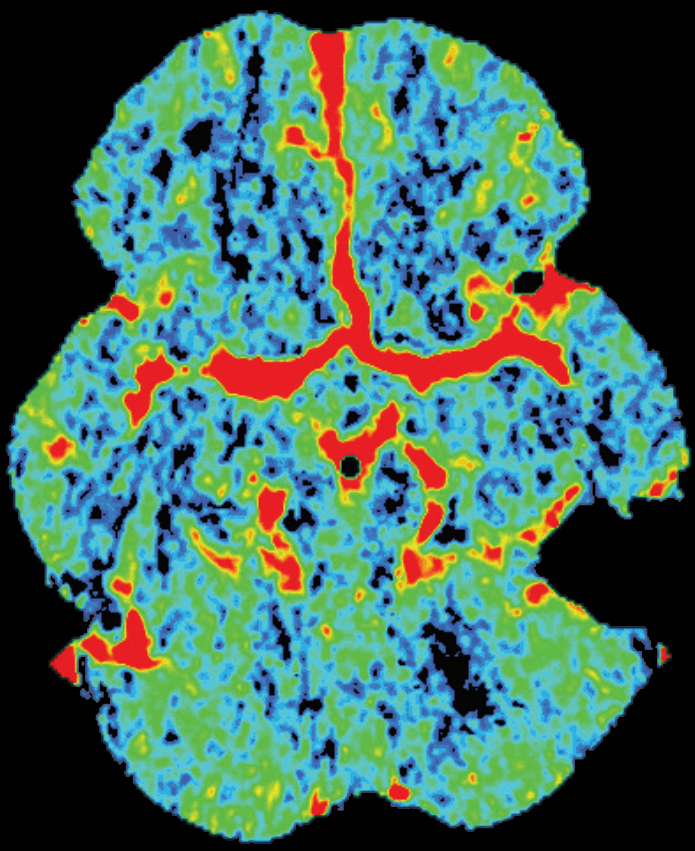
IMAGING IN POSTERIOR CIRCULATION STROKE



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Imaging in posterior circulation stroke

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Imaging in posterior circulation stroke

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(met een samenvatting in het Nederlands)

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te Arnhem

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CONTENTS

CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

Epidemiology, anatomy and pathophysiology

Stroke is the leading cause of disability in developed countries.[1] About twenty percent of all transient ischaemic attacks and ischaemic strokes are located in the posterior circulation (PC).[2] Despite the relatively high incidence, ischaemic events in the PC have received less attention and often have been managed differently compared with those in the carotid artery territory.

The PC comprises both vertebral arteries, the basilar artery, and the intracranial vessels that they give rise to (Figure 1.1). Together, these arteries supply the brainstem, cerebellum, medial and postero-lateral thalamus, occipital lobes, and sometimes parts of the medial temporal and parietal lobes.

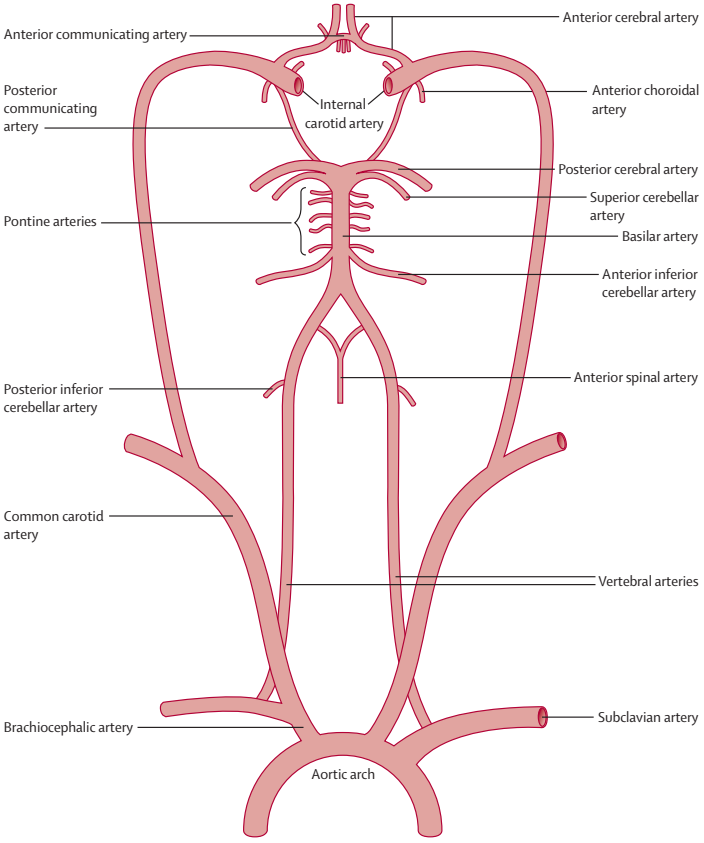

Figure 1.1 The vertebral and basilar arteries and their branches.
Reprinted from Markus et al. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. Lancet Neurol. 2013;12:989-998, with permission from Elsevier.

The most common causes of PC ischaemia are embolism form the heart, large artery atherosclerotic disease, small vessel disease and vertebral artery dissection.[3] Atherosclerosis frequently occurs at or near the origin of the vertebral artery but can also occur in the distal vertebral or basilar artery. Thromboembolism, with or without haemodynamic comprise, is the prevailing cause of ischaemia in vertebrobasilar stenosis.[4–6] PC lacunar infarcts result from disease in the small penetrating arteries that arise from the intracranial vertebral, basilar or proximal posterior cerebral arteries. Vertebral artery dissection is an important cause of stroke in young adults, either occurring after trauma or spontaneously.

Clinical features

Diagnosing PC stroke can be challenging both from a clinical and radiological point of view. The vascular anatomy in the PC can be variable and presenting symptoms are often non-specific and fluctuating. Furthermore, clinical signs and symptoms of anterior and posterior ischaemic stroke may overlap and therefore may cause a delay in making the correct diagnosis.[7,8] Consequently, the interval between referral and treatment was shown to be significantly longer for patients with a PC stroke compared with patients with an anterior circulation (AC) stroke.[9,10] Nevertheless, making the correct diagnosis is important, as clinical decisions, such as initiation of therapy aimed at revascularisation and secondary prevention, are often based on a specific vascular territory. In addition, PC stroke and transient ischaemic attacks (TIAs) are associated with a high risk of recurrent stroke, particularly when there is associated vertebral artery stenosis.[6,11] These strokes, especially in case of acute basilar artery occlusion (BAO), may result in death or substantial disability and therefore effective prevention and treatment is crucial.

PC strokes can present with a large variety of symptoms and signs due to the proximity of brainstem nuclei and large afferent and efferent tracts. In the 407 patients from the New England Medical Centre Posterior Circulation Registry (NEMC-PCR) the most frequent presenting symptoms were dizziness (47%), unilateral limb weakness (41%), dysarthria (31%), headache (28%) and nausea or vomiting (27%).[3] The most frequent signs were unilateral limb weakness (38%), gait ataxia (31%), unilateral limb ataxia (30%), dysarthria (28%) and nystagmus (24%). Most of these are non-specific for PC ischaemia, especially if they occur in isolation. Traditionally, the Oxfordshire Community Stroke Project (OCSP) classification is used for the clinical classification of the vascular territory of infarction.[12] The OCSP clinical classification is a simple classification for acute stroke but correctly identifies the infarct localisation in only 75%.[13]

The NIH Stroke Scale (NIHSS) is nowadays used on a routine basis to assess the clinical features of acute ischaemic stroke and has a proven relationship with stroke severity and outcome.[14–16] However, its usefulness for PC stroke is limited as the scale does not include a detailed assessment of the cranial nerves. As a result the scale underestimates clinical severity in PC stroke and relatively low scores can occur in patients with disabling infarctions of the brainstem or cerebellum.[17]

Imaging

As the clinical diagnosis of PC stroke can be challenging, a definite diagnosis can often only be reached after brain imaging. In the acute setting of suspected ischaemic stroke non-contrast computed tomography (NCCT) is used to exclude cerebral haemorrhage and pathologies other than ischaemic stroke, and to detect early signs of ischaemia. However, NCCT has low sensitivity for the detection of PC stroke due to small lesion size and beam hardening artefacts in this region.[18] Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) is superior for this purpose, particularly in the brainstem, but its availability remains a problem and may be difficult to perform in patients with acute stroke. Furthermore, a recent meta-analysis reported that DWI fails to identify acute ischaemic stroke in a substantial number of patients, especially in the PC.[19] In many dedicated stroke centres CT-angiography (CTA) and CT-perfusion (CTP) are now part of the workup of patients who are suspected of acute ischaemic stroke. CTA provides information on the cause of infarction and on the presence and site of an arterial occlusion. Non-reformatted CTA images, so called CTA-source images (CTA-SI) also have added value in detecting ischaemia.[20,21] Several studies have reported on the diagnostic accuracy of CTP imaging for detecting acute ischaemic stroke.[22] CT perfusion imaging provides information about capillary-level haemodynamics of brain parenchyma. It has the potential to roughly distinguish normal brain tissue from severely hypoperfused but salvageable tissue (penumbra), irreversible damaged (core) and hypoperfused but metabolically stable tissue (benign oligaemia). Both core and penumbra display increased measures of mean transit time and time to peak and decreased cerebral blood flow. Cerebral blood volume is reduced in the core and is normal or increased in the penumbra. Computed tomography with CTP approximately doubles the detection rate of acute ischaemia compared with NCCT in the AC.[23] While there has been extensive research concerning the diagnostic and prognostic value of CTP in the AC, there is only little evidence regarding the PC.[24,25]

Basilar artery occlusion

The basilar artery is the main vessel of the PC. BAO is a rare cause of stroke with a high case fatality rate and an often poor clinical outcome among survivors. Poor outcome of almost 70%, independent of type of treatment has been reported.[26] It accounts for about 1% of all strokes and is reported in about 8% of patients with symptomatic vertebrobasilar territory ischaemia.[27,28] BAO can cause many symptoms such as isolated cranial nerve palsies or hemiplegia, but also complete limb and facial paresis with preserved consciousness (the "locked-in" syndrome), reduced consciousness, and oculomotor abnormalities (from midbrain and bilateral thalamic damage, as part of the "top of the basilar" syndrome), coma, and cardiorespiratory disturbances, depending on the site of occlusion.

Several clinical predictors of outcome after BAO, such as the NIHSS at admission, age, time to treatment, and recanalisation have been identified in earlier studies.[26,29–31] In addition, several potential imaging derived predictors of outcome and recanalisation, such as collateral status and clot length have been suggested.[32,33] However, the value of most of these imaging derived parameters for predicting outcome in BAO remains unclear.

(The Basilar Artery International Cooperation Study) BASICS

In 2015, conclusive evidence emerged from multiple randomised clinical trials for the efficacy and safety of intra-arterial treatment in patients with acute ischaemic stroke in the AC caused by an intracranial large-vessel occlusion.[34] For the PC, the situation is less clear. Until recently, BAO had not been studied in isolation in randomised clinical trials. In the late nineties there has been an attempt to perform a randomised trial (Australian Urokinase Stroke Trial) comparing heparin with heparin plus intra-arterial urokinase, which was terminated prematurely because of a low recruitment rate.[35] Case series of patients with BAO found similar outcomes in patients treated with antithrombotic therapy, intravenous thrombolysis (IVT) or intra-arterial treatment (IAT).[32,36] In 2009, our study group reported the results of the BASICS registry, a prospective registry of patients with an acute BAO.[26] In a series of 619 patients we were not able to identify superiority of any treatment strategy over another. The observations in the BASICS registry underscored that we lack a proven treatment modality for patients with an acute BAO and that clinical practice varies widely. Furthermore, the often-held assumption that IAT is superior to IVT in patients with an acute symptomatic BAO was challenged by our data. Although recanalisation rates are consistently higher after IAT as compared with IVT in observational studies, this was not consistently accompanied by improved outcome.[37,38] The BASICS registry was an observational study

and has the limitations of a non-randomised design. In the light of recent positive trials of patients with proximal middle cerebral artery occlusion and IAT becoming 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 was needed. The inclusion of >600 patients in the registry over a 5-year period suggests that the performance of such a randomised trial in patients with BAO is feasible. With all these issues in mind we started the BASICS trial in 2011. In this randomised, multi-center open label controlled phase III treatment trial we will evaluate the efficacy and safety of IAT in addition to best medical treatment in patients with BAO.

Recently, the Chinese BEST trial (Basilar artery occlusion Endovascular intervention versus Standard medical Treatment), with a similar protocol as BASICS, was terminated prematurely after the enrollment of 131 patients due to an excessive number of crossovers. Based on its pre-specified intention-to-treat analysis, the BEST trial failed to demonstrate a benefit of mechanical thrombectomy over best medical management. However the as-treated analysis showed significant better outcomes of patients who received thrombectomy (unpublished data, presented at World Stroke Conference October 2018). The outcome of the BEST trial has revived the discussion among stroke physicians on the need of further proof of efficacy of IAT in patients with BAO.

This thesis focuses on several clinical and radiological aspects of PC ischaemia, more specifically on the biographical and clinical patient characteristics and multimodality CT imaging and their value in detection of PC ischaemia. Furthermore, we assessed the prognostic value of CT derived predictors for the prediction of several outcome parameters in patients with BAO.

OUTLINE OF THE THESIS

In **Chapter 2** we assessed if biographical and clinical characteristics can aid in the identification of patients with a final diagnosis of a PC infarct when clinical signs in the acute stage suggested ischaemic stroke in the AC. **Chapter 3** describes the additional value of CTP to NCCT and CTA-SI for infarct detection and localisation in patients suspected of acute ischaemic PC stroke. The next chapters describe the influence of various imaging parameters on outcome in patients from the BASICS registry. **Chapter 4** deals with collateral flow, **Chapter 5** with clot length and **Chapter 6** with vertebral artery stenosis. **Chapter 7** contains the protocol of the ongoing BASICS trial.

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CHAPTER 2

Suspicion of acute anterior circulation stroke, but posterior circulation infarct as the final diagnosis

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ABSTRACT

Background and purpose A minority of patients with clinical signs of an acute infarction in the anterior circulation (AC) may have a posterior circulation (PC) infarction as the final diagnosis. Our aim was to report the characteristics of these infarcts and to assess if biographical or clinical characteristics can aid in the identification of these patients.

Methods In the Dutch acute stroke study (DUST) patients underwent non-contrast computed tomography (NCCT), CT angiography and CT perfusion within 9 hours after stroke onset and follow up NCCT or MRI after around three days. For the current study patients with clinically suspected AC stroke without signs of early ischemia on the initial CT were selected. Risk ratios (RR) and corresponding 95% confidence intervals (CI) of patient characteristics for prediction of a PC infarct on follow-up imaging were calculated with Poisson regression.

Results Of 305 patients who fulfilled the inclusion criteria 20 patients (7%) had a PC infarct, 58 patients (19%) had an AC infarct, and 227 patients (74%) had no new infarct on follow up imaging. Most of the PC infarcts (75%) were lacunar infarcts in the pons or the thalamus. None of the baseline characteristics was statistically significant related to the presence of a PC infarct.

Conclusion A relevant minority of patients with a clinical presentation suggestive of an acute ischemic stroke in the AC has a PC infarct on follow up imaging. We did not find specific clinical characteristics that were associated with these infarcts.

INTRODUCTION

Correct localization of an infarction in the brain based only on clinical examination can be challenging. Important decisions, such as initiation of therapy aimed at revascularization and secondary prevention, are often based on a specific vascular territory. Traditionally, in the acute stage the Oxfordshire Community Stroke Project (OCSP) classification is used for the clinical classification of the vascular territory of infarction,[1] but this score correctly identifies the infarct localization in only 75%.[2]

The NIH Stroke Scale (NIHSS) is nowadays used on a routine basis to assess the clinical features of acute ischemic stroke. This scale has a proven relationship with stroke severity and outcome.[3–5] However, the NIHSS is not intended to identify the vascular territory of the stroke.

In many dedicated stroke centers multimodal computed tomographic (CT) imaging with non-contrast computed tomography (NCCT), CT angiography (CTA) and CT perfusion (CTP) is part of the workup of patients who are suspected of acute ischemic stroke. These modern CT-techniques have a high sensitivity and specificity for the detection of both anterior circulation (AC) and posterior circulation (PC) infarction.[6,7] However, still a significant percentage of patients has false negative imaging on admission. Earlier studies have shown that small supratentorial (lacunar) infarcts and infarcts in the pons and midbrain region can be difficult to visualize. Limited brain coverage of CTP is also known to cause false negative findings.[7,8]

In the present study we investigated a consecutive series of patients admitted to a stroke unit with a clinical presentation suggestive of an acute ischemic stroke in the AC. Our aim was to assess how frequent clinical features that suggest an acute AC infarct are eventually caused by an infarct in the PC. In addition, we investigated whether certain baseline and clinical patient characteristics are helpful to identify these patients.

METHODS

Patients

All patients participated in the prospective, multicenter, observational Dutch acute stroke study (DUST; ClinicalTrials.gov NCT00880113).[9] The DUST population consists of patients (n=1476) with acute ischemic stroke in whom the diagnostic values of CTA and CTP within nine hours after onset of the neurological deficit were investigated. Patients were enrolled

between May 2009 and August 2013 in six university and eight non-university hospitals in The Netherlands. NIHSS was assessed at admission. On the baseline form of the DUST the treating physician had to record if the ischemic lesion that had caused the neurological deficits was suspected to be located in the supply of the AC or of the PC territory. All patients underwent NCCT, CTP and CTA on admission. Follow-up NCCT was performed around day 3 or MRI if clinically indicated.

Ethical approval was obtained from the medical ethics committee of the University Medical Center Utrecht, The Netherlands, in addition to local approval from all participating hospitals. Informed consent was obtained from patients or their legal representative. The medical ethics committee waived the need for informed consent for patients who died before informed consent could be obtained.

For the current study, we selected patients with a clinical diagnosis of acute ischemic stroke in the AC without signs of early ischemia on the admission multimodal CT imaging. Patients with missing follow-up imaging, follow-up imaging <12 hours or >14 days and imaging of insufficient quality were excluded.

Location of an AC infarct on follow-up imaging was allocated according to the Alberta Stroke Program Early CT score (ASPECTS). PC infarcts were assessed according to the eight posterior circulation Alberta Stroke Program Early CT score (PC-ASPECTS) regions: pons, midbrain and right or left thalamus, cerebellum or posterior cerebral artery (PCA) territory.[10] Additionally, the side of pontine and midbrain infarcts was documented. Subsequently, infarct volumes were obtained with manual delineation as described previously.[11]

Analyses

Baseline data were reported with standard descriptive statistics. Risk ratios (RR) and corresponding 95% confidence intervals (CI) of baseline and clinical patient characteristics, including separate NIHSS items, for prediction of PC infarction on follow-up imaging were calculated with Poisson regression.

RESULTS

Baseline variables

Eighty-three of 1476 patients were excluded because of irretrievable admission scans (Figure 2.1). Another 259 patients were excluded because of either a missing record of

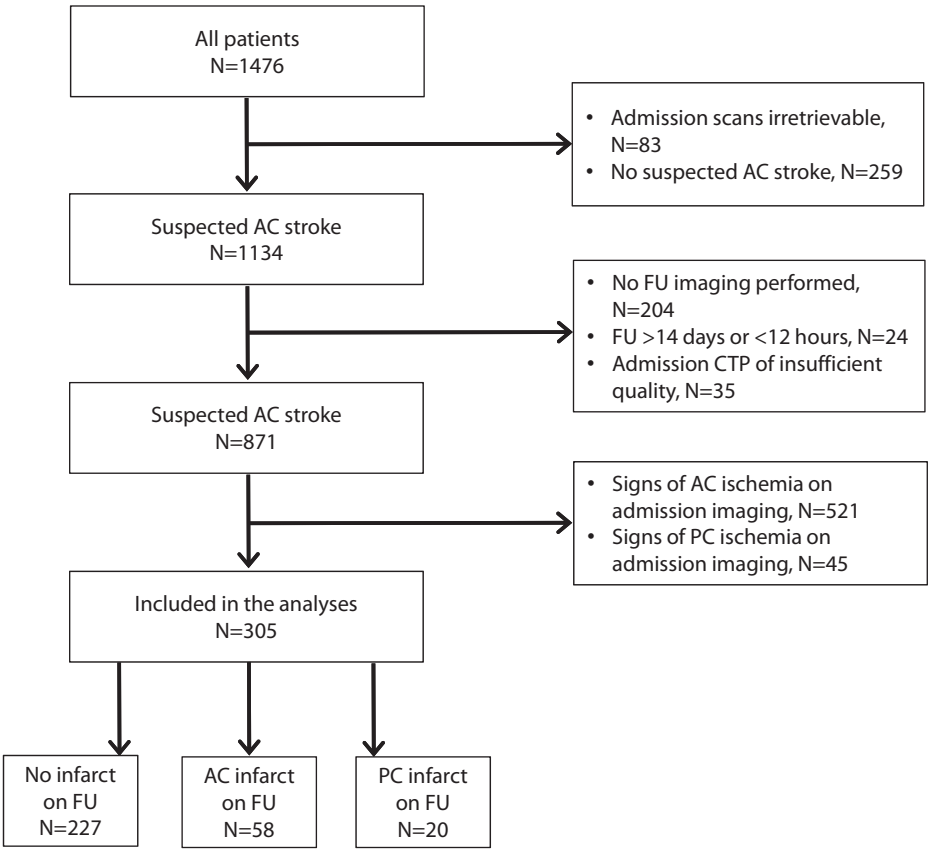

Figure 2.1 Flowchart of patients included and excluded in the study.
AC, anterior circulation; PC, posterior circulation; CTP, computed tomography perfusion; FU, follow-up.

localisation of the ischemic lesion that had caused the neurologic deficits on admission (N=75) or because PC infarction was suspected (N=184). Discharge diagnosis of these 259 excluded patients comprised a TIA in 23 patients (8 AC, 14 PC, 1 not localised) and an infarct in 213 patients (44 AC, 146 PC, 4 watershed, 16 not localised). Twenty-two patients had no ischemic diagnosis and 1 discharge diagnosis was missing.

Three hundred and five of the remaining 1134 patients who showed clinical features that suggested AC infarction fulfilled the in- and exclusion criteria. Baseline characteristics and their association with a PC infarct on follow-up CT-scanning are summarized in Table 2.1. The mean age was 68±13 years, 178 patients (58%) were male, and the median NIHSS was 4 (interquartile range (IQR) 2–6). Twenty patients (7%) had a new PC infarct (PC infarct group) on follow-up imaging. The group without PC infarct comprised 227 patients (80%)

Table 2.1 Patient characteristics and risk posterior circulation infarct

		Risk posterior circulation infarct		
	All	Characteristic present	Characteristic absent	RR (95% CI)
Number of patients	305 (100)			
Clinical measures				
Age, years, mean (SD)	68 (13)	…	…	0.99 (0.97–1.02)
Female sex	129 (42)	6/129 (4.7%)	14/176 (8.0%)	0.59 (0.23–1.48)
Cardiovascular disease	207 (68)	11/207 (5.3%)	8/89 (9.0%)	0.59 (0.25–1.42)
Stroke/TIA	94 (31)	2/94 (2.1%)	18/207 (8.7%)	0.25 (0.06–1.03)
Hypertension	163 (53)	11/163 (6.7%)	9/138 (6.5%)	1.04 (0.44–2.42)
Diabetes	59 (19)	3/59 (5.1%)	17/244 (7.0%)	0.73 (0.22–2.41)
Hyperlipidaemia	121 (40)	5/121 (4.1%)	15/169 (8.9%)	0.47 (0.17–1.25)
Angina pectoris	38 (13)	4/38 (10.5%)	16/258 (6.2%)	1.70 (0.60–4.81)
Myocardial infarction	43 (14)	2/43 (4.7%)	17/258 (6.6%)	0.71 (0.17–2.95)
Atrial fibrillation	25 (8)	2/25 (8.0%)	18/277 (6.5%)	1.23 (0.30–5.00)
Previous vascular intervention	66 (22)	3/66 (4.5%)	16/223 (7.2%)	0.63 (0.19–2.11)
Smoking (current and former)	181 (62)	10/181 (5.5%)	10/109 (9.2%)	0.60 (0.26–1.40)
Glucose (mmol/L)	7.1 (2.6)	…	…	1.04 (0.89–1.21)
Systolic blood pressure, mm Hg (SD)	163 (30)	…	…	1.00 (0.99–1.02)
Diastolic blood pressure, mm Hg (SD)	87 (17)	…	…	1.00 (0.98–1.01)
NIHSS, median (IQR)	4 (2–6)	…	…	1.07 (0.98–1.17)
1a. LOC	11	0/11 (0.0%)	20/294 (6.8%)	…
1b. LOC questions	59	4/59 (6.8%)	16/246 (6.5%)	1.04 (0.36–3.00)
1c. LOC commands	31	0/31 (0.0%)	20/274 (7.3%)	…
2. Best gaze	17	1/17 (5.9%)	19/288 (6.6%)	0.89 (0.13–6.27)
3. Visual	33	2/33 (6.1%)	18/272 (6.6%)	0.92 (0.22–3.77)
4. Facial palsy	161	15/161 (9.3%)	5/144 (3.5%)	2.68 (1.00–7.20)
5a. Motor arm left	81	7/81 (8.6%)	13/224 (5.8%)	1.49 (0.62–3.60)
5b. Motor arm right	116	6/116 (5.2%)	14/189 (7.4%)	0.70 (0.28–1.77)
6a. Motor leg left	56	7/14 (9.5%)	13/231 (5.6%)	1.68 (0.70–4.06)
6b. Motor leg right	93	6/81 (7.4%)	14/224 (6.3%)	1.19 (0.47–2.98)
7. Limb ataxia	56	6/56 (10.7%)	14/248 (5.6%)	1.90 (0.76–4.72)
8. Sensory	93	8/93 (8.6%)	12/212 (5.7%)	0.85 (0.37–1.95)
9. Best language	90	6/90 (6.7%)	14/214 (6.5%)	1.02 (0.40–2.57)
10. Dysarthria	140	11/140 (7.9%)	9/164 (5.5%)	1.43 (0.61–3.36)
11. Extinction and inattention	27	5/27 (18.5%)	15/277 (5.4%)	3.42 (1.35–8.68)
Time from symptom onset to scan, min	152 (107)	…	…	…
IV-rtPA	186 (61)	11/186 (5.9%)	9/119 (7.6%)	…
Follow-up with MRI	36 (9)	7/36 (19.4%)	13/269 (4.8%)	…
New infarct on follow-up imaging	78 (26)	20/78 (25.6%)	0/227 (0.0%)	…
Infarct volume (ml), median (IQR)	1.4 (0.8–3.1)	…	…	…

AC, anterior circulation; PC, posterior circulation; SD, standard deviation; NIHSS, NIH Stroke Scale; IQR, interquartile range; MRI, Magnetic Resonance Imaging; LOC, level of consciousness; IV-rtPA, intravenous recombinant tissue plasminogen activator.

without a new infarct on follow-up imaging and 58 patients (20%) with a new AC infarct on follow-up imaging. One hundred seventy-four of 227 patients without a new infarct on follow-up imaging (207 CT, 20 MRI) had a discharge clinical diagnosis of infarct (163 AC, 11 PC), 28 patients of TIA (27 AC, 1 PC) and 25 patients at the end had another diagnosis.

Women had less often a PC infarct than men (4.7% vs. 8.0%). Patients with a previous stroke or TIA tended to have fewer PC infarcts than those without (2.1% vs. 8.7%). However, none of these and other baseline characteristics were statistically significant related to PC infarcts.

We could not demonstrate clinically relevant statistically significant higher probability of separate NIHSS items for one of both groups. Patients in the PC infarct group had a longer time from symptom onset to CT scan (181 minutes (SD 137) versus 150 minutes (SD 105)) than patients without PC infarct. The percentage of patients treated with intravenous recombinant tissue plasminogen activator (IV-rtPA) and other clinical and biographical characteristics were comparable between groups. Patients with an infarct in the PC on follow-up imaging more often underwent an MRI than patients without an infarct in the PC (35% versus 10%). Infarct volumes were slightly lower in patients with a PC infarct (median 1.0 ml (IQR 0.6–2.0)) than in patients with an AC infarct (median 1.7 ml (IQR 0.9–3.3)).

Characteristics of infarcts in the PC

Ten PC infarcts were located in the thalamus, 5 in the pons, 4 in the cerebellum and one left occipital infarct was found in the PCA territory (mean volume 0.8, 1.0, 11.3 and 19.9 ml, respectively). Cases with PC infarct that were initially misclassified as AC infarct are summarized in Table 2.2 with their corresponding positive NIHSS items, infarct location and infarct volume. In 7 patients the location of the final PC infarct was not visible on baseline CTP.

DISCUSSION

A small but relevant proportion of patients (7%) in our cohort of patients with clinical signs and symptoms that suggested an acute AC stroke had a PC infarct on follow up imaging. Three quarters of these infarcts were lacunar infarcts in the pons or the thalamus. None of the baseline characteristics were statistically significant different between groups.

The NIHSS is a valid, reliable, and reproducible scale to describe the severity of a stroke.[5,12–14] NIHSS scores on admission are associated with functional outcome, infarct volume and

Table 2.2 Cases, NIHSS items, infarct location and volume

Case		Time symptom onset – scan (min)	NIHSS	NIHSS: score per abnormal item	IVT	Infarct location on FU scan	Infarct volume (ml)	Location of final infarct visible on baseline CTP
1.	F, 70y	135	4	Facial 1, right leg 1, sensory 1, extinction 1	Yes	TL	1.5	Yes
2.	M, 69y	100	8	Facial 1, left arm 2, left leg 2, dysarthria 2, extinction 1	Yes	PR	0.3	No
3.	M, 71y	143	3	Left arm 1, left leg 1, dysarthria 1	Yes	TR	0.7	Yes
4.	M, 82y	225	13	LOC questions 1, facial 2, right arm 3, right leg 3, ataxia 1, sensory 1, dysarthria 2	No	TL	0.7	No
5.	M, 69y	126	4	Left arm 1, left leg 1, ataxia 1 dysarthria 1	Yes	CL	15.4	No
6.	M, 40y	62	16	Gaze 1, facial 1, left arm 4, left leg 4, ataxia 2, sensory 1, dysarthria 1, extinction 2	Yes	TR	1.2	Yes
7.	F, 83y	587	1	Facial 1	No	TR	0.3	Yes
8.	M, 71y	450	9	Facial 2, right arm 1, right leg 1, ataxia 1, sensory 1, language 1, dysarthria 2	No	PL	1.4	No
9.	F, 70y	231	2	Facial 1, language 1	No	TL	0.9	No
10.	M, 70y	99	4	Facial 2, right arm 1, right leg 1	Yes	PL	0.9	Yes
11.	M, 44y	135	8	Facial 1, left arm 2, left leg 3, dysarthria 2	Yes	PR	2.1	Yes
12.	M, 64y	100	2	Facial 1, language 1	No	CR	1.0	Yes
13.	F, 71y	250	3	Facial 1, right arm 1, language 1	No	PL	0.3	No
14.	M, 67y	51	2	Ataxia 1, sensory 1	No	TL	0.3	Yes
15.	F, 68y	86	3	Ataxia 2, sensory 1	No	TL	0.6	Yes
16.	F, 58y	111	2	Sensibility 1, dysarthria 1	Yes	CL	2.3	Yes
17.	M, 48y	53	12	LOC questions 1, facial 2, right arm 4, right leg 3, language 2	Yes	TL	0.7	Yes
18.	M, 67y	229	10	LOC questions 2, visual 2, facial 1, right arm 1, right leg 1, language 1, dysarthria 1, extinction 1	No	OL	19.9	No
19.	M, 72y	135	7	Facial 1, left arm 3, left leg 2, sensory 1	Yes	CR	26.5	Yes
20.	M, 69y	315	12	LOC questions 2, visual 2, facial 2, left arm 2, left leg 2, dysarthria 1, extinction 1	Yes	TR	1.1	Yes

NIHSS, NIH Stroke Scale; IVT, IV-rtPA; FU, follow-up; CTP, computed tomography perfusion; M, male; F, female; y, years; LOC, level of consciousness; TL, thalamus left; TR, thalamus right; PR, pons right; PL, pons left; CR, cerebellum right; CL, cerebellum left; OL, occipital left.

angiographic findings.[4,15–18] Although the NIHSS is the most widely used scoring system in patients with stroke its usefulness in PC is controversial. Previous studies have emphasized the limitations of the NIHSS score for patients with a PC infarct because the NIHSS is weighted towards the deficits of AC stroke rather than PC stroke.[19,20] Still, the potential of the separate items of this scale to discriminate between AC and PC stroke is of clinical relevance. Unfortunately, we did not find any clinically relevant statistically significant higher probability of separate NIHSS items for one of both groups.

We are unaware of any earlier studies investigating the ability of separate NIHSS items to distinguish between infarct localization in the AC or PC in patients with negative baseline imaging. We identified two earlier studies that investigated the differences in neurologic deficits between consecutive patients with AC infarcts and PC infarcts with positive baseline MRI.[21] This is in contrast with the current study in which patients with positive baseline imaging were excluded. The first study found that central facial palsy, disturbed consciousness and aphasia occurred less often in the PC infarct group and ataxia occurred more often in the PC infarct group.[21] The second study investigated the NIHSS as a predictor for outcome in AC infarcts and PC infarcts.[22] This study found that the subscores of the NIHSS items ataxia and visual fields were higher in patients with PC stroke than in patients with AC stroke. Most of the other NIHSS items scores, such as level of consciousness, gaze, facial palsy, motor arm, motor leg, language and extinction and inattention were significantly higher in patients with AC stroke than in patients with PC stroke.[22]

Our study has some limitations. In the current study a multimodal CT protocol was used to detect ischemia on admission. Earlier studies have shown that the diagnostic accuracy of the combination of NCCT, CTP and CTA is modest for detection of lacunar infarcts in the PC territory.[7,23] Therefore, the use of CT as initial diagnostic modality could have underestimated the number of patients with clinical signs of PC infarct. Limited brain coverage of CTP is also known to cause false negative findings.[8] For these reasons MRI has been advocated to be the proper diagnostic modality for patients with suspected PC stroke.[24] However, others reported that during the first hours of symptom onset a considerable percentage of patients with PC stroke has a false negative diffusion weighted imaging (DWI) study.[25,26] Therefore, the use of MRI as primary imaging modality could likewise have led to an underestimation of lesion frequency. Differentiation between suspected AC and PC stroke on admission at the emergency department was not performed systematically, but was left to the discretion of the treating physician. Despite this limitation, this pragmatic approach reflects everyday practice in which rapid diagnosis and treatment of patients with suspected ischemic stroke is of crucial importance.

Earlier reports have shown that the clinical manifestations of PC and AC stroke may have a high degree of similarity.[21,27] Moreover, a considerable percentage of stroke patients has negative baseline imaging.[8] Thus, identifying alternative potential indicators aiding in the discrimination between AC and PC stroke may be of clinical relevance. In the current study we could not identify baseline and clinical characteristics that can discriminate between AC and PC stroke, indicating that this differentiation remains a challenge for the clinician.

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CHAPTER 3

Additional diagnostic value of CT-perfusion for detection of acute ischemic stroke in the posterior circulation

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ABSTRACT

Background and purpose Detection of acute infarction in the posterior circulation is challenging. We aimed to determine the additional value of CT-perfusion (CTP) to non-contrast CT (NCCT) and CT-angiography source images (CTA-SI) for infarct detection and localisation in patients suspected of acute ischemic stroke in the posterior circulation.

Methods Patients with suspected acute ischemic posterior circulation stroke were selected from the Dutch acute Stroke study (DUST). Patients underwent NCCT, CTA and CTP within nine hours after stroke onset and CT or MRI on follow-up. Images were evaluated for signs and location of ischemia. Discrimination of three hierarchical logistic regression models (NCCT (A), added CTA-SI (B) and CTP (C)) was compared with C-statistics.

Results Of 88 patients, 76 (86%) had a clinical diagnosis of ischemic stroke on discharge, and 42 patients (48%) showed a posterior circulation infarct on follow-up imaging. Model C (area under the curve form the receiver operating characteristic curve (AUC-ROC)=0.86, 95% confidence interval 0.77–0.94) predicted an infarct in the posterior circulation territory better than models A (AUC-ROC=0.64, 95% confidence interval 0.53–0.76, $P_{C\ vs.\ A}<0.001$) and B (AUC-ROC=0.68, 95% confidence interval 0.56–0.79, $P_{C\ vs.\ B}<0.001$).

Conclusion CTP has significant additional diagnostic value to NCCT and CTA-SI for detecting ischemic changes in patients suspected of acute posterior circulation stroke.

INTRODUCTION

Posterior circulation stroke accounts for 20% of ischemic strokes. Clinical signs and symptoms of anterior and posterior ischemic stroke may overlap, causing a delay in making the correct diagnosis.[1] In the acute stage non-contrast computed tomography (NCCT) is used to exclude cerebral hemorrhage and pathologies other than ischemic stroke, and to detect early signs of ischemia. CT angiography (CTA) can provide information on presence and site of an arterial occlusion. CTA-source images (CTA-SI) can also help to detect ischemic changes.[2] CT perfusion (CTP) can detect ischemic perfusion defects, with pooled analysis sensitivity of 80% (95% confidence interval (CI) 72–86%) and specificity of 95% (95% CI 86–98%) for early diagnosis of stroke.[3] The additional diagnostic value of CTP compared to NCCT and CTA for stroke in the posterior circulation has not been analyzed.

We investigated the additional diagnostic value of CTP to CTA-SI and NCCT for infarct detection and localisation in patients suspected of acute ischemic stroke in the posterior circulation.

METHODS

Patients

All patients participated in the prospective, multicenter, observational Dutch acute stroke study (DUST; ClinicalTrials.gov NCT00880113) in which the diagnostic values of CTA and CTP within nine hours after onset of the neurological deficit were investigated in patients with acute ischemic stroke.[4] We selected consecutive patients between May 2009 and December 2012 with suspected acute ischemic stroke in the posterior circulation as defined in the Oxfordshire classification.[5] Reasons for exclusion were poor image quality, not all three posterior circulation Alberta Stroke Program Early CT Score (PC-ASPECTS)[6] levels included in the CTP slab, or missing follow-up imaging.

Imaging

Protocols of NCCT, CTA and CTP imaging have been reported previously.[4] Location of ischemic changes in the posterior circulation territory was allocated according to the 8 PC-ASPECTS regions: pons, midbrain and right or left thalamus, right or left cerebellum and right or left posterior cerebral artery (PCA) territory (Figure 3.1).[6]

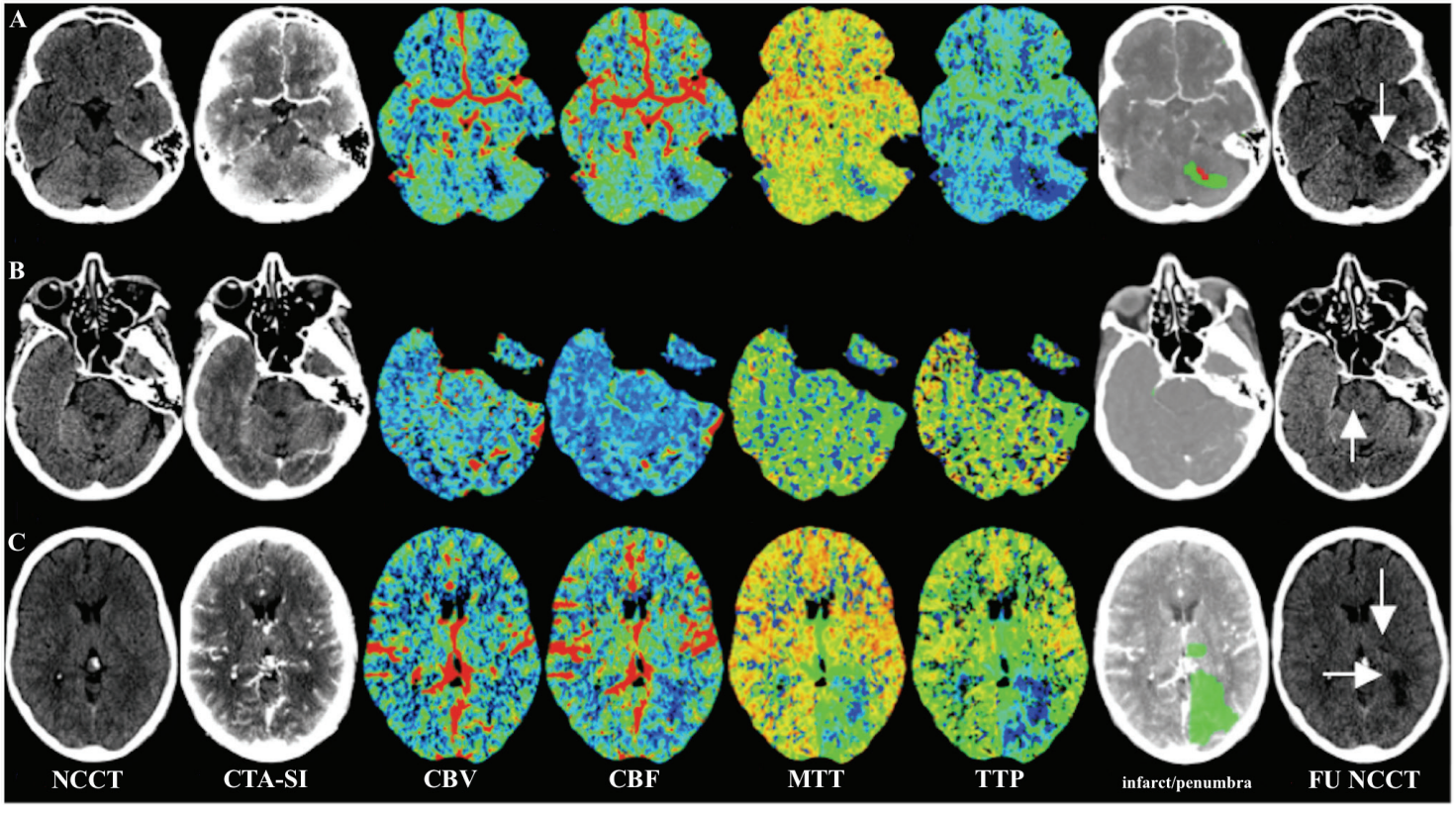

Figure 3.1 Illustration of multimodal computed tomography (CT) in posterior circulation stroke.
A) Left cerebellar stroke: no early ischemic signs on noncontrast CT (NCCT) and CT angiography source images; evident abnormalities on CTP; follow-up NCCT shows demarcation of the ischemic area (arrow). B) Absence of early ischemic changes and abnormalities on all techniques; follow-up NCCT shows a small pons infarct on the right (arrow). C) Left posterior cerebral artery territory stroke with thalamic involvement; only CTP maps show the ischemic regions that turn to infarction on follow-up NCCT (arrows). CBF indicates cerebral blood flow; CBV, cerbral blood volume; MTT, mean transit time, and TTP, time to peak.

Follow-up imaging consisted of NCCT, or if clinically indicated MRI (including diffusion-weighted imaging and fluid attenuated inversion recovery), and was performed around day 3 after admission or earlier if patients deteriorated or were discharged from hospital.

Statistical analysis

Three logistic regression models were developed, including NCCT (model A), with addition of CTA-SI (model B), and addition of CTA-SI and CTP (model C). The diagnostic value of each model was assessed with the area under the curve (AUC) from the receiver operating characteristic curve (ROC). Additional diagnostic value of the models was assessed by comparing the AUC-ROCs.[7]

RESULTS

Eighty-eight patients with suspected posterior circulation stroke fulfilled the inclusion criteria (Table 3.1). Mean time from symptom onset to imaging was 227±154 minutes. Admission NCCT detected 13 (31%), CTA-SI 14 (33%) and CTP 31 (74%) of the 42 patients with an infarct in the posterior circulation on follow-up imaging (Table 3.2). Positive predictive values (PPVs) were high for all diagnostic modalities. The negative predictive value (NPV) of CTP (80%) was higher compared to NCCT (61%) and CTA-SI (62%). Small infarct size or artifacts caused false negative CTP in eleven patients, including six in the brainstem.

Follow-up imaging showed 62 infarcts in 704 assessed regions (Table 3.2). NCCT detected 15 (24%), CTA-SI 17 (27%) and CTP 41 (66%) infarcts. CTP detected significantly more ischemic lesions in the cerebellum, PCA territory, and thalami than NCCT and CTA-SI. For all techniques lesion detection was poorest in pons and midbrain.

The AUC was 0.64 (95% CI 0.53–0.76) for model A (NCCT), 0.68 (95% CI 0.56–0.79) for model B (NCCT + CTA-SI), and 0.86 (95% CI 0.77–0.94) for model C (NCCT + CTA-SI + CTP). There was no significant difference between model A and model B ($p=0.08$). Model C predicted an infarct in the posterior circulation territory significantly better than both model A ($p<0.001$) and model B ($p<0.001$).

Table 3.1 Patient characteristics

Number of patients	88
Age in years, mean (SD)	63 (13)
Male sex	59 (67)
NIHSS, median (IQR)	2.5 (2–5)
Time of symptom onset to start CT protocol	
0–4.5 hours	61 (69)
4.5–9 hours	27 (31)
Intravenous thrombolysis	43 (49)
Mechanical thrombectomy	3 (3.4)
Follow-up imaging	
NCCT	75 (85)
MRI	13 (15)
Final clinical diagnosis	
Ischemic stroke[a]	76 (86)
Posterior circulation	71 (93)
Detected on FU imaging	42 (59)
Anterior circulation	6 (8)
Detected on FU imaging	3 (50)
TIA	3 (3)
Posterior circulation	3 (100)
Non ischemic	9 (10)

All values are given as number (%), unless otherwise indicated. CT indicates computed tomography; FU, follow-up; IQR, interquartile range; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.
[a] One patient had both anterior and posterior circulation stroke.

DISCUSSION

Our findings show that adding CTP to NCCT and CTA-SI in the diagnostic work-up in patients suspected of an ischemic stroke in the posterior circulation significantly increases diagnostic accuracy. Detection of acute ischemia in the brainstem remains challenging.

We are aware of only one other study investigating stroke detection with CTP in posterior circulation stroke. In this study no significant differences between detection of infratentorial and supratentorial stroke lesions were found.[8] Sensitivity and specificity for detection of infratentorial ischemic lesions was respectively 91% and 93%. The longer duration from stroke onset to imaging in this study (mean 540 versus 227 minutes) probably accentuated ischemic changes and therefore increased sensitivity. Lacunar strokes were excluded, whereas small infarcts caused false negative findings in our study.

Table 3.2 Detection of ischemia

	Infarct on follow-up					
	Yes	No	PPV	NPV	Sensitivity	Specificity
Any patient						
NCCT	13	1	93 (66–100)	61 (49–72)	31 (18–47)	98 (88–100)
CTA-SI	14	1	93 (68–100)	62 (50–73)	33 (20–50)	98 (88–100)
CTP	31	3	91 (76–98)	80 (66–89)	74 (58–86)	93 (82–99)
Total	42	46				
Cerebellum						
NCCT	8	1	89 (52–100)	89 (83–93)	30 (14–50)	99 (96–100)
CTA-SI	11	1	92 (62–100)	90 (85–94)	41 (22–61)	99 (96–100)
CTP	23	6	79 (60–92)	97 (93–99)	85 (66–96)	96 (91–99)
Total	27	149				
Thalamus						
NCCT	1	1	50 (1–99)	94 (89–97)	8 (0–38)	99 (97–100)
CTA-SI	0	0	NA	93 (88–96)	0 (0–26)	100 (98–100)
CTP	6	4	60 (26–88)	96 (92–99)	50 (21–79)	98 (94–99)
Total	12	164				
PCA territory						
NCCT	5	1	83 (36–100)	95 (91–98)	38 (14–68)	99 (97–100)
CTA-SI	5	0	100 (48–100)	95 (91–98)	38 (14–68)	100 (98–100)
CTP	11	5	69 (41–89)	99 (96–100)	85 (55–98)	97 (93–99)
Total	13	163				
Pons/midbrain						
NCCT	1	4	20 (0–72)	95 (90–98)	10 (0–45)	98 (94–99)
CTA-SI	1	4	20 (0–72)	95 (90–98)	10 (0–45)	98 (94–99)
CTP	1	4	20 (0–72)	9 5(90–98)	10 (0–45)	98 (94–99)
Total	10	166				

Numbers given for PPV, NPV, sensitivity, and specificity are percentages (95% CI). CI indicates confidence interval; CTA-SI, computed tomography source images; CTP, computed tomography perfusion; NA, not applicable; NCCT, noncontrast computed tomography; NPV, negative predictive value; PCA, posterior cerebral artery; PPV, positive predictive value.

Intravenous trombolytic therapy (IVT) may also have influenced sensitivity and specificity since it can achieve timely restoration of reperfusion. Consequently ischemic but still viable regions may not progress to infarction in treated patients, leading to false positive findings. False positive findings may also be caused by follow-up NCCT as small (lacunar) infarcts and brainstem infarcts can be difficult to visualize on NCCT.[9]

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CHAPTER 4

Collateral flow predicts outcome after basilar artery occlusion: the posterior circulation collateral score

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ABSTRACT

Background and aim Our aim was to assess the prognostic value of a semi quantitative computed tomography angiography-based grading system, for the prediction of outcome in patients with acute basilar artery occlusion, based on the presence of potential collateral pathways on computed tomography angiography: the posterior circulation collateral score (PC-CS).

Methods One hundred forty-nine patients with acute basilar artery occlusion from the Basilar Artery International Cooperation Study were included. We related poor outcome at one month, defined as a modified Rankin scale score of 4 or 5, or death to collateral flow with Poisson regression. We used a 10 points grading system to quantify the potential for collateral flow in the posterior communicating arteries and the cerebellar arteries. Additionally, the relation between the presence and size of posterior communicating arteries and outcome was analyzed.

Results Thirty-six patients had poor (PC-CS: 0–3), 59 patients intermediate (PC-CS: 4–5) and 54 patients good (PC-CS: 6–10) collaterals. Multivariable analyses showed a statistically significant lower risk of poor outcome in patients with a good PC-CS than in patients with a poor PC-CS (risk ratio (RR) 0.74, 95% confidence interval (CI) 0.58–0.96), but not for patients with an intermediate PC-CS compared with patients with a poor PC-CS (RR 0.95, 95% CI 0.78–1.15). Multivariable analyses showed a statistically significant lower risk of poor outcome for the presence of at least one posterior communicating artery and for larger caliber of posterior communicating arteries (RR 0.79, 95% CI 0.66–0.95 and 0.76, 95% CI 0.61–0.96, respectively).

Conclusions The PC-CS predicted poor outcome at one month. In a separate analysis, both the absence and smaller caliber of posterior communicating arteries predicted poor outcome.

INTRODUCTION

Despite recent advances in acute stroke treatment, basilar artery occlusion (BAO) is strongly associated with mortality and poor functional outcome among survivors.[1] Several clinical predictors of outcome after BAO, such as the National Institutes of Health Stroke Scale (NIHSS) score at admission, age, time to treatment and recanalization have been identified in earlier studies.[1-4] In addition, several potential imaging derived predictors of outcome have been proposed.[5-7]

Collaterals have been recognized to influence recanalization, reperfusion, hemorrhagic transformation, and subsequent neurological outcomes in patients with anterior circulation stroke.[8-11] Retrograde blood flow from the anterior circulation through the posterior communicating arteries (PCoAs) may serve as a primary collateral pathway, potentially providing immediate diversion of cerebral blood flow to ischemic occipital and infratentorial regions.[12] PCoA size has been used as an indicator of collateral flow in small series of patients with BAO using computed tomography angiography (CTA)[13,14] and digital subtraction angiography (DSA).[15]

Secondary collateral pathways comprise arteriolar anastomoses from the inferior and posterior divisions of the middle cerebral artery (MCA), potentially supplying the posterior cerebral artery (PCA) and leptomeningeal anastomoses between the branches of the intradural segments of the vertebral arteries and branches of the basilar artery.[12,16] In addition, the anterior and posterior spinal arteries communicate with branches of the proximal intracranial arteries supplying the medulla and the pons.[17]

Earlier studies have mainly used DSA for collateral assessment in BAO.[5,13,15,16,18] Nowadays, the clinical diagnosis of BAO is usually confirmed with CTA. The non-invasive nature of CTA and its wide and rapid availability make it the preferred diagnostic modality to assess vascular anatomy in the acute stage and potentially to determine collateral status. The presence of PCoA can readily be evaluated on thin section CTA. However, secondary leptomeningeal and pial collaterals between the main branches of the vertebral and basilar artery, the anastomoses between distal MCA and PCA branches and the anastomoses between the spinal arteries and vertebral and basilar branches cannot be assessed reliably.

AIMS AND HYPOTHESIS

We hypothesized that quantification of the residual patency of main vertebrobasilar side branches (posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA) and superior cerebellar artery (SCA)) and the presence and caliber of PCoA reflects the potential collateral pathways and consequently predicts outcome in terms of functional independence.

The aim of our study was to assess the prognostic value of a semi quantitative CTA based grading system, incorporating primary and potential secondary collateral pathways in acute BAO: the posterior circulation collateral score (PC-CS). In addition, we investigated the prognostic value on outcome of primary collateral pathways by assessing the presence and caliber of PCoAs separately.

METHODS

Study population

Patients from the Basilar Artery International Cooperation Study (BASICS) were included. BASICS was a prospective, observational, international registry of consecutive patients aged 18 years or older who presented with an acute symptomatic BAO, confirmed by imaging. The BASICS protocol has been described previously.[1] Overall, 619 patients were included in this registry.

Inclusion criteria for the current study were confirmation of BAO on CTA, which had to be available in Digital Imaging and Communications in Medicine (DICOM) format of sufficient quality. CTA was performed according to the local protocol. We included patients who were recruited at sites that performed a CTA in at least 10 patients.

The primary outcome measure was poor outcome at one month, defined as a modified Rankin scale (mRS) score of 4 or 5 (severe disability) or death.

Grading system

In contrast to DSA and CT perfusion CTA does not provide temporal information on collateral flow in patients with BAO. Furthermore, visibility or non-visibility of vertebrobasilar side branches and PcoAs depends on location and length of BAO. We therefore used a semi-quantitative grading system to quantify the potential for collateral flow in the posterior

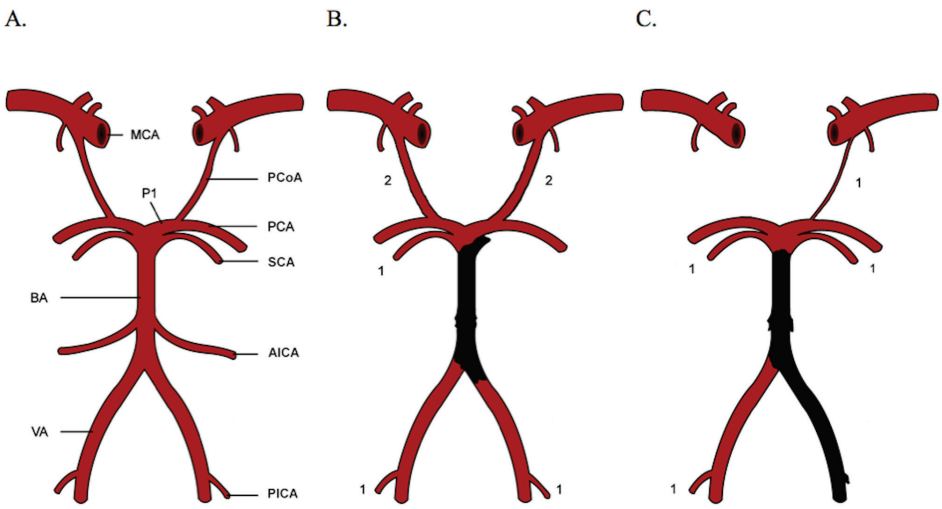

Figure 4.1 Illustration of the posterior circulation collateral score (PC-CS).
A) The posterior circulation collateral score (PC-CS) allocates potential collateral pathways in the posterior circulation a maximum of 10 points; 1 point for each patent posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA) and superior cerebellar artery (SCA), 1 point for each patent posterior communicating artery (PCoA) with a caliber smaller than the ipsilateral P1 segment of the posterior cerebral artery (PCA) and 2 points for each PCoA with a caliber equal or larger than the ipsilateral P1 segment. B) Basilar artery occlusion (BAO) with a bilateral patent PICA, patent right SCA and bilateral patent large caliber PCoA resulting in a 'good' PC-CS of 7. C) BAO with a patent right PICA, bilateral SCA and small left PCoA resulting in an 'intermediate' PC-CS of 4.

circulation in acute BAO. In this 10-point grading system, each patent PICA, AICA and SCA is allocated with 1 point. Identification of a PCoA is allocated with 1 point if its diameter is smaller than the ipsilateral P1 segment and 2 points if its diameter is equal or larger than the ipsilateral P1 segment (Figure 4.1). Fetal variants of the PCA, defined as a PCA arising from the anterior circulation and absence of P1 segments, were not included in this score.

A poor PC-CS is defined as a score of 0–3, intermediate PC-CS as 4–5 and a good PC-CS as a score of 6–10. Two investigators (EJRJH and FMV) independently reviewed the CTA images. If the assessment was inconsistent, the final verdict was made by an experienced neurointerventionalist (JAV). Interrater reliability was assessed with kappa statistics.

Data analysis

Baseline data were reported with standard descriptive statistics. The frequency of poor outcome was compared among the three PC-CS groups with risk ratios (RRs) and corresponding 95% confidence intervals (CIs) with Poisson regression. Additionally, in multivariable analysis,

adjustments were made for the three factors (age, type of treatment and time to treatment) affecting the crude RR the most. In addition, the relation between the presence and size of PCoAs and outcome was analyzed separately. As the baseline NIHSS is a reflection of the severity of the initial stroke and therefore is affected by the collateral status, it was not considered as a potential confounder in developing the multivariable model.[19,20] Missing baseline data (<5% for each variable) were imputed with regression imputation for optimal adjustment for baseline differences between the groups of interest.[21]

RESULTS

CTA images in DICOM format of sufficient quality of 149 patients were available. Mean slice thickness was 1.09 mm (range 0.625–3.0 mm). Patients included in the current study had slightly higher NIHSS scores (median 24) than those without adequate CTA data (median 21), otherwise these two groups were comparable (data not shown). Mean age of the included patients was 64 years and the majority of patients were male (66%). Median time from estimated time of BAO to CTA was 270 minutes. Thirty-six patients (24%) had a poor, 59 patients (40%) an intermediate and 54 patients 36%) a good PC-CS. Prevalence of common risk factors for stroke was comparable between groups (Table 4.1). Patients with a poor PC-CS more often had a severe deficit (defined as coma, tetraplegia, or a locked-in state) at time of treatment than patients with an intermediate or good PC-CS (75%, 63% and 61%, respectively). Consequently, patients with a poor PC-CS had a higher median NIHSS than patients with an intermediate or good PC-CS (28, 25 and 20, respectively). Nine patients (25%) with a poor PC-CS received no medical treatment compared with 2 (3%) and 2 (4%) patients with an intermediate and good PC-CS, respectively.

Interrater agreement between EJRJH and FMV for classification of PC-CS group (poor, intermediate, good) and for assessment of the PCoAs (not identifiable, smaller than ipsilateral P1 segment, equal or larger than ipsilateral P1 segment) resulted in a kappa of 0.59 both. Interrater agreement for the inconsistencies yielded kappas of 0.82 (PC-CS group) and 0.87 (PCoAs) between EJRJH and JAV.

Figure 4.2 illustrates the mRS distribution after one month in the three PC-CS groups. Table 4.2 shows the RRs for poor outcome when the PC-CS groups are compared. After adjustment for age, time to treatment and type of treatment there was a statistically significant lower risk in patients with a good PC-CS with respect to poor outcome compared with patients with a poor PC-CS (RR 0.74, 95% CI 0.58–0.96). Adjustment for sex, age, prodromal stroke or

Table 4.1 Baseline characteristics according to posterior circulation collateral score (PC-CS) group

	Posterior circulation collateral score 0–3 (poor) n=36	Posterior circulation collateral score 4–5 (intermediate) n=59	Posterior circualtion collateral score 6–10 (good) n=54
Age, mean (standard deviation)	66 (14)	67 (14)	62 (16)
Women (%)	12 (33)	23 (39)	16 (30)
Hypertension (%)	22 (61)	39 (66)	33 (61)
Diabetes mellites (%)	11 (31)	7 (12)	13 (24)
Hyperlipidemia (%)	8 (22)	13 (22)	19 (35)
Atrial fibrillation (%)	6 (17)	8 (14)	12 (22)
Coronary artery disease (%)	3 (8)	10 (17)	8 (15)
Peripheral arterial disease (%)	3 (8)	3 (5)	4 (7)
Smoking (%)	8 (22)	10 (17)	11 (20)
Prodromal transient ischemic attack (%)	15 (42)	28 (48)	17 (32)
Prodromal minor stroke (%)	7 (19)	8 (14)	13 (24)
Deficit			
Mild to moderate (%)	9 (25)	22 (37)	21 (39)
Severe (%)	27 (75)	37 (63)	33 (61)
NIHSS, median (interquatile range)	28 (19–37)	25 (13–32)	20 (8–29)
NIHSS >20 (%)	26 (72)	37 (63)	26 (48)
Treatment			
Acetylsalic acid/heparin (%)	8 (22)	19 (32)	20 (37)
Intravenous thrombolysis (%)	4 (11)	4 (7)	7 (13)
Intravenous thrombolysis/intra arterial treatment (%)	1 (3)	5 (9)	6 (11)
Intra arterial thrombolysis/intra arterial thrombolysis and mechanical thrombectoy/ mechanical thrombectomy(%)	14 (39)	29 (49)	19 (35)
No treatment (%)	9 (25)	2 (3)	2 (4)
Time to treatment			
0–3 h (%)	7 (19)	12 (20)	21 (39)
3–6 h (%)	7 (19)	20 (34)	10 (19)
>6 h (%)	13 (36)	10 (19)	21 (39)
Location of occlusion			
Distal third (%)	12 (33)	21 (36)	18 (33)
Middle third (%)	7 (19)	14 (24)	12 (22)
Proximal third (%)	17 (47)	24 (41)	24 (44)
Cause of stroke			
Embolic (%)	9 (25)	19 (32)	25 (46)
Atherosclerosis (%)	13 (36)	29 (49)	17 (32)
Dissection (%)	1 (3)	2 (3)	3 (6)
Other (%)	0 (0)	1 (2)	0 (0)
Unknown (%)	13 (36)	8 (14)	9 (17)

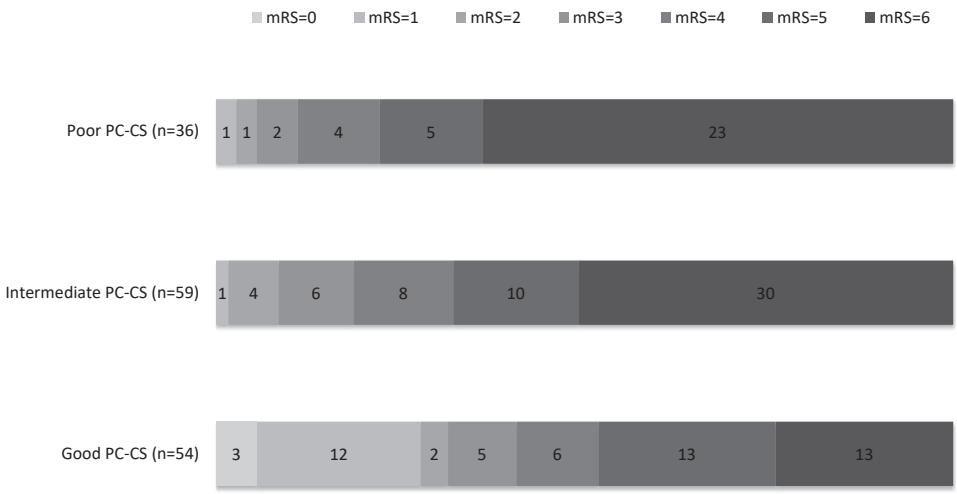

Figure 4.2 Distribution of mRS at 1 month in the three different posterior circulation collateral score (PC-CS) groups.

Table 4.2 Risk ratios for poor outcome according to posterior circulation collateral score (PC-CS) – univariable and multivariable analyses

	Posterior circulation collateral score intermediate (4–5) vs. poor (0–3) n=59	Posterior circulation collateral score good (6–10) vs. poor (0–3) n=54
Poor outcome[a]	48 (81%)	32 (59%)
Unadjusted risk ratio (95% CI)	0.92 (0.77–1.08)	0.67 (0.52–0.86)
Age (95% CI)	0.91 (0.77–1.07)	0.68 (0.53–0.87)
Time to treatment (95% CI)	0.96 (0.79–1.17)	0.72 (0.56–0.93)
Treatment (95% CI)	0.97 (0.80–1.16)	0.72 (0.56–0.94)
2 factors (95% CI)	0.97 (0.80–1.17)	0.74 (0.57–0.95)
3 factors (95% CI)	0.95 (0.78–1.15)	0.74 (0.58–0.96)

[a] Poor outcome for PC-CS 0–3: 32/36 = 89%.
2 factors: treatment, time to treatment.
3 factors: treatment, time to treatment, age.

symptoms, time to CTA, thrombus location, diabetes mellitus, hyperlipidemia, hypertension, atrial fibrillation, smoking status, a history of peripheral artery or coronary artery disease and post treatment basilar artery patency only marginally influenced the risk ratios. There was no difference in the risks of poor outcome of patients with an intermediate PC-CS compared with patients with a poor PC-CS (RR for poor outcome 0.95, 95% CI 0.78–1.15).

Separate analysis of the presence of PCoAs (present vs. not present, assessed for both sides) showed a statistically significant lower crude risk for poor outcome when at least one PCoA was present (Table 4.3). After adjustments for the three factors affecting the crude RR the most (age, time to treatment and treatment), this difference was statistically significant (RR 0.79, 95% CI 0.66–0.95). Results were similar for 1 or 2 patent PCoAs. When caliber of PCoAs was taken into account a statistically significant lower risk of poor outcome was seen in patients with larger (total score ≥2) caliber PCoAs (RR 0.76, 95% CI 0.61–0.96) (Table 4.4).

Table 4.3 Risk ratios for poor outcome according to posterior communicating artery (PCoA) patency – univariable and multivariable analyses

	≥1 posterior communicating artery vs. no posterior communicating artery n=79
Poor outcome[a]	50 (63%)
Unadjusted risk ratio (95% CI)	0.72 (0.59–0.86)
Age (95% CI)	0.74 (0.61–0.88)
Time to treatment (95% CI)	0.75 (0.63–0.90)
Treatment (95% CI)	0.74 (0.61–0.90)
2 factors (95% CI)	0.77 (0.64–0.93)
3 factors (95% CI)	0.79 (0.66–0.95)

[a] Poor outcome for no patent PCoA: 62/70 = 89%.
2 factors: treatment, time to treatment.
3 factors: treatment, time to treatment, age.

Table 4.4 Risk ratios for poor outcome according to posterior communicating artery (PCoA) caliber – univariable and multivariable analyses

	Posterior communicatin artery caliber = 1 vs. 0 n=21	Posterior communicating artery caliber ≥2 vs. 0 n=58
Poor outcome[a]	15 (71%)	35 (60%)
Unadjusted risk ratio	0.81 (0.61–1.07)	0.68 (0.54–0.85)
Age (95% CI)	0.81 (0.62–1.07)	0.70 (0.57–0.88)
Time to treatment (95% CI)	0.83 (0.63–1.09)	0.72 (0.58–0.90)
Treatment (95% CI)	0.83 (0.64–1.08)	0.71 (0.56–0.90)
2 factors (95% CI)	0.85 (0.66–1.10)	0.73 (0.58–0.92)
3 factors (95% CI)	0.86 (0.67–1.10)	0.76 (0.61–0.96)

PCoA caliber: 1 point for PCoA smaller than ipsilateral P1 segment, 2 points for PCoA equal or larger than ipsilateral P1 segment.
[a] Poor outcome for no patent PCoA: 62/70 = 89%.
2 factors: treatment, time to treatment.
3 factors: treatment, time to treatment, age.

DISCUSSION

We propose a CTA based score, the PC-CS, for quantification of potential collateral flow in patients with an acute BAO. This PC-CS independently predicted poor outcome at one month, defined as an mRS score of 4–6 in these patients. In the separate PCoAs assessment the absence of patent PCoAs independently predicted poor outcome and larger caliber of PCoA was associated with a relative low risk of poor outcome.

Good angiographic filling of collaterals supplying the posterior circulation was considered a predictor of favorable outcome in some small series.[15,16,22] but could not be confirmed in one other study.[5] Recently Qureshi proposed a new DSA derived score to categorize the collateral circulation in patients with a basilar artery stenosis or occlusion but this score has not yet been validated in larger cohorts.[23,24] Others reported that a better collateralization status (according to the American Society of Interventional and Therapeutic Neuroradiology/ Society of Interventional Radiology (ASITN/SIR) collateral grading system) independently predicted recanalization (defined as a Trombolyis in Cerebral Infarction (TICI) score 2b or 3).[18] However, non-invasive collateral grading systems are expected to become more important in the future, as most stroke patients will not undergo diagnostic DSA.[25]

Larger PCoA size has been linked with better outcome after deliberate basilar and vertebral artery ligation in the treatment of intracranial aneurysms.[26] Others have not been able to show a relationship between PCoA size and outcome in IAT treated patients with a BAO.[27]

Although the BASICS registry is the largest prospective registry of consecutive patients with an acute BAO, the observational design inherently has limitations. First, with 149 patients included in the current study the sample size is still small. Second, the choice of treatment was left to the discretion of the clinicians, and was inevitably influenced by the suspected prognosis and effect of treatment. The results of the BASICS registry showed no significant difference in outcome between treatment groups. We therefore assumed it to be unlikely that a difference in outcome between the PC-CS groups would be the result of a treatment effect. Multivariable analysis can never adjust completely for systematic differences between PC-CS groups, but the risk of poor clinical outcome remained significantly higher in the poor PC-CS group than in the high PC-CS group after adjustments for the factors influencing the crude risk the most (age, treatment and time to treatment). Third, inter-rater agreement between the first two authors was moderate, however, that for the inconsistent pairs yielded good agreement between the radiologist and senior neurointerventionalist. This suggests that agreement in clinical practice is likely to be acceptable.

The PC-CS is the first CTA derived score for quantification of collateral flow in the posterior circulation. Our results need to be validated in other cohorts, like the currently recruiting BASICS trial.[28]

FUNDING

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CHAPTER 5

Clot length predicts recanalisation but not outcome after basilar artery occlusion

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ABSTRACT

Introduction The aim of our study was to evaluate the effect of clot length on both recanalisation and outcome in acute basilar artery occlusion (BAO).

Patients and methods One hundred forty-nine patients with an acute BAO from the Basilar Artery International Cooperation Study (BASICS) were included. Clot length was assessed on computed tomographic angiography. Thrombus length was divided in tertiles and was related with recanalisation and outcome at one month, with Poisson regression. Modified Rankin scale scores of 4 or 5, or death were considered poor outcomes. Additionally, clot length was analysed as a continuous variable.

Results Forty-nine patients (33%) had a short (4–11 mm), 50 (34%) an intermediate (12–22 mm) and 50 (34%) a long clot (≥23 mm). Multivariable analyses showed a significantly lower probability of recanalisation but no statistically significant difference in poor outcome for patients with a long clot compared with patients with a short clot (RR 0.64, 95% CI 0.42-0.98 and RR 1.10, 95% CI 0.88–1.37, respectively). No statistically significant differences were found for patients with an intermediate clot length compared with patients with a short clot length (RR 0.97, 95% CI 0.75–1.25 and RR 1.11, 95% CI 0.88–1.40, respectively). Analyses of clot length as a continuous variable showed a 10% reduction in chance of recanalisation and a 2% increase in risk of poor outcome with every centimetre increase in clot length (RR 0.90, 95% CI 0.78–1.04 and RR 1.02, 95% CI 0.98–1.05, respectively).

Conclusions Clot length predicted recanalisation but not outcome at one month in patients with a BAO. We found 2% more poor outcome and 10% less recanalisation with every centimetre increase in clot length.

INTRODUCTION

Several imaging predictors of recanalisation and outcome after basilar artery occlusion (BAO) have been proposed.[1,2] Amongst these imaging predictors, clot length has been shown to affect recanalisation rates of middle cerebral artery occlusion (MCAO)[3–5] and BAO[6] after intravenous therapy (IVT) with recombinant tissue Plasminogen Activator (rtPA). Clot length measurements may be useful for neurointerventionalists when determining the appropriate size of a device to use and may assist in decision making when to intervene. However, delaying or withholding intra-arterial treatment (IAT) in the presence of a short clot in MCAO seems undesirable in the light of the recent positive anterior circulation trials.[7] Unlike acute MCAO, BAO lacks a proven treatment strategy and, as a result, current treatment strategies of BAO vary widely between centres.[8,9] Although recanalisation has been shown to be an important predictor of outcome in patients with BAO,[1,10,11] recanalisation alone does not guarantee good outcome and functional independence.[12,13]

In contrast to the effect of clot length on recanalisation in IVT treated patients with BAO, little research has been conducted to investigate the effect of clot length on clinical outcome in these patients. Therefore, the aim of our study was to evaluate the effect of clot length on both recanalisation and outcome in acute BAO.

PATIENTS AND METHODS

Study population

Patients from the Basilar Artery International Cooperation Study (BASICS) who met the inclusion criteria below were included. BASICS, the largest prospective registry of consecutive patients with acute symptomatic BAO confirmed by imaging, consisted of 619 patients. The BASICS protocol has been described previously.[14] The ethics committee of the University Medical Center Utrecht, The Netherlands approved the BASICS protocol. 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.

Inclusion criteria for the current study were confirmation of BAO on computed tomographic angiography (CTA). To ensure experience of centers in the performance and interpretation of CTA we included patients who were recruited at sites that performed a CTA in at least 10

patients. CTA was performed according to the local protocol and studies had to be available in Digital Imaging and Communications in Medicine (DICOM) format of sufficient quality.

The primary outcome measures were recanalisation and poor outcome at one month. Recanalisation was defined as a patent basilar artery on CTA, magnetic resonance angiography (MRA) or transcranial Doppler (TCD) or a thrombolysis in myocardial infarction (TIMI) score of 2 or 3 on digital subtraction angiography (DSA). In IAT treated patients, recanalisation was assessed at the end of the angiographic procedure. In patients receiving only antithrombotic treatment (which comprised antiplatelet drugs or systemic anticoagulation) or IVT, recanalisation was assessed in the hours to days after treatment. Recanalisation was not routinely assessed in patients who received no treatment. Poor outcome was defined as a modified Rankin scale (mRS) score of 4 or 5 or death.

Imaging analysis

Thrombus length on CTA was assessed with the 3D curved multiplanar reconstruction function in the v4.1.1 open-source OsiriX DICOM viewer (Figure 5.1). Scans were read centrally by EJRJH. When the clot extended into the vertebral artery and/or the posterior cerebral artery the total clot length was scored. When clot extended in both vertebral or both posterior cerebral arteries the shortest clot length was scored. Whenever the proximal or distal end of the clot could not be identified this was recorded and the largest identifiable clot length was scored.

Data analysis

Baseline data are reported with standard descriptive statistics. Whenever the proximal or distal end of the clot could not be identified 5 mm was added arbitrarily to the measured clot length. We defined three clot length groups of equal size. Short clot length was defined as 4–11 mm, intermediate clot length as 12–22 mm and long clot length as ≥23 mm. The frequency of poor outcome and recanalisation was compared among the three groups with risk ratios (RRs) and corresponding 95% CIs with Poisson regression. Additionally, in multivariable analysis, adjustments were made for the factors most affecting the crude risk ratio (RR). Treatment was categorized into 5 groups: antithrombotics without IVT or IAT; IVT; IVT followed by IAT; IAT alone, in combination with mechanical thrombectomy or mechanical thrombectomy alone and no treatment. Because the baseline National Institutes of Health Stroke Scale (NIHSS) is a reflection of the severity of the initial stroke and therefore, hypothetically, is affected by the clot length, it was not considered as a

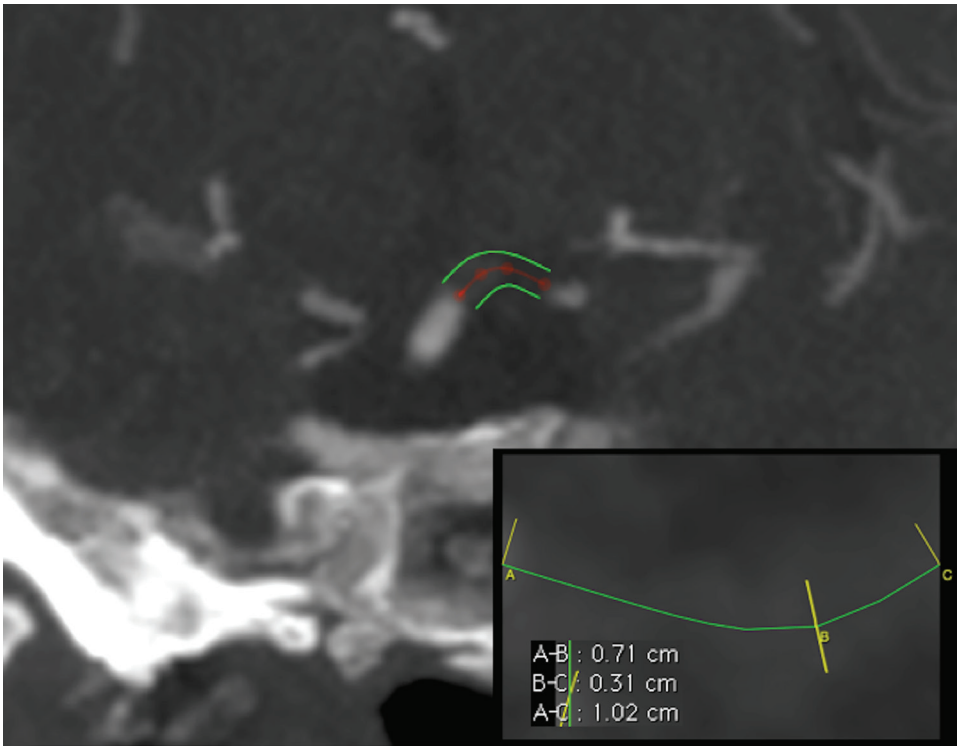

Figure 5.1 Thrombus length assessment on CTA of a patient with a top of the basilar artery occlusion with clot extending into the left posterior cerebral artery.

potential confounder in developing the multivariable model.[15,16] Additionally, clot length was analysed as a continuous variable. Missing baseline data (<5% for each variable) were imputed with regression imputation for optimal adjustment for baseline differences between the groups of interest.[17]

RESULTS

One hundred forty-nine patients fulfilled the inclusion criteria. Patients included in the current study had slightly higher NIHSS-scores (median 24) than those without adequate CTA data (median 21), otherwise the two groups were comparable (data not shown). Mean age of the included patients was 65 years and the majority of patients were men (66%). Forty-nine patients (33%) had a short, 50 (34%) an intermediate and 50 (34%) a long clot. Prevalence of common risk factors for stroke and other baseline variables are shown in

Table 5.1 Patient characteristics according to thrombus length group

	Short (4–11 mm) n=49	Intermediate (12–22 mm) n=50	Long (≥23 mm) n=50
Age, mean (SD)	66 (16)	65 (15)	65 (13)
Women	22 (45)	15 (30)	14 (28)
Hypertension	28 (57)	32 (64)	34 (68)
Diabetes mellitus	8 (16)	8 (16)	15 (30)
Hyperlipidemia	10 (20)	12 (24)	18 (36)
Atrial fibrillation	15 (31)	10 (20)	1 (2)
Coronary artery disease	7 (14)	6 (12)	8 (16)
Peripheral arterial disease	2 (4)	4 (8)	4 (8)
Smoking	7 (14)	13 (26)	9 (18)
Prodromal TIA	16 (33)	20 (40)	24 (48)
Prodromal minor stroke	7 (14)	12 (24)	9 (18)
Deficit			
Mild to moderate	23 (47)	11 (22)	18 (36)
Severe	26 (53)	39 (78)	32 (64)
NIHSS, median (IQR)	21 (19)	25 (12)	27 (25)
NIHSS >20	25 (51)	34 (68)	30 (60)
Treatment			
Asa/heparin	18 (37)	12 (24)	17 (34)
IV rTpa	5 (10)	4 (8)	6 (12)
IV/IA	6 (12)	3 (6)	3 (6)
IA/IA mech/mech	18 (37)	27 (54)	17 (34)
No treatment	2 (4)	4 (8)	7 (14)
Stenting	5 (10)	7 (14)	4 (8)
Time to treatment			
0–3	15 (31)	14 (28)	11 (22)
3–6	15 (31)	15 (30)	7 (14)
>6	17 (35)	17 (34)	25 (50)
Location of occlusion			
Distal third	32 (65)	15 (30)	4 (8)
Middle third	8 (16)	14 (28)	11 (22)
Proximal third	9 (18)	21 (42)	35 (70)
Cause of stroke			
Embolic	28 (57)	19 (38)	6 (12)
Atherosclerosis	10 (20)	23 (46)	26 (52)
Dissection	4 (8)	1 (2)	1 (2)
Other	0 (0)	0 (0)	1 (2)
Unknown	7 (14)	7 (14)	16 (32)

SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASA, Acetylsalicylic Acid; rTpa, recombinant tissue plasminogen activator; IV, intravenous; IA, intra-arterial; mech, mechanical.

Table 5.1. Patients with a short clot more often were women, more often had a history of atrial fibrillation and prodromal TIA, less often had a history of hyperlipidaemia and less often had atheroslerosis as suspected cause of stroke compared with patients with longer clots. Patients with short clots more often had a mild deficit (not in a coma, with tetraplegia or in a locked- in state). Time from stroke onset to treatment was longer for patients with long clots and these patients more frequently received no treatment. Patients with short clots more often had a distal occlusion whereas patients with long clots more often had proximal occlusions. Post treatment basilar artery patency was assessed in 118 of 136 (87%) treated patients and in 2 of 13 patients who received no treatment. In patients in whom post treatment patency of the basilar artery was assessed successful recanalisation was achieved in 31 patients (74%) with short, 28 patients (72%) with intermediate and 17 patients (44%) with long clot length (Table 5.2). Figure 5.2 illustrates the mRS distribution after one month in the three clot length groups.

Table 5.2 Recanalisation according to clot length group

Recanalisation	Short clot (4–11 mm) n=49	Intermediate clot (12–22 mm) n=50	Long clot (≥23 mm) n=50
Patent	31 (63)	28 (56)	17 (34)
Occlusion	11 (22)	11 (22)	22 (44)
Not performed	7 (14)	11 (22)	11 (22)

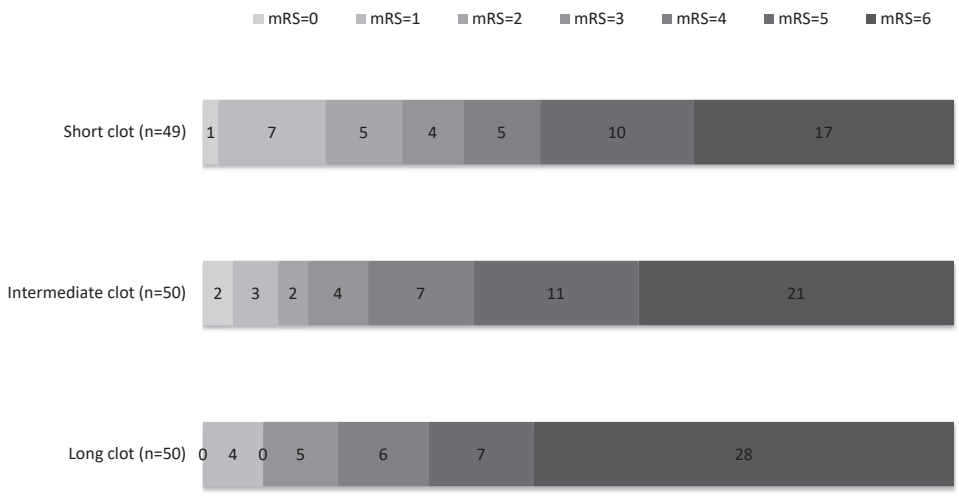

Figure 5.2 Distribution of modified Rankin Scale at 1 month in the three different clot length groups.

Risk ratios for recanalisation and poor outcome are shown in Tables 5.3 and 5.4. After adjustment for atrial fibrillation, location of occlusion and time to treatment there was a significantly lower probability of recanalisation in patients with a long clot compared with patients with a short clot (RR 0.64, 95% CI 0.42–0.98). Adjustment for treatment and cause of stroke hardly affected the RR estimate. There was no significant difference in the probability of recanalisation in patients with an intermediate clot length compared with patients with a short clot length (RR 0.97, 95% CI 0.75–1.25). After adjustment for cause of stroke, time to treatment and treatment type there was no significant difference in the risk of poor outcome for patients with a short clot compared with patients with a long clot and for patients with an intermediate clot length compared with patients with a short clot length (RR 1.10, 95% CI 0.88–1.37 and RR 1.11, 95% CI 0.88–1.40, respectively). Adjustments for the other baseline variables only marginally influenced the risk ratios.

Table 5.3 Risk ratios for recanalisation according to clot length group – univariable and multivariable analyses

	Intermediate (12–22 mm) vs. short (4–11 mm) n=39	Long (≥23 mm) vs. short (4–11 mm) n=39
Recanalisation[a]	28 (72%)	17 (44%)
Unadjusted RR	1.00 (0.77–1.30)	0.61 (0.41–0.90)
RR adjusted for		
Age	1.02 (0.79–1.32)	0.62 (0.41–0.92)
Sex	0.98 (0.75–1.29)	0.59 (0.40–0.89)
Hypertension	0.99 (0.76–1.29)	0.60 (0.40–0.88)
Diabetes mellitus	1.00 (0.77–1.29)	0.59 (0.40–0.88)
Hyperlipidemia	1.00 (0.78–1.30)	0.62 (0.42–0.93)
Atrial fibrillation	1.03 (0.79–1.35)	0.66 (0.43–1.00)
Coronary artery disease	1.00 (0.77–1.30)	0.61 (0.41–0.90)
Peripheral arterial disease	1.01 (0.78–1.31)	0.62 (0.41–0.92)
Smoking	1.00 (0.77–1.30)	0.61 (0.41–0.90)
Prodromal TIA	1.01 (0.78–1.31)	0.62 (0.42–0.93)
Prodromal minor stroke	0.99 (0.76–1.29)	0.60 (0.41–0.90)
Treatment	0.88 (0.69–1.13)	0.63 (0.44–0.91)
Time to treatment	0.99 (0.77–1.27)	0.65 (0.43–0.97)
Location of occlusion	0.95 (0.73–1.23)	0.56 (0.38–0.84)
Cause of stroke	1.00 (0.75–1.33)	0.61 (0.41–0.97)
2 factors	0.99 (0.76–1.28)	0.61 (0.40–0.93)
3 factors	0.97 (0.75–1.25)	0.64 (0.42–0.98)

[a] Recanalisation for short clot: 31/42=74%.
2 factors: atrial fibrillation, location of occlusion.
3 factors: atrial fibrillation, location of occlusion, and time to treatment.

Table 5.4 Risk ratios for poor outcome according to clot length group – univariable and multivariable analyses

	Intermediate (12–22 mm) vs. short (4–11 mm) n=50	Long (≥23 mm) vs. short (4–11 mm) n=50
Poor outcome[a]	39 (78%)	41 (82%)
Unadjusted RR	1.19 (0.93–1.54)	1.26 (0.98–1.60)
RR adjusted for		
Age	1.21 (0.95–1.54)	1.27 (1.00–1.62)
Sex	1.23 (0.96–1.58)	1.30 (1.02–1.65)
Hypertension	1.19 (0.93–1.53)	1.25 (0.98–1.59)
Diabetes mellitus	1.19 (0.93–1.54)	1.25 (0.98–1.60)
Hyperlipidemia	1.20 (0.93–1.55)	1.29 (1.02–1.64)
Atrial fibrillation	1.21 (0.94–1.55)	1.30 (1.01–1.68)
Coronary artery disease	1.20 (0.93–1.54)	1.25 (0.99–1.60)
Peripheral arterial disease	1.20 (0.93–1.54)	1.30 (0.99–1.60)
Smoking	1.21 (0.94–1.56)	1.26 (0.99–1.61)
Prodromal TIA	1.18 (0.92–1.52)	1.23 (0.96–1.56)
Prodromal minor stroke	1.18 (0.92–1.51)	1.25 (0.98–1.59)
Treatment	1.13 (0.89–1.43)	1.22 (0.98–1.52)
Time to treatment	1.18 (0.92–1.50)	1.20 (0.94–1.52)
Location of occlusion	1.18 (0.90–1.54)	1.26 (0.94–1.67)
Cause of stroke	1.15 (0.90–1.48)	1.15 (0.90–1.48)
2 factors	1.13 (0.89–1.45)	1.10 (0.86–1.39)
3 factors	1.11 (0.88–1.40)	1.10 (0.88–1.37)

[a] Pour outcome for short clot: 32/49=65%.
2 factors: cause of stroke, time to treatment.
3 factors: cause of stroke, time to treatment, treatment.

Additionally, clot length was analysed as a continuous variable. After adjustments for the three most important variables influencing the crude RR (cause of stroke, time to treatment, treatment for poor outcome and atrial fibrillation, location of occlusion and time to treatment for recanalisation) we found a 10% reduction in chance of recanalisation with every centimetre increase in clot length and an 2% increase in risk of poor outcome (RR 0.90, 95% CI 0.78–1.04 and RR 1.02, 95% CI 0.98–1.05, respectively).

Comparison of the relation between clot length on one hand and outcome and recanalisation on the other between treatment groups yielded insufficient numbers for reliable conclusions.

DISCUSSION

We found that increasing clot length independently predicted recanalisation but not outcome in patients with a BAO. Increasing clot length did not predict poor outcome at one month in these patients, defined as a mRS score of 4–6. In the analysis of clot length as a continuous variable we found 10% less recanalisation and 2% more poor outcome with every centimetre increase in clot length.

The BASICS registry is the largest prospective registry of consecutive patients with an acute BAO. However, the observational design inherently incurs limitations to the current study. First, with 149 patients included the sample size is still relatively small. Second, the relatively higher percentage of patients in the intermediate and long clot length group that received no treatment and as a consequence less often received follow-up imaging is a potential confounder. Third, time of recanalisation assessment differed between treatment groups, potentially biasing recanalisation rates. Fourth, the choice of treatment was left to the discretion of the clinicians, and was inevitably influenced by the suspected prognosis and effect of treatment. Multivariable analysis can never adjust completely for systematic differences between clot length groups. The risk of poor clinical outcome did not differ statistically significant between the long clot length group and the short clot length group after adjustment for the factors most influencing the crude risk (cause of stroke, time to treatment and treatment type). Stroke etiology strongly affected outcome in univariable analysis. This finding is plausible as atherosclerotic disease not only affects the basilar artery but also potential collateral routes and brainstem perforators. In contrast to good outcome, the probability of recanalisation remained significantly higher in the short clot length group compared with the long cloth length group after adjustments for the factors most influencing the crude risk (atrial fibrillation, location of occlusion and time to treatment). A presumptive explanation for the lack of influence of treatment type on recanalisation could be the relatively low percentage of patients treated with mechanical thrombectomy (30 of 149 patients (20%)). Numbers of stenting were small and comparable between groups and therefore unlikely to have influenced the results.

Most earlier studies investigating clot length focussed on MCAO. An initial report found that a hyperdense thrombus longer than 8mm on non-contrast computed tomography (NCCT) predicted non-response to intravenous thrombolysis.[4] Others have shown this relation to be more variable and reported that CT perfusion-derived length of occlusion in IVT treated patients with proximal MCAO was an independent predictor of recanalisation after 24 hours and outcome after 3 months.[5] This study also identified an optimal cut-off value of 12 mm

length of occlusion in the M1 segment as a statistically significant independent predictor of recanalisation.

Little research has been conducted on the relationship between clot length, recanalisation and outcome in BAO. Our results support the earlier reported findings that thrombus length is independently associated with recanalisation in patients with BAO.[6] The earlier study, investigating only IVT treated patients, reported shorter thrombi in patients with recanalisation compared with patients without recanalisation (mean 9.7 vs. 16.6 mm). The current study confirms these findings independently from treatment, which is important as current treatment of BAO varies widely between centers and most patients are not treated with IVT alone.[9] Our findings also support the results of another study, investigating prognostic signs of severity on computed tomography (CT) in patients with a BAO treated with IVT, IAT, IVT followed by IAT or without treatment.[18] This study reported longer clots in poor outcome patients (mRS 4–6) compared with favourable outcome patients (mean 16.5 vs. 11.4 mm) but the difference was not statistically significant, probably because of the small study sample (n=37).

Longer clots will obstruct more vertebrobasilar (VBA) side branches and, as a consequence, will therefore induce more ischaemic damage in the dependent brain tissue. Furthermore, with more obstructed VBA side branches, less collateral routes will be available, which has been shown to be an independent predictor of outcome.[19]

BAO, in contrast to MCAO, still lacks a proven treatment strategy. Therefore, clot length measurement, in combination with other clinical and radiological predictors of recanalisation and outcome, may assist in treatment decision-making. Recently, promising new CTA derived thrombus characteristics were introduced in patients with anterior circulation stroke. Thrombus perviousness, which can be assessed by the simultaneous measurement of thrombus attenuation on NCCT and CTA, was shown to be strongly associated with outcome and recanalisation rate.[20] Another study demonstrated that presence of antegrade flow across a cerebral vessel occlusion on 4-dimensional CTA is associated with an increased chance of vessel recanalisation.[21] Further research on thrombus characteristics in BAO should proceed and the results of the present study need to be validated in larger and randomised cohorts, like the currently recruiting randomised controlled BASICS trial.[22]

SOURCES OF FUNDING

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CHAPTER 6

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

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ABSTRACT

Background 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 141 patients with acute BAO enrolled in the Basilar Artery International Cooperation Study (BASICS) registry of whom baseline CT angiography (CTA) of the intracranial VAs was available. In 72 patients an additional CTA of the extracranial VAs was available. 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.

Findings Sixty-six of 141 (47%) patients had uni- or bilateral intracranial VA occlusion or stenosis ≥50%. Of the 72 patients with intra- and extracranial CTA, 46 (64%) had uni- or bilateral VA occlusion or stenosis ≥50% and 9 (12%) had bilateral VA occlusion. Overall, VA occlusion or stenosis ≥50% was not associated with the risk of poor outcome. Patients with intra- and extracranial CTA and bilateral VA occlusion had a higher risk of poor outcome than patients without bilateral VA occlusion (aRR 1.23; 95% CI 1.02–1.50).

Interpretation 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.

INTRODUCTION

Basilar artery occlusion (BAO) is associated with a high mortality rate and poor functional outcome among survivors.[1,2] The most frequent underlying aetiology 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 collateral circulation in patients with generalised atherosclerosis as opposed to patients with a sudden occlusion caused by an embolism from the heart. VA stenosis, particularly if intracranial, is a strong predictor of future stroke in patients with a recent TIA or stroke 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 occlusion or stenosis ≥50% in a dominant VA, VA hypoplasia and a continuous thrombus in one or both VAs and the BA.

METHODS

Patients

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.[2] The methods of BASICS have been described previously.[7] The BASICS registry was approved by the ethics committee of the University Medical Centre 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 6.1). In addition we required a CTA of good 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.

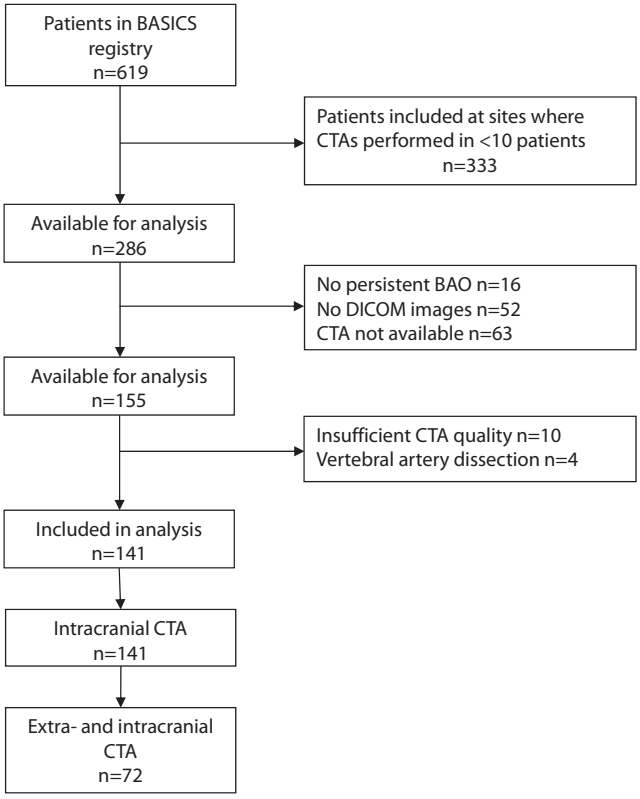

Figure 6.1 Flow chart.
CTA indicates CT angiography; BAO, basilar artery occlusion.

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 the 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] In VA asymmetry, the larger VA was defined as the dominant vertebral artery. The presence of a continuous thrombus in one or both VAs and the BA was assessed separately.

Statistical analyses

The frequency of baseline characteristics between patients with and without VA occlusion or stenosis ≥50–99% in the intracranial or extra- and intracranial VAs was 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 6.1). Compared with excluded patients, included patients more often received no treatment, but were similar otherwise (Supplementary table S6.1). 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 intracranial VA and 21 (15%) of both intracranial VAs (Table 6.1 and Figure 6.2). Uni- or bilateral intracranial 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 both the intra- and extracranial VAs, 32 (44%) had uni- or bilateral VA occlusion, 46 (64%) uni- or bilateral VA occlusion or stenosis ≥50%, and 9 (12%) had bilateral VA occlusion (Table 6.1). VA hypoplasia was found in 6 patients (8%).

Table 6.1 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 indicates vertebral artery; BA, basilar artery.

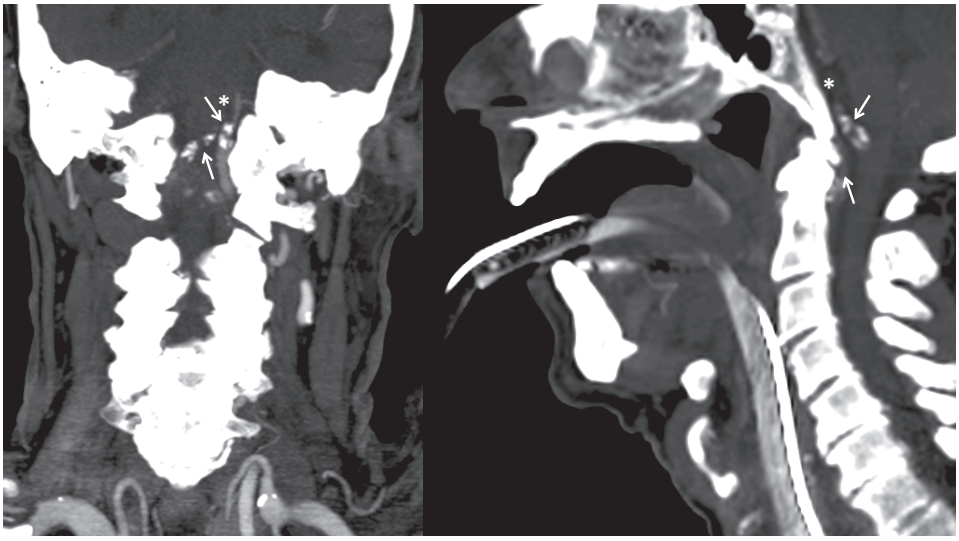

Figure 6.2 CT angiography showing acute basilar artery occlusion and bilateral vertebral artery occlusion. 77 years old male admitted because of acute vertebrobasilar stroke with rapid progression to coma. CT angiography showing basilar artery occlusion (*) and bilateral vertebral artery occlusion (arrows) with extensive atherosclerosis.

Baseline characteristics of patients with and without VA occlusion or stenosis ≥50% are presented in Table 6.2. 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 hyperlipidaemia. In 85 patients (60%), intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) was performed, in 22 patients (16%) stenting or percutaneous transluminal angioplasty of the BA or VA had been performed during IAT. This 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 6.3 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 6.3). 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 bilateral VA occlusion. The presence of VA occlusion or stenosis ≥50% in any portion of the VA or in the dominant VA was not associated with poor outcome or death (Table 6.3 and Supplementary table S6.2). Patients with an intracranial CTA and 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) (Supplementary table S6.2). 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 about two-thirds had a stenosis in the intra- or extracranial VA. Overall, the presence of VA occlusion or VA stenosis ≥50% did not influence clinical outcome. However, patients with BAO and bilateral intra- or extracranial VA occlusion had a higher risk of a poor clinical outcome.

In line with the current study, about half of the patients with a symptomatic BA stenosis or occlusion in two previous registries had concomitant VA atherosclerosis.[5,12] Embolism from the heart or extracranial VA 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

Table 6.2 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)[a]	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)
Hyperlipidaemia	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)
Smoking	10 (15%)	16 (21%)	0.7 (0.4–1.5)	8 (17%)	4 (15%)	1.1 (0.4–3.4)
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%)	[b]	12 (26%)	7 (27%)	[c]
4–6h	9 (14%)	28 (37%)	[b]	13 (28%)	6 (23%)	[c]
7–9h	13 (20%)	5 (7%)	[b]	7 (15%)	2 (8%)	[c]
>9h	16 (24%)	17 (23%)	[b]	10 (22%)	9 (35%)	[c]
Severe deficit at time of treatment[d]	39 (59%)	54 (72%)	0.7 (0.5–1.0)	26 (57%)	16 (62%)	0.9 (0.6–1.4)
NIHSS score[a]	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 (standard deviation), number (%), or median (interquartile range).
CTA indicates CT angiography; CI, confidence interval; TIA, transient ischaemic 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.
[a] Prevalence ratio is expressed as the ratio per additional year of age or point at NIHSS.
[b] p=0.01, overall chi square test.
[c] p=0.58, overall chi square test.
[d] Severe deficit at time of treatment indicates coma, locked-in state, or tetraplegia.

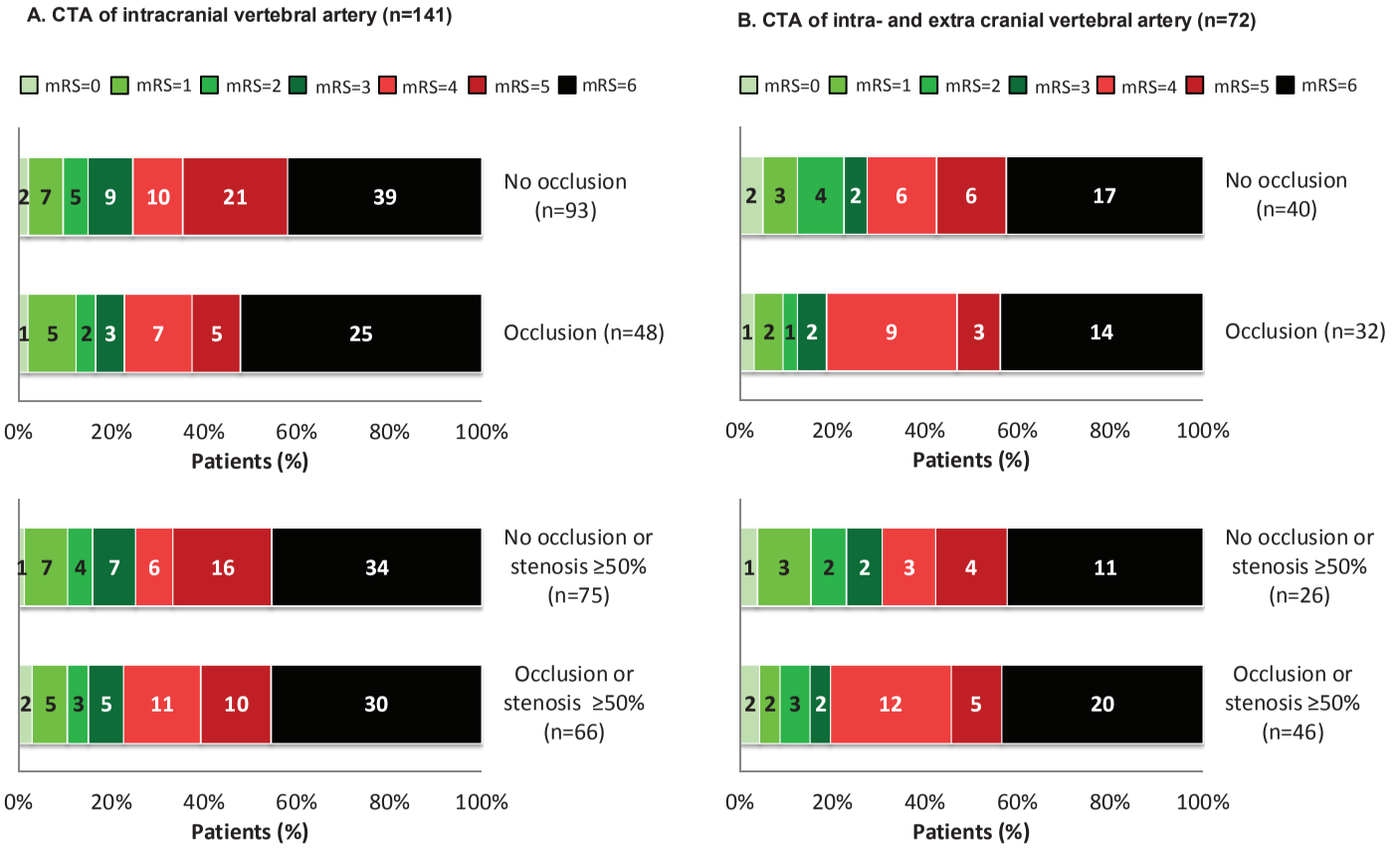

Figure 6.3 Outcome at one month according to presence of vertebral artery occlusion or stenosis ≥50%.
CTA indicates CT angiography; mRS modified Rankin scale score.

Table 6.3 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)[a]
Death	25/48 (52%) vs 39/93 (42%)	1.24 (0.87–1.78)	1.20 (0.84–1.71)[a]
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)[a]
Death	14/21 (67%) vs 50/120 (42%)	1.60 (1.11–2.31)	1.30 (0.90–1.86)[a]
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)[a]
Death	30/66 (45%) vs 34/75 (45%)	1.00 (0.70–1.44)	1.04 (0.73–1.49)[a]
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)[b]
Death	14/32 (44%) vs 17/40 (43%)	1.03 (0.60–1.75)	0.97 (0.60–1.55)[a]
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)[b]
Death	7/9 (78%) vs 24/63 (38%)	2.04 (1.28–3.27)	1.34 (0.77–2.32)[a]
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)[b]
Death	20/46 (44%) vs 11/26 (42%)	1.03 (0.59–1.79)	1.01 (0.61–1.67)[a]

Data are number (%) or risk ratio (95% CI).
CTA indicates CT angiography; RR, risk ratio; poor outcome, modified Rankin scale score of 4, 5, or death; VA, vertebral artery.
[a] Adjustment for age, sex, and treatment.
[b] Adjustment for sex, treatment, and atrial fibrillation.

time to develop collateral circulation than patients with atherosclerosis and consequently tolerate ischaemic 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 ischaemic stroke due to BA stenosis and chronic BA occlusion had been included. In the current study the majority of patients received IVT or IAT, whereas in previous registries the majority of patients was treated with antithrombotics

or heparin.[5,12] In addition, our study might be underpowered to detect the contribution of unilateral VA occlusion or stenosis ≥50% to the prognosis in acute BAO. In patients with unilateral VA occlusion or stenosis ≥50% flow from the contralateral VA might partly compensate.

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 recanalisation rate due to a higher clot burden. In a previous study mortality in patients with 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. CTA has a high sensitivity and specificity for diagnosing VA stenosis 50–99% compared with intra-arterial angiography.[15,16]

The BASICS registry is the largest prospective international registry of consecutive patients with acute, symptomatic BAO. Therefore, the results from this registry will represent the daily practice of the presentation and treatment of patients with BAO.

However, 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 visualisation of the VAs by CTA in the acute phase of BAO. Nonetheless, the only difference in baseline characteristics between in- and excluded patients was a slightly higher number of patients without treatment in the included patients.

In the last decade endovascular treatment options have evolved rapidly, both for acute ischaemic stroke and secondary prevention in patients with large vessel stenosis. Currently, two trials are investigating the role of stenting in symptomatic VA stenosis,[17,18] and one trial

compares IV and IV/IA treatment in acute BAO.[19] Arguments for stenting of the VA directly during intra-arterial treatment for BAO are optimisation 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.

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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SUPPLEMENTARY DATA

Supplementary table S6.1 Baseline characteristics in current study in relation to BASICS population

	BASICS –CTA intracranial (n=141)	BASICS total (n=478)	Prevalence ratio (95% CI)[a]
Male sex	91 (65%)	298 (62%)	1.0 (0.9–1.2)
Age (years)	65 (15)	63 (15)	1.0 (1.0–1.1)
Hypertension	87 (62%)	296 (62%)	1.0 (0.9–1.2)
Diabetes mellitus	27 (19%)	108 (23%)	0.8 (0.6–1.2)
Hyperlipidaemia	37 (26%)	130 (27%)	1.0 (0.7–1.3)
Atrial fibrillation	25 (18%)	108 (23%)	0.8 (0.5–1.2)
Coronary artery disease	17 (12%)	92 (19%)	0.6 (0.4–1.0)
Smoking	26 (18%)	79 (17%)	1.1 (0.7–1.7)
Prodromal minor stroke	57 (40%)	242 (51%)	0.8 (0.6–1.0)
Treatment			
No treatment	13 (9%)	14 (3%)	3.2 (1.5–6.5)
AT	43 (30%)	140 (29%)	1.0 (0.8–1.4)
IVT	13 (9%)	67 (14%)	0.7 (0.4–1.2)
IVT-IAT	10 (7%)	31 (6%)	1.1 (0.6–2.2)
IAT	62 (44%)	226 (47%)	0.9 (0.8–1.1)
Time to treatment			
0–3h	40 (28%)	139 (29%)	[b]
4–6h	37 (26%)	153 (32%)	[b]
7–9h	18 (13%)	66 (14%)	[b]
>9h	33 (23%)	106 (22%)	[b]
Severe deficit at time of treatment[c]	103 (66%)	280 (59%)	1.1 (1.0–1.3)
NIHSS score	25 (15–32)	21 (11–30)	1.1 (1.0–1.2)
NIHSS score >20	86 (61%)	250 (52%)	1.2 (1.0–1.4)
Occlusion proximal or middle BA	89 (63%)	328 (69%)	0.9 (0.8–1.1)

Data are mean (SD), number (%), or median (IQR).
CI indicates confidence interval; TIA, transient ischaemic 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; NIHSS, National institutes of Health Stroke Scale score.
[a] Comparing patients with and without CTA of intracranial vertebral arteries.
[b] p=0.82, overall chi square test.
[c] Severe deficit at time of treatment indicates coma, locked-in-state or tetraplegia.

Supplementary table S6.2 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 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)[a]
Death	15/27 (56%) vs 34/75 (45%)	1.23 (0.81–1.86)	1.19 (0.80–1.76)[a]
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)[a]
Death	22/37 (59%) vs 42/104 (40%)	1.47 (1.03–2.10)	1.44 (1.02–2.02)[a]
CTA of extra- and intracranial VA n=72			
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)[b]
Death	10/14 (71%) vs 11/26 (42%)	1.69 (0.97–2.95)	1.70 (0.93–3.12)[a]
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)[b]
Death	11/20 (55%) vs 20/52 (39%)	1.43 (0.85–2.42)	1.34 (0.83–2.17)[a]
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)[b]
Death	2/6 (33%) vs 29/66 (44%)	0.76 (0.24–2.43)	0.79 (0.22–2.89)[a]

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

CHAPTER 7

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

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Trials. 2013;14:200

ABSTRACT

Background 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 utilised 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 haemorrhage. 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 minimise 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 dichotomised 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 (www.wma.net 21-10-2008) 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 (www.basicstrial.com).

AUTHORS' CONTRIBUTIONS

EJRJH participated in writing the protocol and is concerned with patient recruitment and data management. WJS wrote the protocol, applied for financial support and is involved in patient recruitment. AA participated in writing the protocol and is responsible for data analysis. LJK, PM and KWM participated in writing the protocol, applied for financial support and are involved in patient recruitment. HJA, EB, AC, MM, VP, MR, JAV, CACW and AZ participated in writing the protocol and are involved with patient recruitment. All authors have read and approved the manuscript.

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CHAPTER 8

General discussion

Despite its relative high incidence (about 20% of all ischaemic strokes),[1,2] posterior circulation (PC) ischaemic stroke has received less attention and often has been managed differently compared with anterior circulation (AC) ischaemic stroke. Atypical symptoms associated with PC stroke lead to misdiagnosis. A third (37%) of PC strokes are misdiagnosed in the emergency department, more than three times as often as AC strokes.[3] Delayed or incorrect diagnosis results in inadequate acute care and poorer outcomes. PC strokes have longer door to needle times for intravenous thrombolysis (IVT) than AC strokes,[4,5] and patients with PC stroke are more likely to arrive in hospital after the 4.5 hour time window for thrombolysis.[6] Potential causes include clinical and imaging related diagnostic difficulties and perceived differences in pathophysiology and risk.

In the following discussion I will address the clinical and imaging aspects of PC ischaemic stroke with special attention to the differences between AC and PC ischaemic stroke and correct infarct localisation. In addition, I will review the diagnostic accuracy and difficulties of multimodal computed tomography (CT) and magnetic resonance imaging (MRI) for detection of PC ischaemic stroke followed by a summary of the pathophysiology and causes of PC ischaemic stroke. Subsequently, I will review imaging derived predictors of outcome in patients with acute basilar artery occlusion (BAO) to end with future perspectives on the Basilar Artery International Cooperation Study (BASICS) trial and imaging of posterior circulation ischaemic stroke in general.

Clinical aspects

Brain regions supplied by the AC are relatively well defined. AC stroke tends to present with classical and well-known stroke symptoms (motor, sensory, or speech or visuospatial disturbance). In contrast to the AC, the PC supplies several brain regions with a high concentration of differing functions, and has greater anatomical variability. Due to the proximity of brainstem nuclei and large afferent and efferent tracts PC ischaemia can present with a wide range of symptoms and signs, some of which (such as vertigo, reduced conscious level and diplopia) are considered unspecific stroke symptoms.[7]

While there are certain classical signs and symptoms that favour the diagnosis of PC stroke such as crossed motor or sensory deficits, diplopia, visual field deficits, and first neuron Horner's syndrome, these signs occur infrequently (<10%), as was shown in a recent study.[8] In another study, classical PC syndromes were also only rarely found.[9] Hence, it is difficult to identify most patients with PC ischaemia based on these relatively rare clinical manifestations. Observations in a previous study that approximately 10 to 20% of patients

with a diagnosis of presumed AC stroke actually had a PC stroke supports this contention.[10] The misdiagnosis rate in the previous study might even be underestimated because of the small number of patients included and the limited sensitivity of CT in detecting infarctions involving the posterior fossa. In an observational study, investigators reported that there is no apparent difference in the frequency of the most common symptoms and signs between PC ischaemia and AC ischaemia.[8] Some neurological deficits were highly specific for diagnosing PC ischaemia, but their sensitivity suggests that symptoms or signs considered typical of PC ischaemia are uncommon.

Diagnostic instruments are less effective in patients with an ischaemic stroke in the PC as compared with patients with an ischaemic stroke in the AC.[11,12] The Face Arm Speech Time (FAST) test failed to diagnose 40% of patients with PC stroke compared with 10% of patients with AC stroke.[11] Sensitivity in PC stroke detection could be raised from 60 to 80% by adding either visual disturbance or ataxia to the FAST test, but this has not yet been integrated in routine practice. The National Institutes of Health Stroke Scale (NIHSS) is the most commonly used measure of stroke severity. The NIHSS is nowadays used on a routine basis to assess the clinical features of acute ischaemic stroke and has a proven relationship with stroke severity and outcome.[13–15] However, its usefulness for PC stroke is limited, as the scale does not include a detailed assessment of the cranial nerves. As a result the scale underestimates clinical severity in PC stroke and relatively low scores can occur in patients with disabling infarctions of the brainstem or cerebellum.[16] As PC strokes often present with lower scores on the NIHSS than AC strokes,[17,18] misdiagnosis in the emergency department is more likely. Moreover, the NIHSS offers no discriminating value in the identification of the actual cause of the neurological deficit.

Correct localisation of an infarction in the brain based only on clinical examination can be challenging. Although the NIHSS is not intended to identify the vascular territory of the stroke, its widespread use raised the question if separate items can aid in the identification of these patients (**Chapter 2**). To answer these questions we selected 305 patients with a clinical diagnosis of acute ischaemic stroke in the AC without signs of early ischaemia on the admission CT imaging from a prospective observational study. A small but relevant proportion of 20 patients (7%) had a new PC infarct on follow-up imaging. Three quarters of these infarcts were lacunar infarcts in the pons or the thalamus. The group without PC infarct comprised 227 patients (80%) without a new infarct on follow-up imaging and 58 patients (20%) with a new AC infarct on follow-up imaging. None of the baseline characteristics were statistically significant related to PC infarcts and we could not demonstrate clinically relevant statistically significant higher probability of separate NIHSS items for one of both groups.

These findings are in contrast with two earlier studies that investigated the differences in neurologic deficits between consecutive patients with AC infarcts and PC infarcts. One study reported that central facial palsy, disturbed consciousness and aphasia occurred less often in the PC infarct group and ataxia occurred more often in the PC infarct group.[8] The other study, that investigated the NIHSS as a predictor of outcome in patients with AC infarcts or PC infarcts, found that the sub scores of the NIHSS items ataxia and visual fields were higher in patients with PC stroke than in patients with AC stroke.[12] Most of the other NIHSS items scores, such as level of consciousness, gaze, facial palsy, motor arm, motor leg, language and extinction and inattention were significantly higher in patients with AC stroke than in patients with PC stroke. These studies however, comprised patients with signs of ischaemia on baseline MRI whereas in the study described in **Chapter 2** patients with signs of ischaemia on baseline imaging were excluded.

Diagnostic imaging of PC ischaemia

As clinical diagnosis of PC stroke can be challenging, a definite diagnosis often can only be reached after brain imaging. The same principles apply to investigation of PC ischaemia as to cerebral ischaemia in general, but with some important modifications.

Because practical and logistical aspects of MRI remain a problem and rapid diagnosis is critical for optimising outcomes in patients with acute ischaemic stroke[19,20] CT is still the imaging modality of choice in most dedicated stroke centres for the initial triage of patients with suspected ischaemic stroke. Non-contrast CT (NCCT) is useful to exclude haemorrhage and mass lesions but has modest value for detection of early signs of ischaemia, with a reported sensitivity of 48% for detection of acute ischaemic AC stroke.[21] Sensitivity for detection of early ischaemic changes in the PC is thought to be even lower because of beam hardening and streak artefacts resulting from adjacent dense bone structures and also volume averaging of rapid changes in anatomy in the craniocaudal direction.[22,23] Earlier studies have shown that small (lacunar) infarcts and infarcts in the pons and midbrain region can be difficult to visualise on NCCT, even at 3 days after the ischaemic event.[24] In a retrospective series that analysed 90 consecutive patients with nontraumatic neurological symptoms referred to the posterior fossa that were confirmed on MRI and 90 patients without posterior fossa lesions the combined sensitivity and specificity for detection of ischaemia (N=67%) and other lesions (N=33%) was 45% and 85%, respectively.[25] CTA, specifically CTA-SI, is more accurate in detection of early irreversible AC ischaemia and prediction of final infarct volume compared with NCCT, with reported sensitivity of 70% and specificity of

100%.[21,26] CT perfusion (CTP) can detect ischaemic perfusion defects. A recent meta-analysis reported a pooled analysis sensitivity of 82% (95% confidence interval (CI): 75–88%) and a specificity of 96% (95% CI: 89–99%) for detection of early ischaemic stroke in the AC.[27] While there has been extensive research concerning the diagnostic value of CTP in the AC, there is only little evidence regarding the PC.[28] A previous study, investigating stroke detection with CTP in the PC, found no statistically significant differences when comparing sensitivity, specificity and accuracy of CTP maps for detection of infratentorial and supratentorial stroke lesions.[29] Sensitivity for detection of infratentorial ischaemic lesions was 91% and specificity 93%. However, this retrospective study had several limitations. The mean duration from stroke onset to imaging was 9 hours. A longer time interval could be expected to increase sensitivity since ischaemic changes will be more pronounced. The authors also excluded lacunar stroke,[29] whereas small infarcts are known to be the most important cause of false negative findings in the AC.[28] As the diagnostic value of CTP for the detection of PC stroke had not been accurately analysed thus far, we investigated the added value of CTP to NCCT and CTA in the diagnostic work-up of these patients (**Chapter 3**). CTP significantly increased diagnostic accuracy for detection of infarcts (sensitivity 31%, 33% and 74% and specificity 98%, 98%, 93% for NCCT, added CTA-SI and added CTP, respectively). Our data also showed that the combination of NCCT, CTA and CTP had high sensitivity for the detection of acute ischaemia in the cerebellum and PCA territory. Detection of acute ischaemia in the pons and midbrain remains difficult even with the use of CTP. Our data also suggested there is additional value for the detection of ischaemic lesions in the thalami. Our results were later confirmed in a study that investigated the additional value of whole brain volume CTP to NCCT and CTA-SI for infarct detection in patients with suspected acute ischaemic PC stroke.[30] In a similar analysis a sensitivity of 77% was reported for the model that included NCCT, CTA-SI and CTP compared with a sensitivity of 21% for NCCT alone and 44% for NCCT with added CTA-SI. In a pooled analysis of the latter two studies pooled sensitivity and specificity were 23% (95% CI 18–27%) and 97% (95% CI 92–99%) for NCCT, 42% (95% CI 35–48) and 98% (95% CI 93–100%) for CTA, 76% (95% CI 70–81%) and 93% (95% CI 87–97%) for CTP.[27]

MRI is better than CT for detection of acute ischaemia. Diffusion weighted imaging (DWI) has repeatedly shown to be the most sensitive technique for identifying acute ischaemia due to its ability to detect rapid shifts in the ratio of extracellular to intracellular water content in the brain.[31] A landmark article reported a sensitivity of 83% (95% CI 77–88%) for MRI compared with 16% (95% CI 12–23%) for NCCT for the diagnosis of acute ischaemic stroke.[24] Specificity was 96% (95% CI 92–99%) for MRI and 98% (95% CI 94–99%) for CT. More recently sensitivities of 88–100% and specificities of 95–100% for MRI have been reported.[32,33]

Furthermore, diagnostic accuracy of MRI is similar to that of CT for the detection of acute intracranial haemorrhage.[24,34,35] However, false negative diffusion-weighted imaging scans in ischaemic stroke do arise and were estimated at 17%.[24] Brainstem location was the factor that was associated most with false negative MRI cases (adjusted odds ratio 7.3, 95% CI 2.2–25), the other two factors were time from symptom onset to scan less than 3 hours and NIHSS score of less than 4. These findings could relate to small lesions that escape visual detection, especially in locations such as the brainstem, in which they might be difficult to distinguish from the hyperintensity of incompletely suppressed anisotropic diffusion or susceptibility artifacts.[24] The practitioner must be aware of the possibility of false negatives with DWI for ischaemic stroke and note the presence of clinical factors that predispose to such stroke.[24] A recent meta-analysis was performed to determine the prevalence of DWI negative acute ischaemic stroke.[36] A total of 12 articles comprising 3236 patients with acute ischaemic stroke were included. The meta-analytic synthesis yielded a pooled prevalence of DWI-negative acute ischaemic stroke of 6.8% (95% CI 4.9–9.3). DWI negative stroke was strongly associated with PC ischaemia, as determined by clinical diagnosis at hospital discharge or repeat imaging (odds ratio 5.1, 95% CI 2.3–11.6). These findings suggest that acute ischaemic stroke, specifically in the PC should remain a clinical diagnosis and that clinicians should not exclude patients from urgent IVT or IAT based on a negative DWI scan.

Pathophysiology and causes

Vertebrobasilar (VB) ischaemia due to haemodynamic compromise secondary to occlusive VB disease has been suggested to be an important cause of recurrent PC symptoms, but findings from careful clinical-imaging association studies suggest this is rarely the case.[37] Instead, thromboembolism, with or without haemodynamic compromise, from the site of arterial stenosis seems to be the predominant cause of ischaemia in VB stenosis. Similar to the AC, this suggestion is supported by the detection of circulating emboli on transcranial Doppler ultrasound distal to the stenosis,[38] and by the time profile of risk in symptomatic patients, with high early risk followed by much lower risk despite the continued presence of the stenosis.[39,40]

However, certain aspects of VB atherosclerosis differ from carotid artery atherosclerosis. First, the anatomy of the two vertebral arteries ending in one basilar artery differs substantially from that of the carotid arteries. In addition, the PC displays a wider range of anatomical variation than the AC, including vertebral artery (VA) hypoplasia, posterior inferior cerebellar artery ending of unilateral VA and absence or hypoplasia of P1 segments with a

concomitant fetal variant of the posterior cerebral artery. Second, symptomatic VB stenosis is more often present in patients with PC ischaemic stroke and transient ischaemic attack (TIA; 26%) than symptomatic carotid artery stenosis in patients with AC ischaemic stroke or TIA (12%).[40] Recent population based and hospital observational studies have shown a threefold increased risk of stroke after PC TIA or minor stroke in patients with VB stenosis than in those without.[39–41] Third, in contrast to the presence of symptomatic carotid artery stenosis, extracranial stenosis in the PC is less strongly associated with coronary artery disease and peripheral vascular disease.[40] This suggests that VB atherosclerosis might be a different type of atherosclerosis than carotid artery atherosclerosis. The observation that in a population-based study almost half of the patients with symptomatic VB stenosis had little or no carotid artery plaque supports this concept.[40]

Dissection is also an important cause of PC stroke, especially in young adults. In a retrospective observational study of patients with PC stroke the prevalence of a dissection in the PC, predominantly in a VA, was 25%,[42] compared with 2% in all ischaemic strokes.[43] In both vertebral and carotid dissection, stroke is thought to be caused most often by embolism from a thrombus at the site of dissection, rather than from a reduction in haemodynamic flow secondary to luminal compression.[44]

Basilar artery occlusion: imaging derived predictors of outcome

Basilar artery occlusion (BAO) is associated with a high mortality rate and poor functional outcome among survivors.[45,46] The most frequent underlying aetiology is either atherosclerotic stenosis of the basilar artery (BA) or vertebral artery (VA), or embolism from the heart.[37,47] 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.[48] We hypothesised that patients with BAO and VB atherosclerosis would have better-developed collaterals than patients with acute embolic VB occlusion. Consequently, patients with acute BAO and accompanying VA stenosis or occlusion would have a better prognosis than patients without VA stenosis. However, we could not confirm this theory and found that almost half of the patients with acute BAO had a concomitant intracranial VA stenosis ≥50% or occlusion (**Chapter 6**) which is in line with the findings in two previous registries.[48,49] However, the presence of VA occlusion or VA stenosis ≥50% did not influence clinical outcome in our study. Patients with BAO and bilateral intra- or extracranial VA occlusion even had a higher risk of a poor clinical outcome than patients without bilateral VA occlusion (adjusted risk ratio 1.23, 95% CI 1.02–1.50). This can be

explained by the reduced ability to compensate via collaterals after bilateral VA occlusion and the higher clot burden. A previous series reported that haemodynamically sensitive PC ischaemia is only seen in patients with bilateral intracranial VA occlusion, thereby suggesting that cerebrovascular reserve is severely compromised in these patients.[37,50] Higher clot burden will reduce potential collateral routes and has been shown to predict functional outcome, final infarct size and parenchymal haematoma in middle cerebral artery occlusions (MCAO).[51–53] Additionally, sufficient collateral flow has been recognised to limit infarct growth, increase recanalisation and reperfusion, avert haemorrhagic transformation after endovascular therapy (EVT), and improve subsequent neurological outcomes in patients with large vessel occlusion in the AC.[54–56] In contrast to MCAO, little research has been performed on the role of clot burden and collaterals in BAO. We hypothesised that quantification of the residual patency of main VB side branches (posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA), and superior cerebellar artery (SCA)) and the presence and caliber of posterior communicating arteries (PCoAs) reflects the potential collateral pathways and consequently predicts outcome in terms of functional independence. Retrograde blood flow from the AC through the PCoAs may serve as a primary collateral pathway, potentially providing immediate diversion of cerebral blood flow to ischaemic occipital and infratentorial regions.[57] PCoA size has been used as an indicator of collateral flow in small series of patients with BAO using CTA[58,59] and digital subtraction angiography (DSA).[60] We assessed the prognostic value of a semi quantitative CTA-based grading system, incorporating primary and potential secondary collateral pathways in acute BAO: the posterior circulation collateral score (PC-CS) (**Chapter 4**). This PC-CS independently predicted poor outcome at one month, defined as a mRS score of 4–6 in these patients after adjustment for onset time to treatment (OTT), treatment and age. Multivariable analyses showed a statistically significant lower risk of poor outcome in patients with a good PC-CS than in patients with a poor PC-CS (risk ratio (RR) 0.74, 95% CI 0.58–0.96), but not for patients with an intermediate PC-CS compared with patients with a poor PC-CS (RR 0.95, 95% CI 0.78–1.15). Recently, validation of the PC-CS in an independent cohort showed similar prognostic accuracy.[61] The authors of that study proposed a new radiological score: the Basilar Artery on Computed Tomography Angiography (BATMAN) score. This semi quantitative CTA-based grading system incorporated both collateral quality and clot burden. BATMAN score was independently associated with functional outcome after adjustment for recanalisation and OTT (OR 4.8, 95% CI 1.2–18). In receiver operator characteristic (ROC) analysis, BATMAN score area under the receiver operator characteristic curve (AROC 0.8, 95% CI 0.7–0.9) showed significantly higher accuracy compared with PC-CS (AROC 0.63, 95% CI 0.7–0.9). Thus, the addition of collateral quality to clot burden

in BATMAN score seems to improve prognostic accuracy in BAO patients. Furthermore, interrater agreement was higher for BATMAN score.

In another study the same authors investigated whether collaterals and thrombus burden influenced the associations between revascularisation, time to treatment (TTT) and functional outcome in patients with BAO who were treated with EVT. Successful reperfusion was associated with good outcome after adjustment for age, NIHSS and TTT ≤6/>6 hours amongst all patients (OR 6.5, 95% CI 1.8–24). This association was stronger in patients with favourable BATMAN score (OR 15.8, 95% CI 1.4–175) and PC-CS (OR 9.4, 95% CI 1.4–64) compared with those with unfavourable BATMAN score (OR 3.9, 95% CI 0.7–20) and PC-CS (OR 4.8, 95% CI 0.8–29) (unpublished data from Alemseged, van der Hoeven, et al.).

In addition to the PC-CS, we investigated the prognostic value of primary collateral pathways on outcome by assessing the presence and calibre of PCoAs separately (**Chapter 4**). Multivariable analyses showed a statistically significant lower risk of poor outcome for the presence of at least one patent PCoAs (RR 0.79, 95% CI 0.66–0.95) and for larger calibre PCoAs (RR 0.76, 95% CI 0.61–0.96). In more recent studies the role of PCoAs as the main collateral pathways involved in the pathofysiology of BAO were confirmed.[62] Good collaterals, defined as the presence of bilateral PCoA, were significantly associated with favourable outcome at 90 days (mRS 0–2) (OR 4.2, 95% CI 2.2–8.2).[62] In the BATMAN study population the absence of PCoAs (unilateral or bilateral) was strongly associated with poor outcome (OR 6.8, 95% CI 2–2.1).[63]

Besides clot burden and collaterals, clot length has also received attention as an imaging derived predictor. Clot length has been shown to affect recanalisation rates of MCAO[64–66] and BAO[67] after IVT with recombinant tissue plasminogen activator (rtPA). An initial report found that a hyperdense thrombus longer than 8 mm on NCCT predicted nonresponse to IVT in patients with MCAO.[65] Others have shown this relation to be more variable and reported that CTP-derived length of occlusion in IVT-treated patients with proximal MCAO was an independent predictor of recanalisation after 24h and outcome after 3 months.[66] The previous study also identified an optimal cut-off value of 12 mm length of occlusion in the M1 segment as a statistically independent predictor of recanalisation. Besides the aforementioned study, solely investigating patients treated with IVT, little research has been conducted on the relationship between clot length, recanalisation and outcome in BAO. We hypothesised that longer clots will obstruct more VB side branches and, as a consequence, will therefore induce more ischaemic damage in the dependent brain tissue. Furthermore, with more obstructed VB side branches, less collateral routes will be available,

which has been shown to be an independent predictor of outcome (**Chapter 4**). However, in multivariable analysis of 149 patients with an acute BAO from the BASICS registry, clot length measured on CTA independently predicted recanalisation but not outcome (**Chapter 5**). In the analysis of clot length as a continuous variable, we found 10% less recanalisation (RR 0.90, 95% CI 0.78–1.04) and 2% more poor outcome with every centimetre increase in clot length (RR 1.02, 95% CI 0.98–1.05), but both relations did not reach statistical significance.

FUTURE PERSPECTIVES

BASICS trial

Despite recent advances in acute stroke therapy in the AC,[19] reported outcomes after BAO have not significantly improved over the last 40 years.[45,46,68] In the BASICS registry almost 70% of patients had poor outcome, independent of type of treatment.[46] Observations in the BASICS registry underscore that a proven treatment modality for patients with an acute BAO is lacking and that current practice varies widely. Furthermore, the often-held assumption that IAT is superior to IVT in patients with an acute BAO was challenged.[46] Although recanalisation rates are consistently higher after IAT as compared with IVT in observational studies, this was not consistently accompanied by improved outcome.[68,69] The BASICS registry was observational and has all the limitations of a non-randomised study. As the IAT approach became increasingly available and frequently utilised we felt that an adequately powered large randomised controlled trial investigating the added value of this therapy on top of best medical treatment (BMM) in patients with an acute symptomatic BAO was needed. Therefore, in 2011 our study group initiated the BASICS trial (**Chapter 7**). After publication of the MR CLEAN trial[70] and the other positive AC stroke trials[19] questions arose if there continued to be enough equipoise to continue the BASICS trial. We concluded that continuation of the trial was legitimate for several reasons. First, compared with the middle cerebral artery the BA receives superior collateral flow through both VAs and the Circle of Willis, providing both antegrade and retrograde exposure of the BA thrombus to thrombolytics. This may reduce time to recanalisation and improve recanalisation rates after IVT as compared with the AC. Second, the small diameter and angulation of the VA origin complicates EVT. Third, given the paramount ultrastructural differences between phylogenetically diverse central nervous system structures the resistance of brainstem and cerebellum to hypoxia might be higher compared with the time window in patients with BAO, providing IVT more time to resolve the BA thrombus. Last, we think that our trial is the only opportunity to study the effects of IAT in the PC. However, we did consider that

we should be less stringent with the rules on stopping of the trial. We therefore performed a preliminary meta-analysis of the results of the six positive AC trials in June 2015[70–75] and found a pooled OR of 2.17 (95% CI 1.74–2.70) for good outcome (mRS 0–3) as defined in the BASICS trial. We then proposed to update our sequential stopping rule to the Data and Safety Monitoring Board (DSMB). The main amendment in the updated stopping rule was that the trial would be able to demonstrate an OR of 2.0 with sufficient precision (based on the pooled OR of the 6 AC trials), whereas we previously assumed an increase in good outcome from 30% (based on the percentage of patients with good outcome in the BASICS registry) to 40% for patients treated with IAT compared to BMM, which corresponds to an OR of 1.56. The DSMB approved the amended stopping rule resulting in a new target of approximately 300 patients for the BASICS trial.

Our notion that there is still enough equipoise to continue the trial was supported by a recent meta-analysis of treatment of BAO demonstrating that recanalisation is associated with better outcomes regardless of the way recanalisation was achieved.[76] In this meta-analysis 77% of IAT patients achieved recanalisation compared with only 59% of those treated with IVT. However, the authors stated that the observational study design does not allow a valid comparison of the two therapies and hence, equipoise still exists between the two strategies. They concluded that recanalisation is associated with a two-fold reduction in mortality (RR 0.49, 95% CI 0.44–0.55, number needed to treat (NNT)=2.5) and 1.5 fold reduction in death or dependency (RR 0.67, 95% CI 0.63–0.72, NNT=3) but that these data do not yet support the notion that IAT is superior to IVT and that these results underscore the need for randomised controlled trials in acute BAO.

More recently, the Chinese BEST trial (Basilar artery occlusion Endovascular intervention versus Standard medical Treatment), with a similar protocol as BASICS, was terminated prematurely after the enrollment of 131 patients due to an excessive number of crossovers. Fourteen out of 65 patients in the control group (22%) received EVT, and in the intervention arm, 3 patients received only BMM. Based on its pre-specified intention-to-treat analysis, the BEST trial failed to demonstrate a benefit of mechanical thrombectomy over BMM. However the as-treated analysis showed significant better outcomes of patients who received thrombectomy. (unpublished data, presented at World Stroke Conference October 2018). The outcome of the BEST trial has revived the discussion among stroke physicians on the need of further proof of efficacy of IAT in patients with BAO and the implications for the BASICS trial were thoroughly discussed in the BASICS steering committee. The steering committee believes that sufficient equipoise remains tot continue the BASICS trial in the current form and recommends all centres that agree to continue randomisation. With the

current randomisation rate the BASICS trial is expecting to reach the target number of 300 inclusions in the summer of 2019.

Imaging of posterior circulation ischaemic stroke

With already more than 250 randomised patients the BASICS trial will provide a unique prospectively collected imaging database. Recently proposed scores like the PC-CS,[77] BATMAN[61] and PC-clot burden (V. Puetz, unpublished data) will be externally validated in this population. Also, predictors of recanalisation and outcome like clot length[78] or newly proposed predictors in AC stroke, like thrombus perviousness[79] can be investigated in this cohort.

In the near future accuracy of NCCT for detection of PC stroke is expected to increase as new iterative reconstruction filters can help to improve the resolution in this area.[80] In addition, limited brain coverage of CTP, a known cause of false negative findings,[81,82] can be avoided with near to full-brain coverage of a new generation of CT scanners. These new scanners permit coverage of both the AC and PC territories at the same time. This is especially important as some patients with PC stroke symptoms turn out to have an AC stroke, and vice versa, as discussed earlier.

Because of a growing appreciation in the field of acute ischaemic stroke for the possibility of DWI negativity, various diagnostic approaches have been developed to increase sensitivity of MRI for detecting acute ischaemia. Several studies of MRI perfusion-weighted imaging (PWI), which include gadolinium-based techniques and arterial-spin-labeled techniques, have suggested that PWI provides enhanced sensitivity for detecting acute ischaemia.[33,83] Parallel efforts to increase sensitivity of MRI for detection of acute ischaemic stroke have focused on optimization of the DWI sequence itself. These efforts include increasing the spatial resolution,[84] reducing geometric distortion,[85] and performing a second coronal DWI acquisition through the posterior fossa. Furthermore, many investigators have tested the hypothesis that DWI sensitivity can be optimised by increasing the b value, a value that reflects the strength and duration of the diffusion gradients exerted on water molecules within the brain. Several studies have indicated that higher b values increase sensitivity for detection of small infarcts,[86,87] but this observation has not been consistently replicated.[88] At present, neither complementary MRI sequences like PWI nor high-b-value DWI techniques have gained wide acceptance in the clinical evaluation of patients with acute ischaemic stroke.

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SUMMARY

Stroke is the leading cause of disability in developed countries. About 20 % of all ischaemic strokes are located in the posterior circulation (PC). The PC comprises both vertebral arteries, the basilar artery, and the intracranial vessels that they give rise to. Despite the relatively high incidence, ischaemic events in the PC have received less attention and often have been managed differently compared with those in the anterior circulation (AC). Diagnosing PC stroke can be challenging both from a clinical and radiological point of view. Presenting signs and symptoms are often non-specific and fluctuating and therefore may cause a delay in making the correct diagnosis. As the clinical diagnosis of PC stroke can be challenging, a definite diagnosis can often only be reached after brain imaging. Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) is superior for this purpose but, because of limited availability and practical limitations in the acute setting, multimodal computed tomography (CT) (comprising non-contrast CT (NCCT), computed tomographic angiography (CTA) and computed tomographic perfusion (CTP)) is the imaging modality of choice in most dedicated stroke centres.

This thesis focuses on correct infarct localisation in the PC (**Chapter 2**), diagnostic and prognostic value of various imaging derived parameters in the PC (**Chapter 3–6**) and ends with the protocol of the currently enrolling BASICS trial (**Chapter 7**).

Clinical suspicion of acute AC stroke, but PC infarct as the final diagnosis

Chapter 2 investigates if biographical and clinical characteristics can aid in the identification of patients with clinical signs of an acute infarction in the AC but with a PC infarction as the final diagnosis. Of 305 patients with clinically suspected AC stroke without signs of early ischaemia on initial CT enrolled in the Dutch acute stroke trial (DUST) 20 patients (7%) had a PC infarct. Most of the PC infarcts (75%) were lacunar infarcts in the pons and thalamus. None of the baseline characteristics had a statistically significant relation with the presence of a PC infarct.

Diagnostic value of CT perfusion for detection of ischaemia in the PC

Chapter 3 reports the additional value of CTP to NCCT and CTA source images for infarct detection and localisation in patients suspected of acute ischaemic PC stroke. Of 88 patients with suspected acute ischaemic PC stroke enrolled in the DUST, 76 (86%) had a clinical diagnosis of ischaemic stroke on discharge and 42 patients (48%) showed a PC infarct on follow-up imaging. NCCT, CTA and CTP performed within 9 hours of stroke onset and CT and MRI on follow-up were evaluated for signs and localisation of ischaemia. Discrimination of 3

hierarchical logistic regression models (NCCT [A], added CTA source images [B], and CTP [C]) was compared with C-statistics and showed that CTP has significant additional diagnostic value to NCCT and CTA source images for detecting ischaemic changes in these patients.

Collateral flow predicts outcome after BAO: the posterior circulation collateral score

In **Chapter 4** we propose a 10-point grading system, based on the presence of potential collateral pathways on CTA: the posterior circulation collateral score (PC-CS). We assessed the prognostic value of the PC-CS for the prediction of outcome in 140 patients with acute BAO from the Basilar Artery International Cooperation Study (BASICS) registry. Additionally, we analysed the relation between the presence and size of posterior communicating arteries and outcome. The PC-CS predicted poor outcome, defined as a Modified Rankin Scales (mRS) scores of 4 or 5, or death at one month. Both the absence and smaller calibre of posterior communicating arteries predicted poor outcome.

Clot length predicts recanalisation but not outcome after BAO

We assessed clot length on CTA in 149 patients with an acute BAO from the BASICS registry. Clot length was related to recanalisation and outcome at 1 month with Poisson regression. MRS scores of 4 or 5, or death were considered poor outcomes. We found that clot length predicted recanalisation but not outcome at 1 month in patients with a BAO. Additionally, we found 2% more poor outcome and 10% less recanalisation with every centimetre increase in clot length in the analysis of clot length as a continuous variable (**Chapter 5**).

Prevalence and outcome of vertebral artery stenosis in patients with BAO

In **Chapter 6** we describe the prevalence and outcome of vertebral artery (VA) stenosis ≥50% or occlusion in 141 patients with acute BAO enrolled in the BASICS registry, assessed on intracranial CTA. We hypothesised that patients with generalised atherosclerosis of the VAs might have a better collateral circulation, and thereby a better prognosis, than patients with an acute BAO caused by a potential source of embolism in the heart. Sixty-six of 141 patients (47%) had unilateral or bilateral intracranial VA stenosis ≥50%. Forty-six of 72 patients (64%) with available intra-and extracranial CTA had uni-or bilateral VA occlusion or stenosis ≥50%. Overall, VA occlusion or stenosis ≥50% was not associated with the risk of poor outcome. Patients with intra- and extracranial CTA and bilateral VA occlusion had a higher risk of poor outcome than patients without bilateral VA occlusion.

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 intra-arterial therapy (IAT) in addition to best medical management in patients with BAO. The trial targets to include 300 patients, aged 18 years and older with CTA or MRA confirmed BAO. Patients are randomised between best medical management with additional IAT and best medical management alone. IAT has to be initiated within 6 hours from estimated time of BAO. If treated with intravenous thrombolysis, as part of best medical management, this should be started within 4.5 hours of estimated time of BAO. The primary outcome parameter is favourable outcome at day 90 defined as an mRS of 0–3 (**Chapter 7**).

SAMENVATTING

(SUMMARY IN DUTCH)

Het herseninfarct is de belangrijkste oorzaak van invaliditeit in ontwikkelde landen. Ongeveer 20% van alle ischemische herseninfarcten is gelokaliseerd in de achterste circulatie. De achterste circulatie bestaat uit de arteriae vertebrales, de arteria basilaris en de hieruit aftakkende arteriën. Ischemie in de achterste circulatie heeft ondanks een relatief hoge incidentie minder aandacht gekregen dan ischemie in de voorste circulatie en werd vaak ook anders behandeld. Het diagnosticeren van ischemie in de achterste circulatie kan vanuit zowel klinisch als radiologisch oogpunt een uitdaging zijn. De klachten en symptomen waarmee patiënten zich presenteren zijn vaak aspecifiek en fluctuerend waardoor het stellen van de juiste diagnose vertraging op kan lopen. Doordat het stellen van de klinische diagnose ischemie in de achterste circulatie een uitdaging kan zijn, wordt de definitieve diagnose vaak pas gesteld na beeldvorming van de hersenen. MRI (magnetic resonance imaging) met diffusiegewogen opnamen is hierin superieur maar door de beperkte beschikbaarheid en praktische beperkingen in de acute situatie is beeldvorming met CT (computed tomography), bestaande uit non-contrast CT (NCCT), CT angiografie (CTA) en CT perfusie (CTP), de modaliteit van keuze in de meeste vooraanstaande strokecentra.

Dit proefschrift focust op het correct lokaliseren van infarcten in de achterste circulatie (**Hoofdstuk 2**), de diagnostische en prognostische waarde van verschillende van beeldvorming afkomstige parameters in de achterste circulatie (**Hoofdstuk 3-6**) en eindigt met het protocol van de nog lopende BASICS trial (**Hoofdstuk 7**).

Klinische verdenking op acute ischemie in de voorste circulatie, maar een infarct in de achterste circulatie als uiteindelijke diagnose

In **Hoofdstuk 2** wordt onderzocht of biografische en klinische patiëntkarakteristieken bij kunnen dragen aan de identificatie van patiënten met initiële klinische verschijnselen van acute ischemie in de voorste circulatie, maar met een infarct in de achterste circulatie als uiteindelijke diagnose. Twintig van de 305 patiënten (7%) geïncludeerd in de Dutch acute stroke trial (DUST) met klinische verdenking op ischemie in de voorste circulatie maar zonder tekenen van ischemie op initiële beeldvorming met CT bleken uiteindelijk een infarct in de achterste circulatie te hebben. De meeste van deze achterste circulatie-infarcten (75%) waren lacunaire infarcten in de pons en thalamus. Geen van de baselinekarakteristieken had een statistisch significante relatie met de aanwezigheid van een infarct in de achterste circulatie.

Diagnostische waarde van CT perfusie voor detectie van ischemie in de achterste circulatie

Hoofdstuk 3 rapporteert de toegevoegde waarde van CTP ten opzichte van NCCT en CTA bronbeelden voor infarctdetectie en -lokalisatie bij patiënten waarbij acute ischemie in de achterste circulatie wordt vermoed. Van de 88 patiënten met verdenking op acute ischemie in de achterste circulatie hadden 76 patiënten (86%) bij ontslag de klinische diagnose ischemisch infarct en 42 patiënten (48%) hadden een infarct in de achterste circulatie op follow-up beeldvorming. NCCT, CTA en CTP gemaakt binnen 9 uur van het ontstaan van de klachten en follow-up CT en MRI werden beoordeeld op aanwezigheid en locatie van ischemie. De discriminerende waarde van 3 hiërarchische logistische regressiemodellen (NCCT [A], toegevoegde CTA bronbeelden [B] en CTP [C]) werd vergeleken met behulp van C-statistiek en toonde dat CTP significante toegevoegde diagnostische waarde heeft ten opzichte van NCCT en CTA bronbeelden voor de detectie van ischemie bij deze patiënten.

Collaterale bloedvoorziening voorspelt uitkomst na arteria basilaris occlusie: de posterior circulation collateral score

In **Hoofdstuk 4** doen we een voorstel voor een 10-puntsscore gebaseerd op de aanwezigheid van potentiële collaterale bloedvoorziening op CTA: de posterior circulation collateral score (PC-CS). We onderzochten de prognostische waarde van de PC-CS voor predictie van uitkomst bij 140 patiënten met een acute occlusie van de arteria basilaris afkomstig uit de Basilar Artery International Cooperation Study (BASICS) registratie. Daarnaast onderzochten we de relatie tussen de aanwezigheid en het kaliber van de arteria cerebri communicans posterior en uitkomst. De PC-CS voorspelde een slechte uitkomst, gedefinieerd als een modified Rankin Scale (mRS) score van 4, 5 of overlijden na 1 maand. Zowel afwezigheid als een kleiner kaliber van de arteria cerebri communicans posterior waren voorspellers van een slechte uitkomst.

Stolsellengte voorspelt rekanalisatie maar niet uitkomst na arteria basilaris occlusie

We beoordeelden stolsellengte op CTA van 149 patiënten met een acute arteria basilaris occlusie afkomstig uit de BASICS registratie. Stolsellengte werd gerelateerd aan rekanalisatie en uitkomst na 1 maand met Poissonregressie. MRS scores van 4, 5 of overlijden werden beschouwd als slechte uitkomst. Stolsellengte voorspelde rekanalisatie maar niet uitkomst na 1 maand bij patiënten met een arteria basilaris occlusie. Bij analyse van stolsellengte als

een continue variabele vonden we bij elke centimeter toename in stolsellengte 2% vaker een slechte uitkomst en 10% minder vaak rekanalisatie (**Hoofdstuk 5**).

Prevalentie en uitkomst van arteria vertebralis stenosen bij patiënten met een arteria basilaris occlusie

In **Hoofdstuk 6** beschrijven we de prevalentie en uitkomst van stenosen ≥50% of occlusie van de arteria vertebralis bij 141 patiënten met een acute arteria basilaris occlusie afkomstig uit de BASICS registratie, beoordeeld op intracraniële CTA. We veronderstelden dat patiënten met gegeneraliseerde atherosclerose van de arteriae vertebrales mogelijk een betere collaterale circulatie hebben ontwikkeld en daardoor een betere prognose zouden kunnen hebben dan patiënten met een acute arteria basilaris occlusie veroorzaakt door een cardiale embolus. Zesenzestig van de 141 patiënten (47%) had een uni- of bilaterale intracraniële arteria vertebralis occlusie of stenose ≥50%. Zesenveertig van de 72 patiënten (64%) met een beschikbare intra- en extracraniële CTA had een uni- of bilaterale arteria vertebralis occlusie of stenose ≥50%. Een occlusie of stenose ≥50% van de arteria vertebralis bleek niet geassocieerd met het risico op een slechte uitkomst. Patiënten met intra- en extracraniële CTA en bilaterale occlusie van de arteria vertebralis hadden een hoger risico op een slechte uitkomst dan patiënten zonder bilaterale occlusie van de arteria vertebralis.

BASICS trial: studieprotocol

BASICS is een gerandomiseerd gecontroleerd multicenter open label fase III interventie-onderzoek met geblindeerde uitkomstbeoordeling waarbij de werkzaamheid en veiligheid van intra-arteriële behandeling naast beste medische behandeling van patiënten met een arteria basilaris occlusie wordt onderzocht. Het target van het onderzoek is om 300 patiënten van 18 jaar of ouder met een middels CTA of MRA bevestigde occlusie van de arteria basilaris te includeren. Patiënten worden gerandomiseerd tussen beste medische behandeling met aanvullende intra-arteriële behandeling en alleen beste medische behandeling. Intra-arteriële behandeling moet binnen 6 uur na geschatte tijd van arteria basilaris occlusie worden gestart. Indien patiënten als onderdeel van beste medische behandeling worden behandeld met intraveneuze thrombolyse dan dient deze behandeling te worden gestart binnen 4,5 uur na geschatte tijd van arteria basilaris occlusie. De primaire uitkomstmaat is gunstige uitkomst na 90 dagen gedefinieerd als een mRS van 0–3 (**Hoofdstuk 7**).

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Lieve Manon, wie had gedacht dat die zonnige festivaldag 12 jaar geleden ons hier zou brengen. Zo verschillend als we zijn, zo goed passen we bij elkaar. Al 9 jaar is ons leven een achtbaan en nog steeds ben ik gek op je.

CURRICULUM VITAE

Erik van der Hoeven was born on the 17th of May in 1979 and spent most of his childhood in 's-Hertogenbosch in the province of Noord-Brabant. After finishing elementary school in 1991 he lived with his family in Münchenstein, near Basel in Switzerland for one year where he followed secondary school at the Freies Gymnasium in Basel. In 1998 he graduated from secondary school at the Jeroen Bosch College in 's-Hertogenbosch. In the following two years he was not selected for Medical School due to numerus fixus and studied Pharmacy at the University of Utrecht. In 2000 he started his medical training at the University of Leiden. After graduating in 2006 he worked as surgical resident (not in training) in the IJsselland Hospital in Cappelle aan de IJssel and the Erasmus Medical Center in Rotterdam. In 2009 he started his training in Radiology at the St. Antonius Hospital in Nieuwegein (dr. J.P.M. van Heesewijk) and later followed his academic year of training at the University Medical Center Utrecht (dr. R.A.J. Nievelstein). After finishing his training in Radiology in 2015 he followed a 15-month fellowship in Abdominal Radiology (dr. Th.L. Bollen) at the St. Antonius Hospital in Nieuwegein and Utrecht. As a Radiology resident he joined the BASilar artery International Cooperation Study group and coordinated the BASICS trial from 2010- 2015. During this period he was involved in setting up the BASICS trial and the initiation of more than 20 centers in 7 European countries. He currently is a member of the executive committee of the BASICS trial. Since 2016 Erik is a senior staff radiologist at the St. Antonius Hospital and lives in Zeist, together with Manon and their sons Daan (2010), Bas (2011), Tom (2013) and Gijs (2014).