Vascular Anatomy Predicts the Risk of Cerebral Ischemia in Patients Randomized to Carotid Stenting Versus Endarterectomy

Mandy D. Müller, MSc*; Frank J. Ahlhelm, MD*; Alexander von Hessling, MD; David Doig, MD; Paul J. Nederkoorn, MD; Sumaira Macdonald, MD, PhD; Philippe A. Lyrer, MD; Aad van der Lugt, MD; Jeroen Hendrikse, MD; Christoph Stippich, MD; H. Bart van der Worp, PhD; Toby Richards, MD; Martin M. Brown, MD; Stefan T. Engelter, MD; Leo H. Bonati, MD

Background and Purpose—Complex vascular anatomy might increase the risk of procedural stroke during carotid artery stenting (CAS). Randomized controlled trial evidence that vascular anatomy should inform the choice between CAS and carotid endarterectomy (CEA) has been lacking.

Methods—One-hundred eighty-four patients with symptomatic internal carotid artery stenosis who were randomly assigned to CAS or CEA in the ICSS (International Carotid Stenting Study) underwent magnetic resonance (n=126) or computed tomographic angiography (n=58) at baseline and brain magnetic resonance imaging before and after treatment. We investigated the association between aortic arch configuration, angles of supra-aortic arteries, degree, length of stenosis, and plaque ulceration with the presence of ≥1 new ischemic brain lesion on diffusion-weighted magnetic resonance imaging (DWI+) after treatment.

Results—Forty-nine of 97 patients in the CAS group (51%) and 14 of 87 in the CEA group (16%) were DWI+ (odds ratio [OR], 6.0; 95% confidence interval [CI], 2.9–12.4; *P*<0.001). In the CAS group, aortic arch configuration type 2/3 (OR, 2.8; 95% CI, 1.1–7.1; *P*=0.027) and the degree of the largest internal carotid artery angle (≥60° versus <60°; OR, 4.1; 95% CI, 1.7–10.1; *P*=0.002) were both associated with DWI+, also after correction for age. No predictors for DWI+ were identified in the CEA group. The DWI+ risk in CAS increased further over CEA if the largest internal carotid artery angle was ≥60° (OR, 11.8; 95% CI, 4.1–34.1) than if it was <60° (OR, 3.4; 95% CI, 1.2–9.8; interaction *P*=0.035).

Conclusions—Complex configuration of the aortic arch and internal carotid artery tortuosity increase the risk of cerebral ischemia during CAS, but not during CEA. Vascular anatomy should be taken into account when selecting patients for stenting.

Clinical Trial Registration—URL: http://www.isrctn.com/ISRCTN25337470. Unique identifier: ISRCTN25337470.

(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.014612.)

Key Words: anatomy ■ angiography ■ brain ■ carotid stenosis ■ endarterectomy ■ stents ■ stroke

Atherosclerotic disease of the carotid artery is an important cause of stroke. The selection of patients to whom carotid artery stenting (CAS) can be offered as an alternative to carotid endarterectomy (CEA) is controversial. In the ICSS (International Carotid Stenting Study), 1710 patients with symptomatic carotid stenosis ≥50% were randomly allocated to CAS or CEA.[1] CAS carried a higher risk of nondisabling, procedure-related stroke than CEA, but was as effective at preventing recurrent stroke in the long term. Thus, the choice of the optimal treatment for individual patients should be based on minimizing procedural risks. In patients with symptomatic carotid stenosis, the extra risk of procedural stroke associated

Received July 25, 2016; final revision received February 23, 2017; accepted February 27, 2017.

From the Department of Neurology and Stroke Center (M.D.M., P.A.L., S.T.E., L.H.B.) and Division of Diagnostic and Interventional Neuroradiology (F.J.A., A.v.H., C.S.), University Hospital Basel, Switzerland; Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology (D.D., M.M.B., L.H.B.) and Division of Surgery and Interventional Science (T.R.), University College London, United Kingdom; Department of Neurology, Academic Medical Center Amsterdam, The Netherlands (P.J.N.); Department of Radiology, Freeman Hospital, Newcastle-upon-Tyne, United Kingdom (S.M.); Department of Radiology, Erasmus MC, University Medical Center Rotterdam, The Netherlands (A.v.d.L.); Department of Radiology (J.H.) and Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus (H.B.v.d.W.), University Medical Center Utrecht, The Netherlands; and Neurorehabilitation Unit, University of Basel and University Center for Medicine of Aging, Felix Platter Hospital, Switzerland (S.T.E.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.014612/-/DC1.

*M.D. Müller and Dr Ahlhelm contributed equally.

Correspondence to Leo H. Bonati, MD, Department of Neurology and Stroke Center, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail leo.bonati@usb.ch

with CAS seems to be limited to patients older than 70 years,[2] the reasons of which remain unclear. Anatomic features of the aortic arch and supra-aortic arteries may increase procedural risk in CAS,[3–8] but also in CEA.[9] Randomized trial evidence whether vascular anatomy constitutes a risk for procedural stroke independently of age, and whether it should inform the choice between CAS and CEA, has been lacking.

In the magnetic resonance imaging (MRI) substudy of ICSS, 3× more patients had new ischemic brain lesions after CAS than after CEA.[10] In the present analysis of the ICSS-MRI substudy, we investigated the association between vascular anatomies observed on baseline contrast-enhanced magnetic resonance angiography (CE-MRA) or computed tomographic angiography (CTA) and the risk of subsequent procedure-related cerebral ischemia. We hypothesized that increased difficulty of vascular anatomy would pose patients at greater risk of ischemia during CAS, but not during CEA.

Methods

In the ICSS-MRI substudy, 231 patients with symptomatic carotid stenosis were examined with brain MRI 1 to 7 days before intervention (pretreatment scan) and 1 to 3 days thereafter (post-treatment scan), including diffusion-weighted sequences (DWI) to detect ischemic brain lesions. The primary outcome was procedural cerebral ischemia, defined as the presence of ≥1 new DWI lesion on the post-treatment scan.[10] The study was approved by local ethics committees for non-UK centers and by the Northwest Multicentre Research Ethics Committee in the United Kingdom. Patients provided written informed consent to undergo MRI when the scans were not part of clinical routine.

The following anatomic parameters were defined before assessment and then evaluated on baseline CE-MRA or CTA in each patient by a single trained neurologist (M.D.M.) blinded to the findings on brain MRI. To test inter-rater reliability, the scans of the first 40 patients were additionally assessed by a neuroradiologist (F.J.A.). Degree of stenosis in the internal carotid artery (ICA) considered for treatment and in the ipsilateral external carotid artery was calculated according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria,[11,12] expressed as the percentage of narrowing of the lumen at the site of maximum stenosis compared with the diameter of the nondiseased ICA measured distal to the bulb, where the artery walls run parallel. Patients with ICA near occlusion were not eligible to participate in ICSS. Length of stenosis was defined as the distance between the proximal and the distal shoulder of the plaque, or if not clearly visible, between the proximal and distal point where the stenosis decreased to 80% of its maximum.[9] Ulcerated stenosis was defined if fulfilling the criteria of an ulcer niche seen in profile as a crater penetrating into a stenotic plaque.[13] In addition, the side of carotid stenosis (left versus right) was recorded.

The current configuration of the aortic arch (AO), which represents a combination of variations of the original anatomy and acquired changes, was classified using a modification of the original definition,[14] in line with previous studies[8]: type 1, if all supra-aortic arteries originated at the level of the outer curvature of the aortic arch; type 2, if at least 1 supra-aortic artery originated between the outer and inner curvature; and type 3, if at least 1 supra-aortic artery originated below the level of the inner curvature (Figure 1). Aortic arch variants such as the left common carotid artery (CCA) originating from the brachiocephalic artery were recorded.[8,15]

The angle between the aortic arch and CCA (or brachiocephalic artery) was measured on the plane defined by the aortic arch by drawing a tangential line along the outer curvature of the aortic arch connecting the origin of the left subclavian artery and the brachiocephalic artery. Then the angle apex was positioned at the origin of the CCA or brachiocephalic artery, 1 angle leg was drawn parallel to the tangential line, and the second one was placed in the center of the CCA or brachiocephalic artery (Figure 2A). Subsequently, choosing the projection on which the angle was most pronounced, each angle along the course of the brachiocephalic artery, between the brachiocephalic artery and the CCA (in case of carotid stenosis on the right or stenosis on the left and CCA originating the brachiocephalic artery), and along the CCA and extracranial ICA was recorded if >30°. Angles were measured by positioning the angle apex at the turning point of the artery, and the angle legs in the center of the proximal and distal segment (Figure 2B). The angle between the CCA and ICA was always recorded. Each angle was measured as the change in direction from the caudal to the cranial segment by subtracting the angle between the 2 legs from 180°, as shown by an asterisk (*) in Figure 2.

In addition, we applied a previously published score of anatomic features considered to increase procedural risk in CAS.[7] The score includes type of aortic arch configuration, arch atheroma, presence of bovine arch, that is, origin of the left CCA from the brachiocephalic artery, CCA disease, pinhole stenosis (>90%), external carotid artery stenosis >50%, CCA tortuosity defined as any vessel angulation >90°, and ICA tortuosity defined as any vessel angulation >60°.

Statistical Analysis

Interobserver agreement of anatomic parameters between the 2 raters was tested with intraclass correlation coefficients (ICC) for continuous variables, with values >0.75 indicating excellent, 0.40 to 0.75 fair to good, and <0.40 poor reliability,[16] and Cohen κ for categorical variables, with values >0.81 indicating excellent, 0.61 to 0.80 substantial, and 0.41 to 0.60 moderate agreement.[17]

Associations between side, degree and length of stenosis, plaque ulceration, angle between aortic arch and brachiocephalic artery or CCA, angle between the brachiocephalic artery and CCA (if applicable), largest angle in the CCA, CCA/ICA angle, largest angle in the ICA and type of aortic arch configuration and the primary outcome measure were investigated with binary logistic regression in each treatment group separately. Continuous variables were dichotomized at the population median. All analyses were adjusted for the time interval between treatment and the post-treatment MRI, which was longer in the CEA group than in the CAS group.[10] Analyses were additionally adjusted for age, which is the strongest clinical predictor for procedural stroke or death associated with CAS and may itself be associated with complex vascular anatomy. In addition, we tested whether anatomic parameters which were significantly associated with the primary outcome measure in 1 treatment group also modified the odds ratio (OR) of the primary outcome measure between CAS and CEA, by testing of statistical interaction. SPSS version 22.0 (IBM Corp, Chicago, IL) was used.

Figure 1. Classification of aortic arch configuration according to the origin of the supra-aortic arteries on contrast-enhanced magnetic resonance angiography. The 2 horizontal lines mark the outer and inner curvature of the aortic arch. The figure illustrates a type 2 aortic arch configuration.

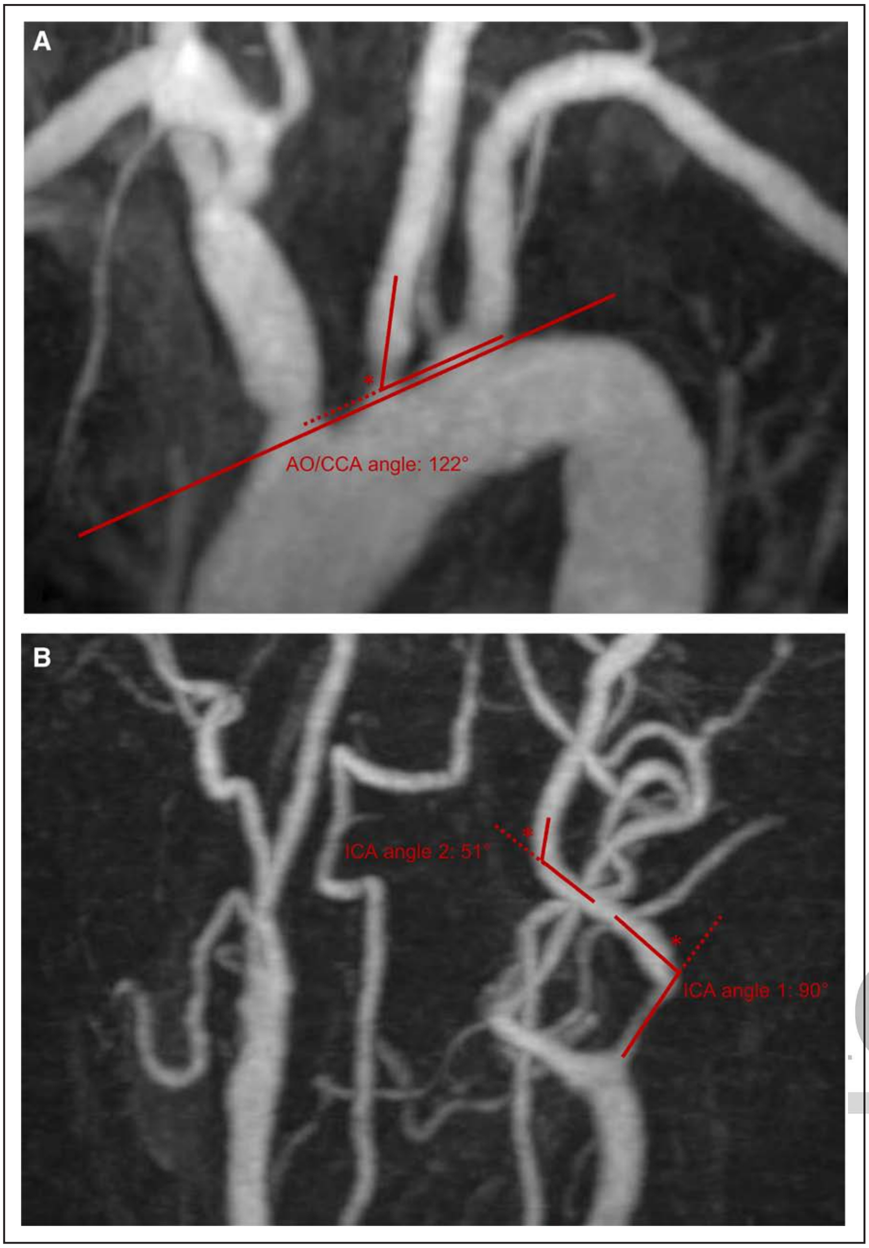

Figure 2. Measurement of vessel angles on contrast-enhanced magnetic resonance angiography. **A**, Assessment of the angle between aortic arch (AO) and left common carotid artery (CCA): first, a parallel line to the upper curvature of the aortic arch is drawn by connecting the origin of the brachiocephalic artery and the left subclavian artery. Then, 1 angle leg is positioned parallel to the tangent and the other in the center of the left CCA respecting its distal course. (Of note, the left vertebral artery in this patient, instead of originating from the subclavian artery, has a combined origin with the latter.) **B**, Assessment of angles in the course of the internal carotid artery (ICA): the angle apex is positioned at the turning point of the vessel and the legs at the center of the ICA respecting its distal and proximal course. Angles were measured as the change in direction from the caudal to the cranial segment by subtracting the angle between the 2 legs from 180°, as shown by an asterisk (*).

Results

Baseline CE-MRA (n=126) or CTA (n=58) was available in 184 of the 231 patients (80%); 97 were assigned to CAS and 87 to CEA (Figure 3). Clinical, anatomic and interventional characteristics were well balanced between groups (Table) and broadly comparable between patients with and without available baseline vascular imaging, with the exception of a longer delay to treatment in the latter group (Table I in the online-only Data Supplement).

Inter-rater agreement was excellent for degree of stenosis (ICC, 0.951), length of stenosis (ICC, 0.886), AO/CCA angle (ICC, 0.948), largest CCA angle (ICC, 0.968), CCA/ICA angle (ICC, 0.887) and largest ICA angle (ICC, 0.944; $P<0.001$), and substantial for aortic arch configuration (0.724; 95% confidence interval [CI], 0.535–0.912; $P<0.001$).

Procedural cerebral ischemia was found in 49 patients in the CAS group (51%) and 14 patients in the CEA group (16%; OR, 6.0; 95% CI, 2.9–12.4; $P<0.001$). In 6 of the 49 patients in the CAS group and in 2 of the 14 patients in the CEA group, the new DWI lesions on the post-treatment scan were associated with symptoms of ischemic hemispheric stroke occurring between initiation of treatment and the post-treatment scan. DWI lesions in the remaining patients were silent.[10] Among both treatment groups combined, stroke symptoms occurred in 5 patients with DWI lesions located in the territory supplied by the right carotid artery and in 3 patients with DWI lesions located in the territory supplied by the left carotid artery (with or without involvement of other territories; Table II in the online-only Data Supplement).

In the CAS group, aortic arch configuration type 2 or 3 as opposed to type 1 (OR, 2.8; 95% CI, 1.1–7.1; $P=0.027$) and the largest angle along the course of the ICA separated at the population median (≥60° versus <60°; OR, 4.1; 95% CI, 1.7–10.1; $P=0.002$) were associated with cerebral ischemia (Figure 4). Both associations remained significant after correction for

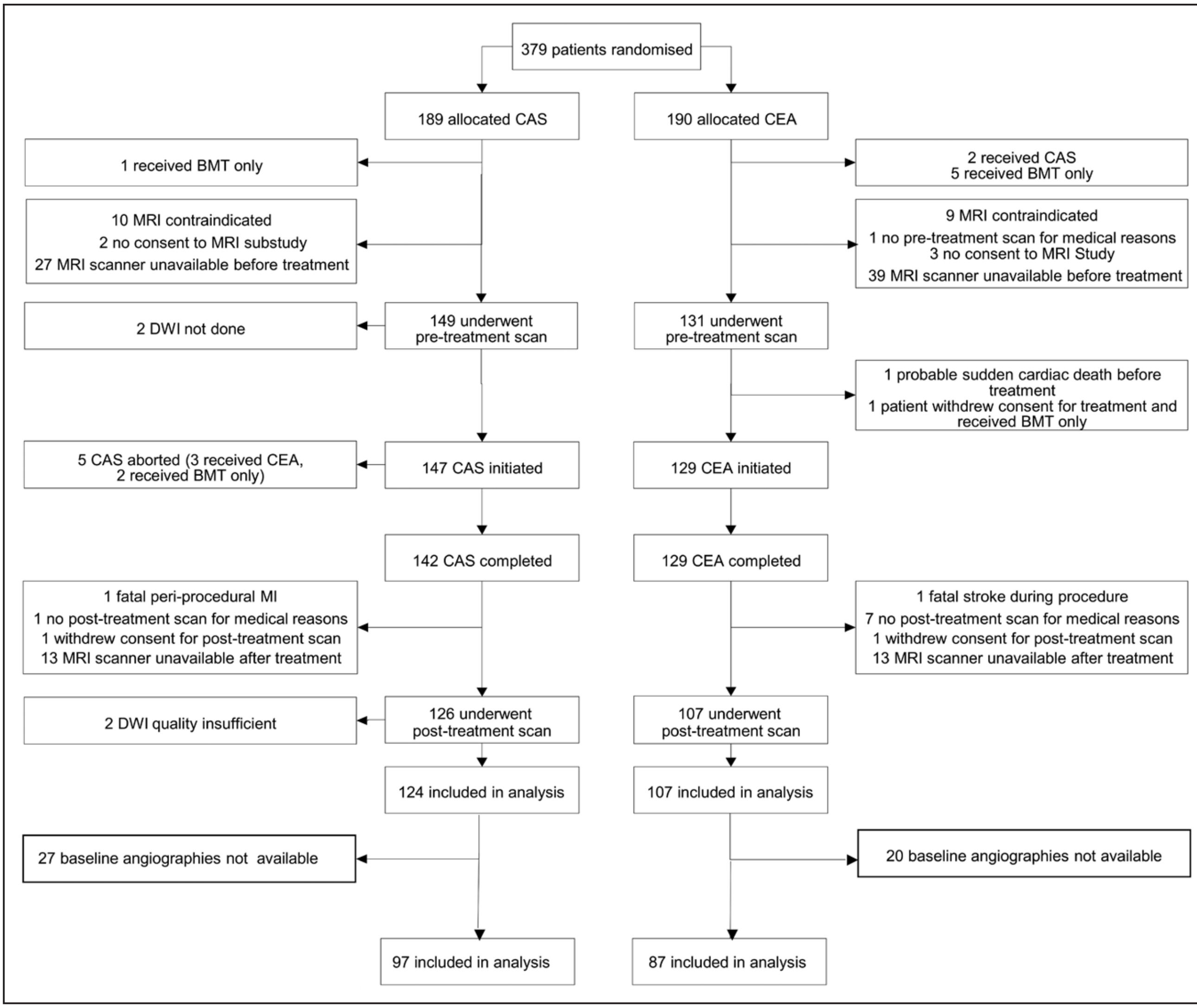

Figure 3. Study flow diagram. Diagram depicting the 2 treatment arms of the study, including events that precluded patients from analysis. Scans are magnetic resonance imaging (MRI). BMT indicates best medical treatment; CAS, carotid artery stenting; CEA, carotid endarterectomy; DWI, diffusion-weighted imaging; and MI, myocardial infarction.

age (OR, 2.9; 95% CI, 1.1–7.7; *P*=0.032; and OR, 3.4; 95% CI, 1.4–8.9; *P*=0.01, respectively). To account for potential confounding, we additionally corrected these associations for the duration of the stenting procedure (OR, 2.9; 95% CI, 1.1–8.1; *P*=0.038 for ICA angle and OR, 2.6; 95% CI, 0.9–7.5; *P*=0.079 for aortic arch configuration, respectively). None of the other parameters predicted the occurrence of cerebral ischemia (Figure 4). In addition, patients with a higher score of anatomic difficulty[7] were also at increased risk for cerebral ischemia (OR, 3.2; 95% CI, 1.3–7.9; *P*=0.014, values separated at the population median 4.3), but not after correction for age (OR, 2.2; 95% CI, 0.8–5.7; *P*=0.123).

In the surgery group, none of the assessed parameters for vascular anatomy or stenosis characteristics (or the expert score for anatomic suitability) were significantly associated with procedural cerebral ischemia. However, we observed a nonsignificant trend that patients with aortic arch configuration type 2 or 3 had a higher risk of cerebral ischemia (OR, 3.5; 95% CI, 0.7–17.1; Figure 4).

We performed a sensitivity analysis excluding patients without available arch angiography from all analyses. Among 89 remaining patients in the CAS group, the association between cerebral ischemia and largest ICA angle ≥60° remained statistically significant (OR, 3.2; 95% CI, 1.2–8.5; *P*=0.023). In the remaining 76 patients in the CEA group, we again found no significant associations.

The interaction between the largest ICA angle and the effect of treatment (CAS versus CEA) on cerebral ischemia was statistically significant: the extra risk of DWI lesions in CAS increased further over CEA if the largest ICA angle was ≥60° (OR, 11.8; 95% CI, 4.1–34.1) than if it was <60° (OR, 3.4; 95% CI, 1.2–9.8; interaction *P*=0.035). The interactions between treatment effect and aortic arch configuration or anatomic suitability score were not significant (Figure 5).

Discussion

In this substudy of a randomized trial comparing CAS versus CEA for symptomatic carotid stenosis, difficult configuration

Table. Patient and Intervention Characteristics

	CAS (n=97)	CEA (n=87)
Age, y; median (IQR)	70.45 (14.4)	71.65 (13.8)
Male, n (%)	65 (67)	65 (74.7)
Vascular risk factors, n (%)		
Hypertension	67 (69.1)	63 (72.4)
Diabetes mellitus	18 (18.6)	19 (21.8)
Hyperlipidemia	56 (57.7)	55 (63.2)
Smoking	73 (75.3)	65 (74.7)
Peripheral artery disease	17 (17.5)	12 (13.8)
Coronary heart disease	24 (24.7)	20 (23.0)
Qualifying event type, n (%)		
Retinal or TIA	56 (57.7)	52 (59.7)
Hemispheric stroke	41 (42.3)	35 (40.2)
Contralateral severe stenosis or occlusion, n (%)	20 (20.6)	16 (18.4)
Delay to treatment, d; median (IQR)	30 (63)	40 (52)
Anatomic risk factors		
Left sided stenosis, n (%)	47 (48.5)	38 (43.7)
Type of aortic arch configuration		
Aortic arch type 1, n (%)	37 (38.1)	28 (32.2)
Aortic arch type 2 or 3, n (%)	52 (53.6)	48 (55.2)
Left CCA originating from the brachiocephalic artery, n (%)	11 (11.3)	10 (11.5)
Aortic arch not visible, n (%)	8 (8.2)	11 (12.6)
Largest CCA angle, median (IQR)	48 (45)	52.5 (35)
Angle CCA/ICA, median (IQR)	24 (22)	27 (21)
Largest ICA angle, median (IQR)	57 (32)	66 (47)
Degree of stenosis, median (IQR)	72.13 (20)	75.0 (23)
Length of stenosis, median (IQR)	6.3 (6)	6.0 (4)
Plaque ulceration, n (%)	16 (16.5)	19 (21.8)
Expert score of anatomic suitability, median (IQR)	4.0 (2.2)	4.3 (2.2)
Cerebral protection device		
Cerebral protection device used, n (%)	31 (36)	…
No cerebral protection device used, n (%)	55 (64)	…
Stent design		
Open cell, n (%)	53 (61.6)	…
Closed cell, n (%)	33 (38.4)	…
Type of anesthesia		
General anesthesia, n (%)	…	71 (81.6)
Local anesthesia, n (%)	…	10 (11.5)
Patch		
Patch used, n (%)	…	49 (56.3)
No patch used, n (%)	…	19 (21.8)
Shunt		
Shunt used, n (%)	…	11 (12.6)
No Shunt used, n (%)	…	76 (87.4)

Baseline data of patients in the stenting and endarterectomy group and details of stenting and endarterectomy procedure. Percentages exclude missing data; missing data were Carotid artery stenting (CAS) group: n=11 patients no interventional details known; carotid endarterectomy (CEA) group: n=6 patients no information on type of anesthesia available, n=19 patients no information on patch use available. CCA indicates common carotid artery; ICA, internal carotid artery; IQR, interquartile range; and TIA, transient ischemic attack.

of the aortic arch and the largest angle along the course of the ICA were found to increase the risk of procedural cerebral ischemia in patients treated with stenting, but not in patients undergoing endarterectomy. ICA angulation differentially increased the extra risk of cerebral ischemia associated with CAS versus CEA.

In most previous studies investigating procedural stroke risk in CAS, vascular anatomy was assessed on digital subtraction angiography (DSA) performed as part of the procedure. To date, no study has compared the impact of vascular anatomy on procedural risks between CAS and CEA. We assessed baseline noninvasive carotid imaging (CE-MRA and CTA) obtained at the time of random assignment to CAS or CEA, before treatment was initiated. These tests are commonly available and used in routine diagnostic work-up for carotid disease. Hence, our findings seem more relevant to inform the choice between CAS and CEA among patients with symptomatic carotid stenosis in routine practice than the results of studies based on preprocedural DSA.

A complex configuration of the aortic arch and the supra-aortic arteries increases the technical difficulty of the stent procedure. Repeated attempts to advance the catheter and guidewire may cause endothelial microtrauma or dislodge atherosclerotic plaque and ultimately cause cerebral emboli. The protocol of ICSS did not contain detailed precautions against these complications, such as advice on catheter and guidewire handling, limiting guidewire maneuver time between flushing, syringe aspiration and cleansing, concentration of heparin in saline flush, use of constant infusion via infusion ports to stopcocks, etc. We are therefore unable to verify that all possible precautions against thromboembolism were taken. This limitation must be borne in mind when interpreting the results of our study.

Despite this important limitation, key findings of our study were supported by previous research. Faggioli et al[15] reported a statistically significant association between aortic arch configuration and variants such as origin of the left CCA from the brachiocephalic artery (termed bovine arch) and the incidence of neurological complications in patients undergoing CAS. In our study, we were able to confirm an increased incidence of cerebral ischemia in patients with type 2 or 3 aortic arch configuration. The aortic arch variant mentioned above was present in 11% of our study population, which is within the frequency range reported in the literature and showed no

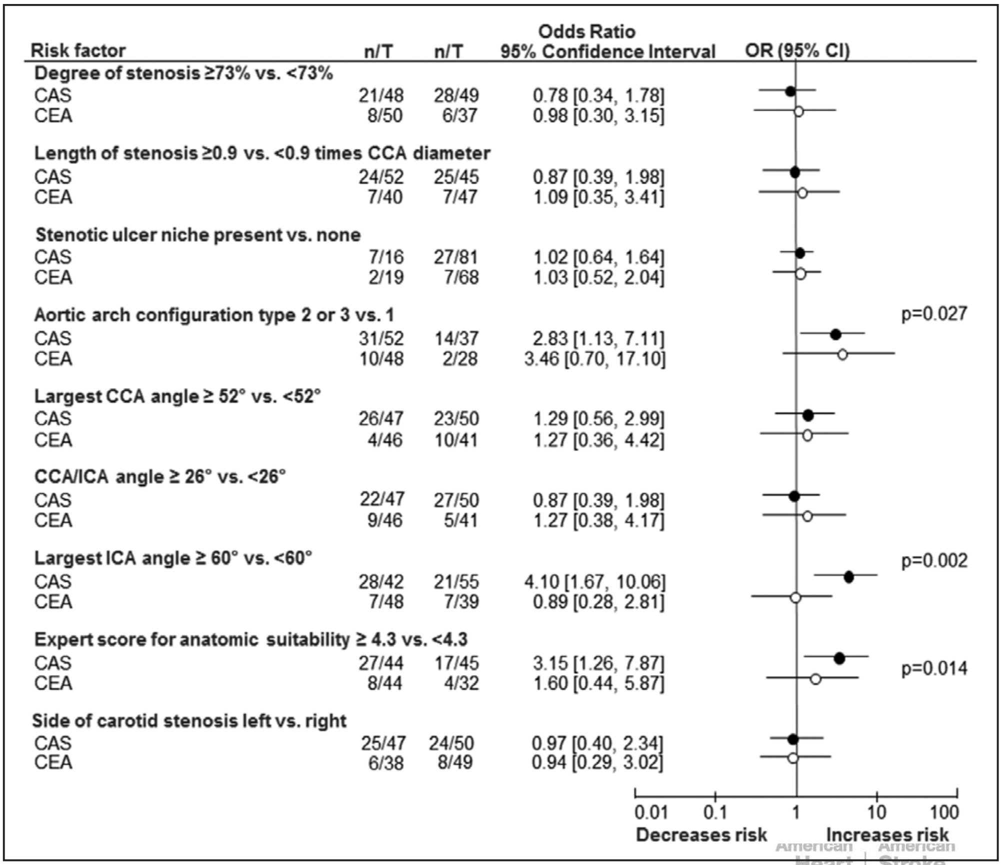

Figure 4. Risk factor analysis**.** Impact of vascular anatomy on the risk of new diffusion-weighted imaging (DWI) lesions after carotid artery stenting (CAS) and carotid endarterectomy (CEA). Data are numbers of patients with new DWI lesions on post-treatment magnetic resonance imaging (MRI) scans (n) and total numbers of patients (T) per group. Circles and horizontal lines are odds ratios (OR) and 95% confidence intervals (CI) for presence of new DWI lesions in patients with vs without each risk factor, adjusted for interval between treatment and post-treatment scan and age. Continuous variables (degree and length of stenosis, angles, and expert score for anatomic suitability) were separated at the median values of the study population. Missing data: in the CAS group, the aortic arch was not visible in 8 patients; in the CEA group, the aortic arch was not visible in 11 patients. CCA indicates common carotid artery; and ICA, internal carotid artery.

association with the occurrence of new lesions on MRI after treatment, possibly because of a lack of power.

With regard to tortuosity of the supra-aortic arteries, a higher risk of stroke or death within 30 days of CAS has been reported in patients with ICA/CCA angulation ≥60° on preprocedural DSA.[6] Other authors described a significant association between tortuosity of the CCA and proximal ICA and the occurrence of complications in CAS, but found no increase in adverse events in patients with tortuous ICA distal to the stenosis.[5] We were able to confirm that greater tortuosity along the course of the ICA increases the incidence of cerebral ischemia in CAS.

A scoring system derived from expert opinion has been developed to grade the difficulty of vascular anatomy (and hence to judge the suitability of the patient) for CAS.[7] Our results suggest that this system might indeed be able to predict the occurrence of ischemic brain lesions in patients with symptomatic carotid stenosis undergoing CAS, although perhaps not independently of age.

We found no significant association between supra-aortic vascular anatomy or stenosis characteristics and procedural cerebral ischemia in the surgery group. Problems with CAS related to navigating difficult vascular anatomy do not apply to endarterectomy where the atherosclerotic lesion can be directly accessed. However, there was a strong nonsignificant trend that patients with aortic arch configuration type 2 or 3 had a higher risk of cerebral ischemia possibly because these configurations are associated with increased atherosclerotic burden or represent markers of vascular risk in general.

By including 2 broadly comparable treatment groups in this observational substudy of a randomized trial, we were able to investigate whether a given anatomic risk predictor would modify the relative risk of cerebral ischemia between CAS and CEA, by formal testing for statistical interaction. The extra risk of DWI lesions associated with CAS increased further over CEA if the largest measured ICA angle was ≥60° (the population median) than if it was <60°. ICA tortuosity therefore seems to be a feature which should specifically be taken into account when deciding between CAS and CEA.

Characteristics of the carotid plaque (degree and length of ipsilateral stenosis and plaque ulceration) studied on CE-MRA and CTA did not predict the occurrence of new DWI lesions after CAS, in line with a previous DSA-based substudy of ICSS.[18] In contrast, several studies showed that the presence of an ulcerated plaque on preprocedural DSA increases the risk for the occurrence of DWI lesions after stenting.[19–21] In

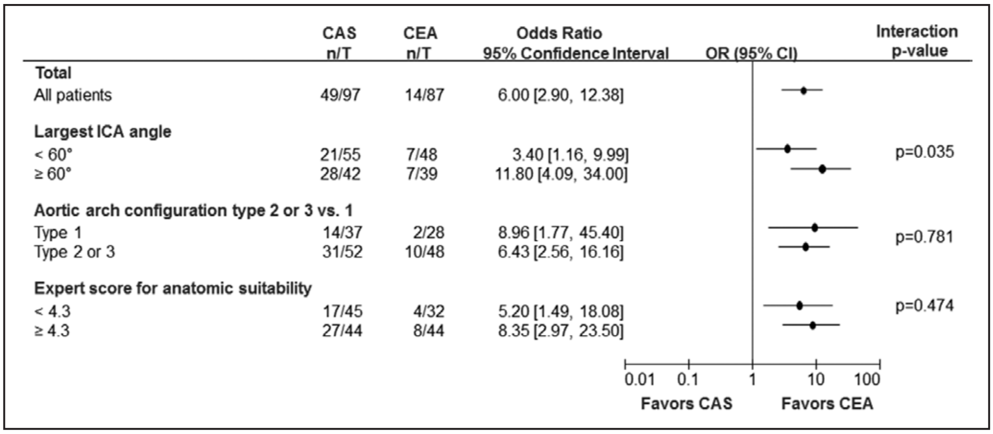

Figure 5. Subgroup analysis. Data are numbers of patients with new diffusion-weighted imaging (DWI) lesions on post-treatment scans (n) and total numbers of patients (T) per treatment group. Circles and horizontal lines are odds ratios (OR) and 95% confidence intervals (CI) for presence of new DWI lesions in patients treated with carotid artery stenting (CAS) vs carotid endarterectomy (CEA), adjusted for interval between treatment and post-treatment scan. Continuous variables were separated at the median values of the study population. Interaction *P* values are shown. Missing data: in the CAS group, the aortic arch was not visible in 8 patients; in the CEA group, the aortic arch was not visible in 11 patients. ICA indicates internal carotid artery.

addition, lesion length has been found to constitute a risk factor for adverse events in CAS,[9,19–21] but also in CEA.[9] CE-MRA and CTA are inferior to DSA in accurately depicting plaque ulceration and lesion length which might explain the discrepant findings between these studies and ours.

Older age has consistently been shown a risk factor for procedural stroke in CAS, but not in CEA.[2] It has been speculated whether the association might be mediated by vascular anatomy. Elongation of the aortic arch and supra-aortic arteries was found to be more prevalent in elderly patients,[4,8] possibly leading to more difficulties during the CAS procedure. Notably in our analysis, the associations between ICA angulation and aortic arch configuration with cerebral ischemia in the stenting group remained significant after correction for age. Hence, vascular anatomy should be taken into account when selecting the appropriate treatment option for an individual patient, independent of the patient's age.

This analysis has further limitations. The fact that the ICSS protocol excluded patients with a stenosis that was thought to be unsuitable for stenting because of proximal tortuous anatomy is likely to have limited the number of patients with very unfavorable anatomy. The full impact of vascular anatomy on CAS risk may therefore have been underestimated in this study. Second, although allocation of treatment was randomized, only 7 of 50 study sites participated in the ICSS-MRI substudy, and not all patients enrolled in ICSS at these sites completed the substudy for various reasons, as previously reported.[10] Analyzing a subset of a clinical trial implies many potential risks: the population of the substudy may differ from the original trial population and treatment groups in the substudy may differ in characteristics not measured in the trial because of selection bias. Third, the classification of aortic arch configuration used in this study did not capture the full spectrum of anatomic variation seen in practice; in particular, we did not assess varying degrees of separation between origins of left CCA and brachiocephalic arteries. Fourth, the limited power of our study has several implications: the observed associations in the CAS group must be interpreted with caution; the lack of adjustment for other clinical predictors of CAS risk because of limited power, such as previous stroke and atrial fibrillation,[21,22] represents an important drawback; and a true impact of vascular anatomy on CEA risk may have been missed. Nonetheless, we think that the observed associations between vascular anatomy and cerebral ischemia in the stenting group are valid because they confirm the findings of previous, nonrandomized studies. Finally, a key limitation for the generalizability of our findings to modern practice is that technical advances in access routes (cervical versus femoral), stent design (eg, multilayered stents), and cerebral protection devices (eg, flow-reversal) have likely lowered the risk of thromboembolic complications in CAS since the time of recruitment in ICSS. Patients with complex vascular anatomy may derive the greatest benefit from these advances. Protection devices were only used in a minority of patients and they were mostly of the distal filter type. A previous analysis of the ICSS-MRI data showed that—contrary to their intended purpose and the results of previous MRI-based studies[23]—the use of distal protection devices was associated with an increased risk of DWI lesions.[10]

Conclusions

In this MRI substudy of a randomized trial, we have shown that ICA angulation and difficult configuration of the aortic arch both represent possible risk factors of cerebral ischemia during stenting for symptomatic carotid stenosis, independent of patient age. No anatomic parameters significantly increasing the risk of endarterectomy were identified. ICA angulation was the sole parameter differentially increasing the risk of cerebral ischemia with stenting versus endarterectomy. The risk of cerebral ischemia might be lower (and the observed associations with aortic arch configuration and carotid anatomy weaker) if technical precautions against thromboembolism were maximized. Nonetheless, vascular anatomy should be taken into account before selecting patients for stenting, irrespective of their age.

Acknowledgments

Lisa M. Jongen from the University Medical Centre Utrecht, The Netherlands, analyzed all brain magnetic resonance imaging scans with Dr Bonati.

Sources of Funding

ICSS (International Carotid Stenting Study) was funded by grants from the Medical Research Council (London, United Kingdom), the Stroke Association (London, United Kingdom), Sanofi-Synthelabo (Paris, France), and the European Commission (Brussels, Belgium). The funding from the Medical Research Council (MRC) was managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership. Funding for magnetic resonance imaging (MRI) scans done as part of the ICSS-MRI substudy was provided by grants from the Mach-Gaensslen Foundation, (Unterägeri, Switzerland), The Netherlands Heart Foundation (Den Haag, The Netherlands), and the Stroke Association (London, United Kingdom). Dr van der Worp was supported by a grant from the Dutch Heart Foundation (2010T075; Den Haag, The Netherlands). Dr Brown's Chair in Stroke Medicine is supported by The Reta Lila Weston Trust for Medical Research (London, United Kingdom). Dr Bonati was supported by grants from the Swiss National Science Foundation (PBBSB-116873 and 33CM30-124119; Berne, Switzerland) and the University of Basel (Basel, Switzerland). This work was partly done at University College London Hospital and University College London, who received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Disclosures

Dr Macdonald has stock options at Silk Road Medical. Dr van der Worp has received speaker's fees from Boehringer Ingelheim and Bayer. Dr van der Lugt has received speaker's fees from GE Healthcare. Dr Engelter has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim, Pfizer Inc, Sanofi-Aventis, and Shire plc; he has served on scientific advisory boards for Bayer and Boehringer Ingelheim and on the editorial board of *Stroke*. Dr Bonati has served on scientific advisory boards for Bayer. The other authors report no conflicts.

References

1. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al; International Carotid Stenting Study Investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet*. 2015;385:529–538. doi: 10.1016/S0140-6736(14)61184-3.
2. Howard G, Roubin GS, Jansen O, Hendrikse J, Halliday A, Fraedrich G, et al; Carotid Stenting Trialists' Collaboration. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials. *Lancet*. 2016;387:1305–1311. doi: 10.1016/S0140-6736(15)01309-4.
3. Werner M, Bausback Y, Bräunlich S, Ulrich M, Piorkowski M, Friedenberger J, et al. Anatomic variables contributing to a higher periprocedural incidence of stroke and TIA in carotid artery stenting: single center experience of 833 consecutive cases. *Catheter Cardiovasc Interv*. 2012;80:321–328. doi: 10.1002/ccd.23483.
4. Lin SC, Trocciola SM, Rhee J, Dayal R, Chaer R, Morrissey NJ, et al. Analysis of anatomic factors and age in patients undergoing carotid angioplasty and stenting. *Ann Vasc Surg*. 2005;19:798–804. doi: 10.1007/s10016-005-8045-4.
5. Faggioli G, Ferri M, Gargiulo M, Freyrie A, Fratesi F, Manzoli L, et al. Measurement and impact of proximal and distal tortuosity in carotid stenting procedures. *J Vasc Surg*. 2007;46:1119–1124. doi: 10.1016/j.jvs.2007.08.027.
6. Naggara O, Touzé E, Beyssen B, Trinquart L, Chatellier G, Meder JF, et al; EVA-3S Investigators. Anatomical and technical factors associated with stroke or death during carotid angioplasty and stenting: results from the endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial and systematic review. *Stroke*. 2011;42:380–388. doi: 10.1161/STROKEAHA.110.588772.
7. Macdonald S, Lee R, Williams R, Stansby G; Delphi Carotid Stenting Consensus Panel. Towards safer carotid artery stenting: a scoring system for anatomic suitability. *Stroke*. 2009;40:1698–1703. doi: 10.1161/STROKEAHA.109.547117.
8. Lam RC, Lin SC, DeRubertis B, Hynecek R, Kent KC, Faries PL. The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting. *J Vasc Surg*. 2007;45:875–880. doi: 10.1016/j.jvs.2006.12.059.
9. Bonati LH, Ederle J, Dobson J, Engelter S, Featherstone RL, Gaines PA, et al; CAVATAS Investigators. Length of carotid stenosis predicts peri-procedural stroke or death and restenosis in patients randomized to endovascular treatment or endarterectomy. *Int J Stroke*. 2014;9:297–305. doi: 10.1111/ijs.12084.
10. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al; ICSS-MRI Study Group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol*. 2010;9:353–362. doi: 10.1016/S1474-4422(10)70057-0.
11. NASCET Steering Committee. North American symptomatic carotid endarterectomy trial. Methods, patient characteristics, and progress. *Stroke*. 1991;22:711–720. doi: 10.1161/01.STR.22.6.711.
12. Fox AJ. How to measure carotid stenosis. *Radiology*. 1993;186:316–318. doi: 10.1148/radiology.186.2.8421726.
13. Streifler JY, Eliasziw M, Fox AJ, Benavente OR, Hachinski VC, Ferguson GG, et al. Angiographic detection of carotid plaque ulceration. Comparison with surgical observations in a multicenter study. North American Symptomatic Carotid Endarterectomy Trial. *Stroke*. 1994;25:1130–1132.
14. Casserly IP, Sachar R, Yadav JS. *Manual of Peripheral Vascular Intervention*. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
15. Faggioli GL, Ferri M, Freyrie A, Gargiulo M, Fratesi F, Rossi C, et al. Aortic arch anomalies are associated with increased risk of neurological events in carotid stent procedures. *Eur J Vasc Endovasc Surg*. 2007;33:436–441. doi: 10.1016/j.ejvs.2006.11.026.
16. Fleiss J. *The Design and Analysis of Clinical Experiments*. New York, NY: Wiley; 1986.
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159–174.
18. Doig D, Hobson BM, Müller M, Jäger HR, Featherstone RL, Brown MM, et al; ICSS-MRI Study Investigators. Carotid anatomy does not predict the risk of new ischaemic brain lesions on diffusion-weighted imaging after carotid artery stenting in the ICSS-MRI substudy. *Eur J Vasc Endovasc Surg*. 2016;51:14–20. doi: 10.1016/j.ejvs.2015.08.012.
19. Gröschel K, Ernemann U, Schnaudigel S, Wasser K, Nägele T, Kastrup A. A risk score to predict ischemic lesions after protected carotid artery stenting. *J Neurol Sci*. 2008;273:112–115. doi: 10.1016/j.jns.2008.07.004.
20. Sayeed S, Stanziale SF, Wholey MH, Makaroun MS. Angiographic lesion characteristics can predict adverse outcomes after carotid artery stenting. *J Vasc Surg*. 2008;47:81–87. doi: 10.1016/j.jvs.2007.09.047.
21. Wimmer NJ, Yeh RW, Cutlip DE, Mauri L. Risk prediction for adverse events after carotid artery stenting in higher surgical risk patients. *Stroke*. 2012;43:3218–3224. doi: 10.1161/STROKEAHA.112.673194.
22. Hawkins BM, Kennedy KF, Giri J, Saltzman AJ, Rosenfield K, Drachman DE, et al. Pre-procedural risk quantification for carotid stenting using the CAS score: a report from the NCDR CARE Registry. *J Am Coll Cardiol*. 2012;60:1617–1622. doi: 10.1016/j.jacc.2012.07.026.
23. Schnaudigel S, Gröschel K, Pilgram SM, Kastrup A. New brain lesions after carotid stenting versus carotid endarterectomy: a systematic review of the literature. *Stroke*. 2008;39:1911–1919. doi: 10.1161/STROKEAHA.107.500603.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Vascular Anatomy Predicts the Risk of Cerebral Ischemia in Patients Randomized to Carotid Stenting Versus Endarterectomy

Mandy D. Müller, Frank J. Ahlhelm, Alexander von Hessling, David Doig, Paul J. Nederkoorn, Sumaira Macdonald, Philippe A. Lyrer, Aad van der Lugt, Jeroen Hendrikse, Christoph Stippich, H. Bart van der Worp, Toby Richards, Martin M. Brown, Stefan T. Engelter and Leo H. Bonati

Stroke. published online April 11, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Supplemental Material

Supplementary Table I - Clinical characteristics of included and excluded patients

	All patients (n=184)	**Missing patients** (n=47)
Age (years) *median (IQR)*	71.3 (13.8)	68.9 (10.2)
Male *n (%)*	130 (70.7%)	32 (68.1%)
Vascular risk factors *n (%)*		
Hypertension	70.7%	61.7%
Diabetes	20.1%	23.4%
Hyperlipidemia	60.3%	78.7%
Smoking	75%	76.6%
Peripheral artery disease	15.8%	17%
Coronary heart disease	23.9%	12.8%
Qualifying event type *n (%)*		
Retinal or TIA	58.7%	63.8%
Hemispheric stroke	41.3%	36.2%
Contralateral severe stenosis or occlusion *n (%)*	36 (19.5%)	14 (29.8%)
Delay to treatment (days) *median (IQR)*	35 (60)	71 (111)

Baseline characteristics of the 184 patients included in the present analysis and of the 47 patients in the ICSS-MRI substudy excluded from the present analysis for reasons of missing baseline angiography. IQR = Interquartile range; TIA = transient ischemic attack.

Supplementary Table II – Laterality and symptom status of DWI lesions after treatment

	CAS		CEA	
Location of new ischemic brain lesions after treatment *N Patients (%)*	**Left sided stenosis** **(n=47)**	**Right sided stenosis** **(n=50)**	**Left sided stenosis** **(n=38)**	**Right sided stenosis** **(n=49)**
No lesions	22 (47%)	26 (52%)	32 (84%)	41 (84%)
Any lesion	25 (53%)	24 (48%)	6 (16%)	8 (16%)
Lesions in the ipsilateral carotid territory / symptomatic lesions	14 / 1	13 / 1	5 / 0	5 / 0
Lesions in the ipsilateral carotid AND in the contralateral carotid or vertebrobasilar territory / symptomatic lesions	9 / 2	9 / 2	0 / 0	3 / 2
Lesions ONLY in the contralateral carotid or vertebrobasilar territory / symptomatic lesions	2 / 0	2 / 0	1 / 0	0 / 0

Laterality and symptom status of new DWI lesions in all 184 patients included in the present analysis according to treatment group and side of carotid stenosis. CAS = Carotid Artery Stenting; CEA = Carotid Endarterectomy.