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ORIGINAL COMMUNICATION

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

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Abstract We assessed the prevalence of vertebral artery (VA) stenosis or occlusion and its influence on outcome in patients with acute basilar artery occlusion (BAO). 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. 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). The risk of death did not depend on the presence of unilateral or bilateral VA occlusion or stenosis ≥50 %. In conclusion, 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.

Keywords Acute stroke · Vertebrobasilar disease · Atherosclerosis · Basilar artery occlusion

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Introduction

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

Patients with a symptomatic BA stenosis or occlusion and extensive atherosclerotic disease of both the VA and BA have been reported to have a better outcome than patients with BAO and normal VAs [5]. This might be

explained by a better collateral circulation in patients with generalized 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 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 1 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 [7]. The methods of BASICS have been described previously [2]. 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 (Fig. 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.

Outcome measures

Outcome measures were poor outcome at 1 month (modified Rankin scale (mRs) score 4 or 5, or death), and death at 1 month.

Intra- and extracranial CTAs were independently reviewed by two investigators (AC and EH), who were blinded to all clinical information. When the assessment of the two readers was inconsistent, a consensus meeting took place. The degree of stenosis in the VA on CTA was calculated by dividing the residual lumen (*N*) by vessel diameter at a point distal to the stenosis where the normal vessel caliber has been restored (*D*), and applying the formula: $(1 - N/D) \times 100\ \% =$ 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.

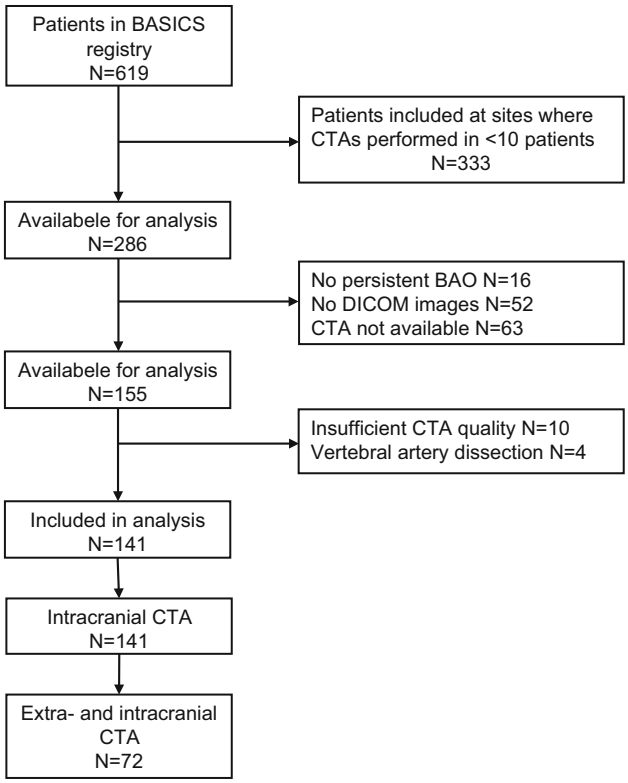

Fig. 1 Flow chart. *CTA* CT angiography, *BAO* basilar artery occlusion

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 1 month were 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 (Fig. 1). Compared with excluded patients, included patients more often received no treatment, but were similar otherwise (Supplementary Table 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 1; Fig. 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 1). VA hypoplasia was found in 6 patients (8 %).

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

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

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

VA vertebral artery, *BA* basilar artery

At 1 month 107 patients (76 %) had a poor outcome, of whom 64 (60 %) had died. Figure 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 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 3 and Supplementary Table 2). Patients with a CTA of the intracranial VAs and a continous 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 2). The presence of extracranial VA hypoplasia did not affect the risk of poor outcome or death.

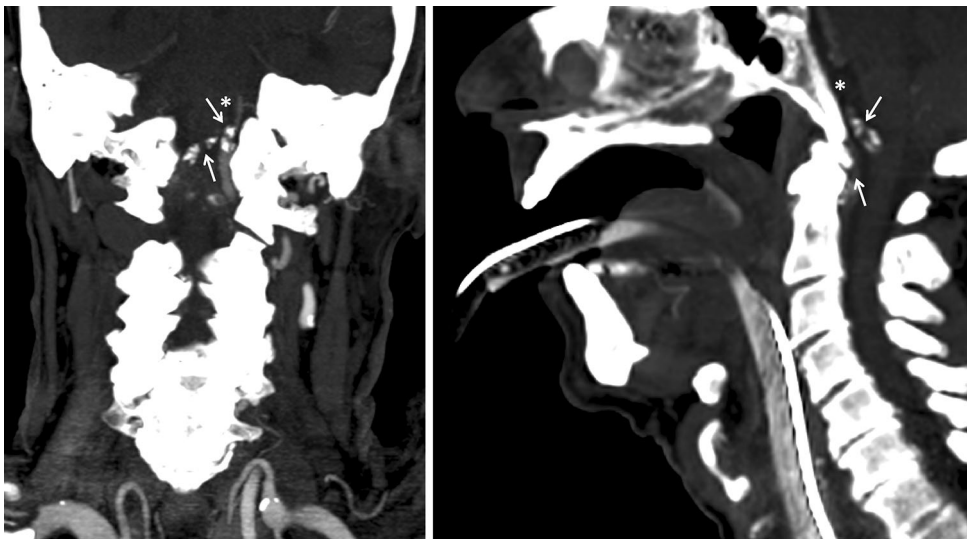

Fig. 2 A 77 years old male admitted because of acute vertebrobasilar stroke with rapid progression to coma. CTA showing basilar artery occlusion (*asterisk*) and bilateral vertebral artery occlusion (*arrows*) with extensive atherosclerosis

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

	CTA of intracranial VA $n = 141$			CTA of extra- and intracranial VA $n = 72$		
	Occlusion or stenosis ≥50 % ($n = 66$)	No occlusion or stenosis ≥50 % ($n = 75$)	Prevalence ratio (95 % CI)	Occlusion or stenosis ≥50 % ($n = 46$)	No occlusion or stenosis ≥50 % ($n = 26$)	Prevalence ratio (95 % CI)
Male sex	50 (76 %)	41 (55 %)	1.4 (1.1–1.8)	32 (70 %)	10 (39 %)	1.8 (1.1–3.1)
Age (years)[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						
0–3 h	19 (29 %)	21 (28 %)	[b]	12 (26 %)	7 (27 %)	[c]
4–6 h	9 (14 %)	28 (37 %)	[b]	13 (28 %)	6 (23 %)	[c]
7–9 h	13 (20 %)	5 (7 %)	[b]	7 (15 %)	2 (8 %)	[c]
>9 h	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)

Table 2 continued

	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)
Occlusion proximal or middle BA	54 (82 %)	35 (47 %)	1.8 (1.3–2.3)	38 (83 %)	7 (27 %)	3.1 (5.6–5.9)

Data are mean (SD), number (%), or median (IQR)

CTA CT angiography, *CI* confidence interval, *TIA* transient ischemic attack, *AT* antithrombotic treatment with aspirin or heparin, *IVT* intravenous thrombolysis, *IVT-IAT* combined treatment with intravenous thrombolysis and intra-arterial therapy, *IAT* intra-arterial therapy, *PTA* percutaneous transluminal angioplasty, *NIHSS* National institutes of Health Stroke Scale score

[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

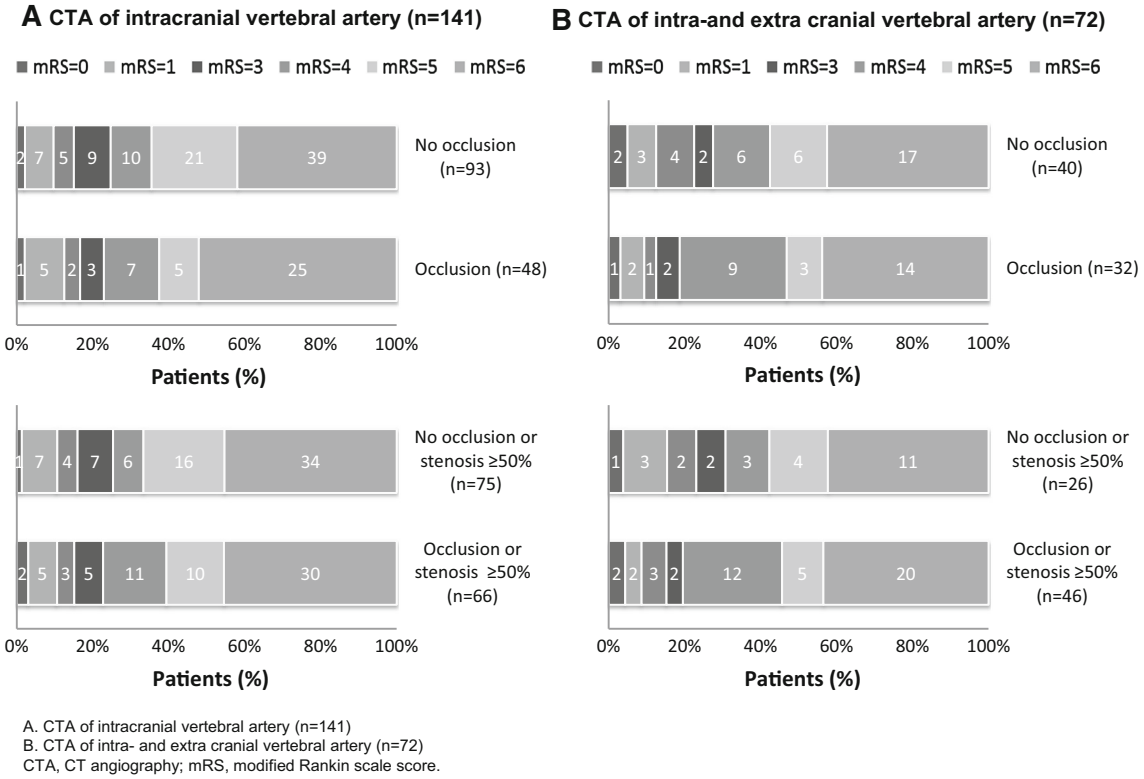

Fig. 3 Outcome at 1 month according to presence of vertebral artery occlusion or stenosis ≥50 %. **a** CTA of intracranial vertebral artery ($n = 141$). **b** CTA of intra- and extra cranial vertebral artery ($n = 72$). *CTA* CT angiography, *mRS* modified Rankin scale score

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

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

	Total	Unadjusted RR	Adjusted RR
CTA of intracranial VA $n = 141$			
Occlusion vs. no occlusion			
Poor outcome	37/48 (77 %) vs. 70/93 (75 %)	1.02 (0.84–1.24)	1.02 (0.84–1.25)[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 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

previous registries had concomitant VA atherosclerosis [5, 12]. Embolism from the heart or extracranial vertebral artery was associated with poor outcome in a previous registry of patients with BA stenosis or occlusion not treated with thrombolysis [5]. It was hypothesized that patients without atherosclerosis, but with an embolic occlusion of the BA, have less time to develop collateral circulation than patients with atherosclerosis and consequently tolerate ischemic symptoms for a shorter period of time. This theory was supported by the finding that patients with widespread atherosclerotic posterior circulation disease had the best prognosis in the previous registry [5]. In the current study, patients with occlusion or stenosis ≥50 % in the extra- or intracranial VA did not have a better outcome than patients without occlusion or stenosis. The difference with the previous registries is probably explained by the important fact that in the present study only patients with acute, symptomatic BAO were included, whereas in the previous registries also patients with a TIA or ischemic stroke due to BA stenosis and chronic BA occlusion had been included. In the current study the majority of patients received IVT or IAT, whereas in previous registries the majority of patients were 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 recanalization 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 visualization 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 ischemic 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 optimization of the intra-arterial entrance to the BA, prevention of recurrent embolism from the VA and recruitment of collaterals during intervention. Whether these interventions for VA stenosis influence outcome in patients with BAO should be assessed in a future study.

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 1 month. Consequently, accompanying VA occlusion or stenosis should not be a reason to withhold any treatment in BAO.

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Conflicts of interest None.

Appendix

The following authors are part of the BASICS Study Group: Weber AM, Donnan GA, Thijs V, Peeters A, de Freitas G, Conforto AB, Miranda-Alves M, Massaro A, Ijäs P, Bogoslovsky T, Lindsberg PJ, Weimar C, Benemann J, Kraywinkel K, Haverkamp C, Michalski D, Weissenborn K, Goertler M, Kloth M, Bitsch A, Mieck T, Machetanz J, Möller P, Huber R, Kaendler S, Rueckert C, Audebert H, Müller R, Vatankhah B, Pfefferkorn T, Mayer TE, Szabo K, Disque C, Busse O, Berger C, Hacke W, Schwammenthal Y, Orion D, Tanne D, Bergui M, Pozzati E, Schonewille WJ, Algra A, Kappelle LJ, Luijckx GJ, Vroomen P, Vergouwen MD, Roos Y, Stam J, Bienfait P, de Leeuw FE, de Kort P, Dippel D, Pagola J, Ribo M, Molina C, Gonzales A, Gil-Peralta A, Norrving B, Arnold M, Fischer U, Gralla J, Mattle H, Schroth G, Michel P, Engelter ST, Wetzel S, Lyrer P, Grandjour J, Michael N, Baumgartner R, Tettenborn B, Hungerbuehler H, Baird T, Muir K, Wijman CA, Finley Caulfield A, Lansberg M, Schwartz N, Venkatasubramanian C, Garami Z, Bogaard S, Yatzu F, Grotta J.

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