonen, hebben we door meer dan 600 patiënten met basilarisafsluiting te includeren binnen 5 jaar, vanuit meer dan 50 deelnemende centra, uit 5 continenten, laten zien dat onze onderzoeksvraag wordt gedeeld door vele ervaren strokecentra, wereldwijd.

De meeste patiënten werden behandeld met IAT (49%), gevolgd door AT (30%) en IVT (20%). Slechts 41 patiënten (7%) werden behandeld met IVT gevolgd door IAT.

Patiënten die behandeld werden met IVT of IAT hadden vaker een ernstige uitval dan patiënten behandeld met AT. Patiënten die behandeld werden met IVT werden vaker binnen 3 uur na het geschatte tijdstip van basilarisafsluiting behandeld dan patiënten behandeld met IAT.

Na correctie voor 5 voorspellende factoren hadden patiënten met een ernstige uitval (NIHSS >20) een significant slechtere uitkomst na AT dan na behandeling met IVT of IAT.

Bij een directe vergelijking tussen IAT en IVT hadden patiënten behandeld met IAT, met een milde tot matige uitval (NIHSS<20), een hoger risico op een slechte uitkomst na correctie voor 6 factoren, terwijl patiënten met een ernstige uitval een vergelijkbare uitkomst lieten zien ongeacht behandeling met IVT of IAT.

Er was bij geen enkel tijdsvenster tot behandeling een statistisch significant verschil in uitkomst tussen IVT en IAT. Geen van de 41 patiënten met een ernstige uitval die meer dan 9 uur na het geschatte tijdstip van basilarisafsluiting behandeld werden, hadden een goede uitkomst.

Symptomatische intracraniële bloedingen werden vaker gezien bij patiënten behandeld met IAT (14%) dan bij patiënten behandeld met IVT (6%), en bij minder dan 1% van de patiënten behandeld met AT.

Deze resultaten ontkrachten de veel voorkomende gedachte dat IAT superieur is aan IVT bij patiënten met een basilarisafsluiting en ondersteunen de noodzaak voor het uitvoeren van een gerandomiseerde studie.

Geslacht

Mannen en vrouwen met een basilarisafsluiting vertonen geen enkel significant verschil wat betreft klinische uitkomst en rekanalisatie, ongeacht de aard van de behandeling. (**Hoofdstuk 6**)

Voorspellingsmodel

Een slechte uitkomst kan betrouwbaar worden voorspeld middels een eenvoudig model dat de volgende factoren bevat: oudere leeftijd, afwezigheid van hyperlipidemie, aanwezigheid van een voorafgaand mild herseninfarct, hogere NIHSS-score, en langere tijd tot behandeling. Het toevoegen van informatie van CT-beelden of van type behandeling heeft geen of slechts beperkte toegevoegde waarde voor de voorspelling van een slechte uitkomst. Voorspellingsmodellen zouden kunnen worden gebruikt om patiënten met een erg goede of slechte uitkomst, ongeacht het type behandeling, uit te sluiten van hoog-risico-interventiestudies. (**Hoofdstuk 7**)

Leeftijd

Ook al hebben patiënten met een basilarisafsluiting die 75 jaar of ouder zijn een verhoogd risico op een slechte uitkomst ten opzichte van jongere patiënten, toch hebben ze nog een 1 op 5 kans op een goede uitkomst. De oudste patiënt met een goede uitkomst was 91 jaar oud, ondanks een NIHSS van 21 bij opname. Deze patiënt werd behandeld met IVT. (**Hoofdstuk 8**)

Tijd is hersen(stam)

Net als bij patiënten met een herseninfarct in de voorste circulatie, hebben patiënten met een basilarisafsluiting een grotere kans op een slechte functionele uitkomst naarmate er meer tijd verstrijkt tot rekanalisatie. Slechts 23% van de patiënte, die na 6 uur van het geschatte moment van basilarisafsluiting behandeld werden had een

goede uitkomst, in vergelijking met 35% bij behandeling binnen 6 uur. De inclusie van patiënten na 6 uur van het geschatte tijdstip van ontstaan van basilarisafsluiting in een gerandomiseerde klinische studie zou een mogelijk positief behandeleffect verminderen en zou daarmee de inclusie van meer patiënten vergen. Na 9 uur is de prognose van patiënten met een ernstige uitval (NIHSS>20) zonder uitzondering slecht, met of zonder behandeling. (**Hoofdstuk 9**)

Rekanalisatie en uitkomst

Zowel rekanalisatie aan het eind van IAT behandeling en een open basilaris bij vervolgonderzoek waren significante voorspellers van een goede uitkomst na 1 maand. Een goede uitkomst werd gezien bij 52% van de patiënten met een open basilaris bij vervolgonderzoek en 30% bij patiënten met een ernstige reststenose of persisterende afsluiting. Een goede uitkomst werd gezien bij 40% van de patiënten met een volledige rekanalisatie (TIMI 3) aan het eind van de IAT en in 15% van de patiënten een niet volledige rekanalisatie of persisterende afsluiting (TIMI 0-2) na IAT. Een behoorlijk aantal patiënten met een persisterende afsluiting of een niet volledige rekanalisatie aan het eind van de IAT behandeling hadden een open basilaris bij vervolgonderzoek. De kans op een goede uitkomst bij deze patiënten was vergelijkbaar met de uitkomst bij patiënten met rekanalisatie aan het eind van de IAT. Deze bevindingen suggereren dat er een subgroep patiënten met basilarisafsluiting is die baat heeft bij late rekanalisatie. Verder onderzoek is nodig naar de frequentie en de klinische relevantie van het opnieuw optreden van afsluiting na initiële rekanalisatie en van het optreden van late rekanalisatie na IAT. (**Hoofdstuk 10**)

Aandoeningen van de vertebralis arteriën

Bijna de helft van de patiënten met een acute basilarisafsluiting heeft tevens een intracraniële vernauwing of afsluiting van één of beide vertebralis arteriën, en meer dan 60% heeft een vernauwing of afsluiting van de intra- of extracraniële vertebralis arteriën. De aanwezigheid van vertebralisafsluitingen of -vernauwingen had geen significante invloed op de functionele uitkomst. Patiënten met een basilarisafsluiting en een bilaterale vertebralisocclusie hebben echter wel een significant verhoogde kans op een slechte functionele uitkomst. (**Hoofdstuk 11**)

Voorafgaande TIA of licht herseninfarct

Een voorafgaand licht herseninfarct lijkt geassocieerd met een slechte uitkomst bij patiënten met een basilarisafsluiting. De slechtere uitkomst bij patiënten met een voorafgaand licht herseninfarct zou kunnen komen doordat de aanwezigheid hiervan een teken is van inadequate collaterale doorbloeding, of een gebrek aan vermogen tot een verbetering van de collaterale doorbloeding. We vonden geen relatie tussen de aanwezigheid van voorafgaande TIA's met een gunstige uitkomst, zoals eerder beschreven in andere patiëntengroepen met herseninfarcten van de achterste circulatie. Een dergelijke gunstige uitkomst zou verklaard kunnen worden door het kweken van een weerstand tegen een gebrek aan doorbloeding en een verbetering van de collaterale circulatie opgewekt door de voorafgaande TIA's. Helaas hebben we niet genoeg data verzameld over het aantal en de duur van de voorafgaande uitvalsverschijnselen en het tijdsinterval tussen de voorafgaande uitvalsverschijnselen en het kwalificerende herseninfarct, om meer te kunnen zeggen over de betekenis hiervan. Deze factoren zouden de voorspellende waarde van voorafgaande uitvalsverschijnselen kunnen versterken. Lopende en toekomstige studies zouden meer klinische en radiologische details moeten vastleggen om de voorspellende waarde van voorafgaande uitvalsverschijnselen te verduidelijken. (**Hoofdstuk 12**)

PC-ASPECTS toegepast op CTA bronbeelden

Bij patiënten met een herseninfarct van de voorste circulatie voorspelt de uitgebreidheid van de vroege ischemische veranderingen op de CT-scan zonder contrast, die voor de behandeling gemaakt wordt, de functionele uitkomst en het behandeleffect op IV en IA-trombolyse. CT-angiografie bronbeelden (CTA-SI) zijn nog nauwkeuriger in het voorspellen van de uiteindelijke grootte van het infarctgebied en de klinische uitkomst. Eerdere studies hebben laten zien dat de pc-ASPECTS (posterior circulation Acute Stroke Prognosis Early CT Score) met een 10 punten beoordelingssysteem, de functionele uitkomst bij patiënten met een basilaris trombose kan voorspellen. Patiënten met een uitgebreide hypodensiteit op CTA-SI (pc-ASPECTS <8) hadden een erg kleine kans op een goede uitkomst.

Wij hebben de pc-ASPECTS-score op CTA-SI geanalyseerd van 158 patiënten in de BASICS registratie. Na correctie voor andere voorspellers van uitkomst, was een

pc-ASPECTS score van ≥8 in onze studie niet geassocieerd met een goede uitkomst. In een post hoc-analyse voorspelde een pc-ASPECTS, gedichotomiseerd bij ≥6 versus <6, wel een goede uitkomst. Een potentiële pc-ASPECTS-per-behandelings-categorie-interactie zal prospectief worden geanalyseerd in een CT-substudie van de BASICS trial. (**Hoofdstuk 13**)

PC-ASPECTS toegepast op Perfusie CT

Perfusie CT (CTP) onderscheidt de ischemische kern van de omliggende penumbra en zou daarmee nog beter in staat kunnen zijn om patiënten te selecteren die baat zouden kunnen hebben bij rekanalisatiebehandeling. Wij bestudeerden de diagnostische en prognostische waarde van de pc-ASPECTS toegepast op CTP in de BASICS registratie. De belangrijkste conclusie die uit onze data getrokken kan worden is, dat gedurende de studieperiode van de BASICS registratie er bij erg weinig patiënten met een basilarisafsluiting een CTP werd verricht, waarvan slechts bij een klein aantal dit onderzoek voldoende goed werd uitgevoerd om de ischemische veranderingen van het gehele achterste-circulatiestroomgebied te bepalen. Door het kleine aantal patiënten waarbij adequate informatie beschikbaar was kan onze observatie dat een uitgebreide reductie van cerebraal bloedvolume (CBV) was gerelateerd aan een grote kans op een slechte uitkomst niet voor waar worden aangenomen. Nieuwe generatie CT-scanners leveren een volledig beeld van de cerebrale perfusie en zullen daarmee het volledig in beeld brengen van de achterste circulatie inclusief de hersenstam vereenvoudigen. Als alternatief zouden bestaande CTP-protocollen verbeterd moeten worden zodat ze ook gebruikt kunnen worden bij patiënten met een acute basilarisafsluiting. Het prognostische belang van CTP bij basilarisafsluiting zal prospectief worden onderzocht, als onderdeel van een radiologische substudie van de BASICS trial. (**Hoofdstuk 14**)

BASICS trial: studieprotocol

BASICS is een gerandomiseerde, gecontroleerde, multi-centrum, open label, fase III, interventiestudie, met geblindeerde beoordeling van uitkomst, die de effectiviteit en veiligheid onderzoekt van de additionele IAT na IVT, bij patiënten met een basilarisafsluiting. De trial heeft als doel 750 patiënten te includeren, met een leeftijd van 18 tot 85 jaar, met een middels CTA of MRA bevestigde

basilarisafsluiting, behandeld met IVT. Patiënten worden gerandomiseerd tussen additionele IAT gevolgd door maximale medicamenteuze behandeling versus maximale medicamenteuze behandeling alleen. IVT moet binnen 4,5 uur van het geschatte tijdstip van basilarisafsluiting gestart worden en IAT binnen 6 uur. De primaire uitkomstmaat is een goede uitkomst bij 90 dagen, gedefinieerd als een mRankin score van 0-3. Het volledige protocol kan gevonden worden op de BASICS trial website: www.basicstrial.com. (**Hoofdstuk 15**)

NIET-WETENSCHAPPELIJKE SAMENVATTING

Een hersenaanval of herseninfarct is vergelijkbaar met een hartaanval of hartinfarct. Hersencellen hebben via het bloed een constante toevoer nodig van zuurstof en voedingstoffen om te overleven. Als de bloedtoevoer van een deel van de hersenen kortdurend wordt verminderd, treedt er een kortdurende disfunctie op van hersencellen. Er is dan sprake van een zogenaamde TIA (transient ischemic attack). Bij een langer durende vermindering of blokkade van de bloedtoevoer zal het langer duren voordat de hersencellen weer functioneren en wordt de kans op onherstelbare schade groter. Als de periode tot volledig herstel langer duurt dan 24 uur, dan spreken we van een beroerte of herseninfarct. In de praktijk wordt er veel gebruik gemaakt van de Engelse term "stroke". De ernst van de uitval hangt vooral af van de grootte van het gebied van verminderde doorbloeding, de mate van vermindering van doorbloeding, en de specifieke functie van het betreffende deel van de hersenen.

Het belangrijkste doel van de acute behandeling is het zo snel mogelijk herstellen van de bloedtoevoer naar het getroffen deel van de hersenen, om permanente schade te voorkomen. De beschikbare middelen voor de acute behandeling van een herseninfarct zijn vergelijkbaar met de middelen die gebruikt worden door een loodgieter bij het oplossen van een verstopping. Het grootste verschil met het werk van een loodgieter is dat deze vooral problemen behandelt van het afvoerende systeem, terwijl de interventieradioloog vooral problemen behandelt van het, onder hoge druk staande, toevoerende systeem, met alle risico's van dien. Er zijn twee belangrijke behandelmogelijkheden. De meest eenvoudige optie is de blokkade op te heffen door oplosmiddel of bloedverdunner via een infuus in de arm aan het systeem toe te voegen, de zogenaamde intraveneuze trombolyse (IVT), in de hoop daarmee de blokkade op te lossen. Een ingewikkeldere optie bestaat uit het ter plaatse van de blokkade inspuiten van deze middelen door middel van een holle slang of katheter, wat de effectiviteit aanzienlijk verhoogt, of via diezelfde katheter de blokkade mechanisch te verwijderen door middel van het gebruik van een mechanische ontstopper of stolseltrekker, de zogenaamde intra-arteriële behandeling (IAT). De eerste optie kan door iedereen gebruikt worden, terwijl voor de tweede optie het inschakelen van een specialist noodzakelijk is.

Het belangrijkste onderwerp van dit proefschrift is de zoektocht naar de meest effectieve behandeling bij afsluiting van het bloedvat dat de hersenstam doorbloed, de

zogenaamde basilarisarterie. De hersenstam ligt zoals de term al doet vermoeden aan de basis van de hersenen. Alle zenuwverbindingen tussen de hersenen en het lichaam passeren door deze nauwe passage. De hersenstam wordt dan ook vaak gezien als de centrale computer van het brein. Zelfs een kleine schade aan de hersenstam kan al grote gevolgen hebben, zoals een complete verlamming, coma of overlijden. Doordat patiënten met een hersenstaminfarct een groot risico hebben op een slechte uitkomst, vinden veel artsen dat al het mogelijke gedaan moet worden om de bloedtoevoer naar de hersenstam te herstellen bij een afsluiting van de basilarisarterie.

Hoofdstuk 5 van dit proefschrift laat zien dat de meeste patiënten worden behandeld met de intra-arteriële behandeling. Waarschijnlijk tot de verbazing van veel loodgieters werd maar bij heel weinig van deze patiënten (7%) de veel eenvoudigere intraveneuze trombolyse als eerste geprobeerd. Kijkend naar de uitkomst van meer dan 600 patiënten, behandeld in 50 strokecentra verspreid over de hele wereld, vonden we geen belangrijk verschil in uitkomst tussen patiënten die met de eenvoudige eerste optie behandeld werden in vergelijking met de veel ingewikkeldere tweede optie, zelfs als we rekening hielden met een ongelijke verdeling van risicofactoren voor een slechte uitkomst tussen de twee behandelgroepen. Het zou natuurlijk heel goed mogelijk kunnen zijn dat de behandelend arts bij de selectie van patiënten voor een bepaalde behandeling met veel meer factoren rekening houdt dan wij met ons rekenprogramma konden nabootsen.

De enige manier om er bij een nieuwe studie zeker van te zijn dat dit gebrek aan verschil niet wordt veroorzaakt door een onevenwichtige selectie van patiënten, voor wat betreft risicofactoren op een slechte uitkomst, is de keuze van behandeling niet over te laten aan de behandelend arts, maar aan het toeval. Door een gewogen loting, via de computer, kunnen er twee vrijwel identieke patiëntengroepen worden gemaakt, waarbij het enige verschil tussen de twee groepen bestaat uit het type behandeling.

Hoofdstuk 15 beschrijft de details van het protocol van een dergelijke studie. Alle patiënten worden behandeld met de algemeen beschikbare, eenvoudig toe te passen intraveneuze trombolyse (IVT). Uitkomsten bij patiënten die uitsluitend worden behandeld met IVT worden vergeleken met de uitkomsten van patiënten die naast IVT ook met de meer ingewikkelde behandeling ter plaatse van het stolsel behandeld worden (IAT).

Appendix BASICS Study Group

BASICS Study Group (with number of patients and names of investigators) was as follows.

Australia (6): University of Melbourne (A.M. Weber, G.A. Donnan); Belgium (21): University Hospital, Leuven (11; V. Thijs), University Hospital St. Luc, Brussels (10; A. Peeters); Brazil (18): University of Rio de Janeiro (11; G. de Freitas), University of Sao Paolo, Hospital das Clinicas (5; A.B. Conforto), Federal University of Sao Paolo (2; M. Miranda-Alves, A. Massaro); Finland (14): University of Helsinki (14; P. Ijäs, T. Bogoslovsky, P.J. Lindsberg); Germany (224): German Stroke Database (77; C. Weimar, J. Benemann, K. Kraywinkel), University Hospital Freiburg (20; C. Haverkamp), Leipzig University (15; D. Michalski), University Hospital Essen (10; C. Weimar), Medical University Hannover (8; K. Weissenborn), 6; University Hospital, Magdeburg (M. Goertler), 4; University Hospital Rostock (A. Kloth), Kliniken Neuruppin (3; A. Bitsch), Bürger Hospital, Stuttgart (3; T. Mieck), Heinrich Braun Krankenhaus, Zwickau (2; J. Machetanz), Sofien and Hufeland Hospital, Weimar (2; P. Möller), University Hospital, Ulm (2; R. Huber), Hospital Heidenheim (2; S. Kaendler), St. Elisabeth Hospital, Ravensburg (47; C. Rueckert), TEMPiS Network Bavaria (38; H. Audebert, R. Müller, B. Vatankhah), University of Munich (26; T. Pfefferkorn, T.E. Mayer), Universitätsklinikum Mannheim (19; K. Szabo), Dresden University (13; C. Disque), Klinikum Minden (2; O. Busse), University of Heidelberg (2; C. Berger, W. Hacke); Israel (19): Sheba Medical Center (19; Y. Schwammenthal, D. Orion, D. Tanne); Italy (6): University of Turin (5; M. Bergui), University of Bologna (1; E. Pozzati); Netherlands (82): St. Antonius Hospital, Nieuwegein (40; W.J. Schonewille), University Medical Center Utrecht (22; W.J. Schonewille, A. Algra, L.J. Kappelle), University Medical Center Groningen (6; G.J. Luijckx, P. Vroomen), Academic Medical Center, Amsterdam (5; M.D. Vergouwen, Y. Roos, J. Stam), Gelre Hospital (4; P. Bienfait), University Medical Center Nijmegen (3; F.E. de Leeuw), St. Elisabeth Hospital, Tilburg (1; P. de Kort), Erasmus Medical Center, Rotterdam (1; D. Dippel); Scotland (23): Southern General Hospital, Glasgow (23; T. Baird, K. Muir); Spain (25): Hospital Val ʻd Hebron, Barcelona (13; J. Pagola, M. Ribo, C. Molina), Hospital Virgen del Rocio, Sevilla (12; A. Gonzales, A. Gil-Peralta); Sweden (3): Lund University (3; B. Norrving); Switzerland (127): Inselspital, Bern (52; M. Arnold, U. Fischer, J. Gralla, H. Mattle, G. Schroth), Centre Hospitalier Universitaire Vaudois, Lausanne (39; P. Michel), University Hospital, Basel (24; S.T. Engelter, S. Wetzel, P. Lyrer), University Hospital Zurich (8; J. Gandjour, N. Michael,

R. Baumgartner), Kantonsspital, St. Gallen (2; B. Tettenborn), Kantonsspital, Aarau (2; H. Hungerbuehler); United States (51): Stanford Stroke Center, Palo Alto, Calif (29; C.A. Wijman, A. Finley Caulfield, M. Lansberg, N. Schwartz, C. Venkatasubramanian), University of Texas, Houston (22; Z. Garami, S. Bogaard, F. Yatzu, J. Grotta).

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BASICS study team (as listed in the appendix of this thesis). Starting the BASICS registry in 2002, I thought our aim to include 500 patients in 5 years was highly optimistic. We never expected to include over 600 patients. With 50 participating centres I'm not able to thank all participants individually. There are two people who have been instrumental to the success of the registry who I would like to thank here in particular. Christina Rueckert from Ravensburg, who by including a large steady number of patients from the very start, gave the registry the momentum to keep growing. Christian Weimar, coordinator of the German Stroke Database (GSD), almost single handed included 77 patients by integrating the BASICS data entry form in the GSD. I will never be able to thank you and the rest of the BASICS study team enough for your altruistic effort.

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Publications

THIS THESIS

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About the author

The author was born in 1963 and grew up in Haarlem, a city with a population of ~150,000, located along the river Spaarne, 20 km west of Amsterdam and near the coastal dunes. He attended the Bornwater primary school in Bloemendaal and the Kennemer Lyceum secondary school in Overveen, and for his final year of secondary school the Montessori Lyceum in Amsterdam. Joining the army in 1983, as part of compulsory military service, was an abrupt end to childhood. Prior to starting medical school at the University of Amsterdam in 1984, he worked as a waterfront director in a summer camp in Connecticut and travelled 6,000 miles by car through the United States. Besides his studies he played rugby at the Amsterdam Students Rugby Club (ASCRUM) and travelled through Asia (including a rotation in parasitology in Jakarta) and South America on "a shoestring". After clerkships in Oxford (ophthalmology, radiology and dermatology), London (neurosurgery and paediatrics) and Boston (neurology) he started his neurology training as an intern at the Beth Israel Hospital in New York in 1991, followed by his residency in neurology at Boston University and a stroke fellowship at the Mount Sinai hospital in New York. He completed his neurology training as a stroke fellow at the Hospital Clinic i Provincial in Barcelona. He worked as a general neurologist in the Clinica Rotger in Palma de Mallorca for 3 years. In 2001 he moved back to The Netherlands and worked at the University Medical Center Utrecht until his current position as a general neurologist, with a special interest in acute stroke therapy, at the St. Antonius Hospital in Nieuwegein. He continues to have an academic affiliation with Utrecht University.