Elsevier Editorial System(tm) for European Journal of Vascular and Endovascular Surgery
Manuscript Draft

Manuscript Number: EJVES13282R

Title: A clinical validation study of anatomical risk scoring for procedural stroke in patients treated by carotid artery stenting in the International Carotid Stenting Study

Article Type: Original Article-Other

Keywords: Carotid artery stenting; vascular anatomy; procedural stroke; risk score

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***2 Multiple Choice Questions and 5 possible answers (highlight correct answer)**

Multiple choice questions

1. Which of the following statements is true?

- Large randomized controlled trials demonstrated similar short-term efficacy for carotid artery stenting (CAS) and carotid endarterectomy in treatment of patients with significant carotid artery stenosis.
- The majority of 30-day strokes after CAS occur on the day of the procedure.
- The International Carotid Stenting Study demonstrated an excess in procedural minor strokes in asymptomatic patients.
- Only ipsilateral strokes can a complication of CAS, contralateral strokes should not be included in the 30-day complication rate.
- Younger patients have higher stroke risks after CAS compared to elderly patients.

2. Which anatomical risk factors are thought by experts to hamper the CAS procedure?

- Tortuous common carotid artery.
- Angulated origin of the internal carotid artery.
- Aortic arch atheroma.
- Internal carotid artery stenosis with circumferential calcification.
- All of the above.

A clinical validation study of anatomical risk scoring for procedural stroke in patients treated by carotid artery stenting in the International Carotid Stenting Study

Short title: A validation of anatomical risk scoring for CAS.

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Key Words: Carotid artery stenting; vascular anatomy; procedural stroke; risk score

Submission category: original research

Declarations of interest: none

Word Count: 2509 (introduction – discussion)

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WHAT THIS PAPER ADDS

Although several anatomical risk factors have been suggested to influence procedural difficulty of carotid artery stenting (CAS), no validated risk score is available to help select suitable patients for CAS. The Delphi anatomical risk (DAR) score was developed to predict difficulty of CAS in relation to procedural stroke risk, and hereby aid in patient selection. This is the first attempt to clinically validate the DAR score within this post-hoc analysis of ICSS. No significant association between the DAR score and procedural stroke risk was found. However, the small sample size potentially rendered the study underpowered and our results should be replicated in the future.

ABSTRACT

BACKGROUND: Vascular anatomy of aortic arch and supra-aortic arteries has been suggested as influencing the risk of carotid artery stenting (CAS). The expert opinion-based Delphi anatomical risk (DAR) score was developed to predict difficulty of CAS in relation to procedural stroke risk, and hereby aid in patient selection.

OBJECTIVES: We aimed to validate the DAR score in the context of a randomised clinical trial.

METHODS: In this post-hoc analysis of the International Carotid Stenting Study (ICSS), we included only patients treated by CAS with available pre-procedural CT angiography (CTA). Patients with tortuous anatomy unsuitable for stenting were excluded from ICSS. CTA-based vascular anatomy was rated by two independent observers. Every possible combination of anatomy resulted in a risk score, divided in four categories of expected risk (low:<5.0; low-intermediate:5.0–5.9; high-intermediate: 6.0–6.9; high:≥7.0). Binomial logistic regression was used to assess the relation between anatomical risk scoring, and procedural risk of any stroke. We also assessed differences between predefined age groups.

RESULTS: 275 patients were included. Interobserver reliability for all anatomical risk factors was high (κ 0.76-0.84). In total, 16 strokes (6%) occurred in the procedural period. We observed no significant relationship between the DAR score and risk of procedural stroke, with the risk of stroke being 9% in the high-risk versus 4% in the low-risk categories (*P*=0.49). A higher mean DAR score was observed in patients ≥70 years compared to younger patients (4.6±1.5 vs 3.9±1.4, *P*<0.001), which was mainly explained by higher rates of arch atheroma (44% vs 20%, *P*<0.001). A prolonged duration of the intervention was significantly associated with increased stroke risk (11% vs 4%, *P*=0.04), but not with the DAR score.

CONCLUSION: We found no statistically significant association between anatomical difficulty, as defined in the DAR score, and procedural stroke risk. However, our small sample size potentially

rendered the study underpowered to detect group differences, and confirmation with a larger sample is essential.

INTRODUCTION

Extracranial atherosclerotic carotid disease is an important risk factor for stroke. Carotid artery stenting (CAS) has gained popularity in the past decade as an alternative to carotid endarterectomy (CEA) for treatment of significant carotid stenosis, and has been shown equally effective in long-term stroke prevention.[1,2] However, most large randomised trials comparing CEA with CAS have shown a higher risk of procedural stroke in patients treated by stenting.[3–6] Thus, the reduction of these procedural strokes is pivotal in treatment optimization. As the majority of procedural strokes occur on the day of stenting,[7,8] a reduction is likely to be achieved through optimal selection of patients with favourable characteristics for CAS. As transfemoral CAS requires guidewire navigation through the aortic arch up to the carotid bifurcation, any difficulty with arterial navigation could increase the risks of arterial damage and subsequent thrombo-embolism. Consequently, several features of vascular anatomy have been suggested to influence the procedural risks of CAS.[9–14]

The Delphi anatomical risk (DAR) score is an expert opinion-based scoring system that grades expected difficulty of CAS based on seven individual anatomical features of the aortic arch and supra-aortic arteries, developed by Macdonald et al as an aid to case selection.[15] The assumption underlying the DAR score is that a higher score predicts the risk of procedural stroke during CAS. A recent substudy from the International Carotid Stenting Study (ICSS) showed that the DAR score predicted the risk of ischaemic lesions on magnetic resonance diffusion weighted imaging (DWI) following CAS, although not after correction for age.[16] To the best of our knowledge, up to now the DAR score has not been validated for the clinically relevant outcome of procedural stroke related to CAS.

We aimed to clinically validate the DAR score criteria within this post-hoc analysis of the ICSS, a large randomised controlled trial that compared CAS and CEA in recently symptomatic patients. Individual anatomical features as well as the DAR score were related to the risk of any procedural stroke up to 30 days in patients undergoing CAS.

MATERIALS AND METHODS

Trial protocol and patient selection

The ICSS trial protocol (ISRCTN 25337470) has been published previously.[17] In summary, patients with recently symptomatic moderate or severe carotid stenosis (>50%) who were eligible for both surgery and stenting were randomly assigned to CEA or CAS. Patients were excluded from ICCS if they had a stenosis known to be unsuitable for stenting because of tortuous anatomy proximal or distal to the stenosis, the presence of visible thrombus, proximal common carotid artery stenotic disease, or pseudo-occlusion ('string sign'). All procedures were performed by interventionists approved by a credentialing committee as having appropriate training and experience of carotid stenting. Individual interventionists who were not able to satisfy the credentialing requirements were identified as probationary investigators. Stenting procedures carried out by probationary investigators were proctored by an experienced carotid interventionist, until the proctor was satisfied that the interventionist could carry out procedures without supervision.

For the purpose of this study, ICSS patients were included only if they had been randomised to CAS, the CAS procedure was completed, and pre-procedural computed tomography angiography (CTA) images were available for analysis (i.e. centrally stored in the ICSS archive). In order to calculate DAR score, imaging had to include the aortic arch and supra-aortic arteries up to the base of skull.

Anatomical risk scoring

The DAR score is a scoring system of carotid anatomy, based on expert consensus, developed to categorise expected difficulty of CAS. The final DAR score is calculated according to the flow chart in the original expert consensus paper.[15] **Table 1** shows seven anatomical risk factors and their definitions as included in the DAR score. Every possible combination of anatomy results in a risk score between 2.4 and 8.5, and has been divided in 4 categories of expected risk (low: <5.0; low-intermediate: 5.0–5.9; high-intermediate: 6.0–6.9; high: ≥7.0).

Two trained independent observers (DdW, EdV) assessed available pre-operative vascular CTAs in order to grade anatomical difficulty and the DAR score. In case of disagreement, consensus was achieved through discussion with a third independent observer (AH).

Procedural stroke (ipsi- and contralateral)

In ICSS, major events were adjudicated by an independent endpoint committee that was unaware of treatment allocation. Stroke was defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. We analysed only procedural stroke, defined as any stroke occurring within 30 days of the stenting procedure, irrespective of the vascular territory of the event.

Duration of procedure

In ICSS, investigators were asked to complete technical data forms for all interventions, which allowed us to study exact duration of the stenting procedure. A prolonged duration of a stenting procedure was arbitrarily defined as any procedure lasting ≥75 minutes.

Statistical analysis

A power analysis was performed using Rstudio (version 1.0.143, RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA; URL http://www.rstudio.com/). Total 30-day stroke risk in ICSS was 7.0%. Assuming a procedural stroke risk of 10% in the highest DAR score group versus 4% in the lowest DAR score group, 566 patients would be needed for the analysis (confirming to a power of 0.8 at an alpha level of 0.05 and a confidence interval of 95%).

~~A doubled to tripled stroke risk in the highest DAR score category compared to the lowest was assumed. In total, 566 patients had to be included in the analyses (highest DAR = 0.10, lowest DAR = 0.04, power = 0.80, alpha = 0.05, confidence interval = 95%).~~

We compared the presence of anatomical risk factors in two predefined age groups (<70 years and ≥70 years) using a chi square test. Binomial logistic regression analysis was used to test procedural risk of stroke according to individual anatomical risk factors and the DAR score. Comparison between the reference group and risk factor under consideration was expressed in an odds ratio with Wald 95% confidence interval. Similarly, we analysed an association between anatomical difficulty and a prolonged duration of the intervention. All analyses were performed for the total cohort and divided by the predefined age groups.

We performed an interobserver reliability analysis for each anatomical risk factor in the DAR score. A Kappa statistic (κ) was used to determine consistency among observers (DdW, EdV). A κ-value of less than 0.20 indicates poor; 0.20-0.39, fair; 0.40-0.59, moderate; 0.60-0.79, good; and 0.80-1.00 i outstanding agreement between observers.[18] Statistical analyses were conducted using SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). We considered a *P*-value of <0.05 statistically significant for all analyses. Data are presented as mean ± standard deviation, unless otherwise specified.

RESULTS

Study population

A total of 1713 patients were enrolled in ICSS, of whom 855 were randomly allocated to CAS. Pre-procedural CTA was available for 275/855 patients (33%), of which 97% had been performed within three months of the procedure. Baseline characteristics are presented in **Table 2**. Mean age at intervention was 70±9 years and the majority were male (71%). **Table 2** also shows the baseline characteristics of all patients included in ICSS as a whole, which confirms representativeness of the selected sample.

Anatomical risk scoring

The overall interobserver reliability for the seven anatomical risk factors was high with all kappa values between 0.76 and 0.84 (**Table 1**). The third observer was consulted in 94/275 patients (34%), in 69/94 patients the disagreement concerned merely one factor. The presence of anatomical risk factors and the DAR score is shown in **Table 3**. The mean DAR score was 4.3 in the total cohort and only 11 (4%) of patients were scored as high difficulty (DAR score ≥7.0). Patients aged 70 years and above had a significantly higher DAR score when compared to younger patients (4.6±1.5 vs 3.9±1.4, P<0.001), which was mainly attributable to higher rates of arch atheroma (44% vs 20%, P<0.001).

Procedural stroke risk (ipsi- and contralateral)

A total of 16/275 (6%) of patients had a stroke during the procedural period, with a higher risk of stroke in patients ≥70 years compared to younger patients (9% vs 3%, P=0.03). All strokes were ischaemic and 7/275 (3%) patients had a stroke that was fatal or disabling.

The risk of stroke according to the DAR score is presented in **Table 4**. Univariate logistic regression showed that the DAR score did not accurately predict procedural stroke, although the low-risk group

(DAR score <5.0) had the lowest risk of stroke in the overall cohort. The risk of stroke in the high-risk group (DAR score ≥7.0) was doubled when compared to the low-risk group but this difference was not statistically significant (9% vs 4%; OR 2.15, 95% CI 0.24-18.91, P=0.49).

We performed several additional analyses. A separate analysis for age groups <70 years vs ≥70 years showed a significantly increased risk of stroke in the high-intermediate group (DAR score 6.0-6.9) when compared to the low risk group in patients <70 years (OR 13.13, 95% CI 1.62-105.86, P=0.02; data not shown). However, this was based on solely four strokes in the age group <70 years, which is reflected in the wide confidence interval. Furthermore, we grouped the DAR score into two categories of expected risk instead of four (low risk: <6.0, high risk: ≥6.0), which did not result in any statistical significance (stroke risk 11% vs 5%; OR 2.28, 95% CI 0.70 – 7.50, P=0.17; data not shown).

Table 5 presents the risk of stroke according to the individual anatomical risk factors. None of the evaluated anatomical features showed a significant association with procedural stroke when analysed separately. Arch atheroma, the anatomical feature that was overexpressed in patients over 70 years of age, did not increase the risk of stroke in the total cohort. A separate analysis for the two predefined age groups showed a significantly higher risk of stroke in the patients <70 years with bovine and type III arch (25% vs 1%; OR 32.67, 95% CI 1.63-656.41, P=0.02; data not shown). However, this was based on solely one stroke in the four patients <70 years with bovine and type III arch, also reflected in the wide confidence interval.

Duration of intervention

Duration of intervention was available for 242/275 (88%) patients and in these patients the median procedure duration was 65 (range 15-400) minutes. According to our pre-defined definition, a total of 76/242 (31%) CAS interventions were prolonged for 75 minutes or more. A prolonged duration of the intervention was significantly associated with increased risk of stroke (11% vs 4%; OR 3.14, 95%

CI 1.05-9.39, *P*=0.04; data not shown). However, no association was found between higher DAR score and prolonged CAS intervention (data not shown).

DISCUSSION

Several features of vascular anatomy have been proposed to predict difficulty of CAS, and are suggested to increase the risk of procedural stroke after CAS. In the current study, we attempted to validate the anatomical risk score as a substudy of ICSS, and demonstrated that the DAR score can be reliably assessed with good interobserver agreements. As our sample size was too small to reach adequate power, no definite conclusions could be drawn on the relationship between the DAR score and procedural risk of stroke after CAS. Of note, as our analysis was confined to CAS patients, no conclusions can be drawn regarding comparisons with carotid endarterectomy.

Perhaps now more than ever, patient selection for carotid interventions is a topic of broad interest, and guidelines pay careful attention to optimizing the selection of suitable patients for CAS.[19] If we had shown that vascular anatomy predicted procedural stroke after CAS, assessment of anatomy could be used to identify high-risk patients, and thereby reduce the periprocedural complication risk. In a recent substudy of ICSS, it was suggested that the DAR score was able to predict the occurrence of new postprocedural DWI lesions after CAS, although not after correction for age.[16] To our knowledge, this is the first study to validate the DAR score for the clinically relevant outcome of procedural stroke after CAS. Unfortunately, with only 275 patients our study was insufficiently powered to allow final conclusions. However, some interesting findings could be observed. A doubling of stroke risk was seen in the high-risk compared to the low-risk DAR categories. Second, a prolonged duration of intervention was significantly associated with increased risk of stroke. This might reflect the degree of difficulty of the intervention, which is likely to be associated with anatomical difficulty, although not statistically significant in our study. Lastly, we did demonstrate that patients over 70 years of age had a significantly higher DAR score compared to younger patients, and strokes were over three times as common in this elderly patient group. The higher degree of anatomical difficulty in older patients was largely explained by a higher incidence of aortic arch atheroma. This is in line with previous studies in which octogenarians were shown to have increased incidence of aortic arch calcifications and innominate stenosis.[20,21] Consequently, it has been suggested that the observation of increased procedural risk in elderly patients is related to increased anatomical complexity.[22] In the current study, elderly patients had both a higher procedural risk and a higher DAR score. However, although twice as many strokes were seen in the high anatomical risk patients, this did not reach statistical significance.

The only relevant anatomical exclusion criteria from ICSS were the presence of a stenosis thought to be unsuitable for stenting because of tortuous anatomy proximal or distal to the stenosis and pseudo-occlusion. These criteria might be thought to correspond to the factors included in the DAR score of angulated distal ICA and pinpoint stenosis. However, it is notable that although 166 patients in the current study were included in ICSS with one or more of these two factors, they did not have a significantly higher rate of procedural stroke. Thus, our results support excluding such patients only if the anatomy is considered unfavourable for stenting by an experienced interventionist.

Our findings need to be interpreted in the light of the following limitations of our study. Firstly, only a third of ICSS CAS patients had the required baseline CTA available, resulting in a representative but relatively small ~~sample size~~cohort. We deliberately excluded patients in whom only digital subtraction angiography and/or magnetic resonance angiography had been performed, in order to achieve a dataset as homogenous as possible. It is notable that there were only small numbers of patients in the high-risk groups. This might be a reflection of patient selection in ICSS, and the ICSS CAS population included likely reflected DAR intermediate to low-risk patients in everyday practice. Second, although stroke rate was high in our cohort, the absolute number of strokes was small. The limited power made it less likely to find more modest contributors to risk of procedural strokes. Thirdly, in accordance with the DAR score, only anatomical factors were studied. Plaque characteristics may also be an important predictor of stroke, especially in patients with challenging anatomy.[23–25] In this study we limited analysis to anatomical risk factors included in the DAR score. A tortuous CCA was rated most difficult in the DAR score expert consensus study, and was excluded from the final risk score because it would rate too difficult in combination with other anatomical risk factors.[15] In addition, several other anatomical factors like severe (circumferential) lesion calcification[26,27] or lesion length,[10,28] might also contribute to procedural hazard, but had not been included in the final DAR score.

Finally, it is notable that among the anatomical factors included in the DAR score, only pinpoint stenosis might be expected to influence risk during stent deployment. The others would be expected only to increase the risk of stroke resulting from carotid cannulation. The latter causes stroke in only a minority of stented cases. In ICSS as a whole, an analysis of the mechanisms of procedural stroke only identified 4 non-ipsilateral strokes out of 55 stented patients with procedural ischaemic stroke that could be related to cannulation and only one case that could be attributed to technical difficulties related to anatomical factors.[7] We were unable to determine whether the DAR score would have predicted stroke in these cases because of the very small number of events.

Conclusions and recommendations

This is the first clinical validation analysis of the Delphi anatomical risk score for procedural stroke after CAS. We showed no statistically significant association between anatomical difficulty, as defined in the DAR score, and procedural stroke risk, in this recently symptomatic patient group. However, the small sample size potentially rendered the study underpowered to give firm conclusions, and a trend towards higher stroke rate in high anatomical risk categories could be noted. Nonetheless, we have shown that the DAR score is a feasible and consistently reported instrument when based on CTA imaging. Furthermore, because only small numbers of stroke can be expected to be associated with anatomical risk factors, our study should be replicated in the future. In order to obtain a sufficient number of baseline CTAs and events, it is important that currently running trials, as well as trials still to be designed, and registries, include these imaging work-up in their study protocols.

CONFLICT OF INTEREST: none.

FUNDING: none.

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TABLES

Table 1. The seven anatomical risk factors that comprise the Delphi anatomical risk (DAR) score, their definitions, and interobserver reliability per risk factor.

Anatomical risk factor	Definition	Kappa (95% CI)	*P*-value
Arch atheroma	Severe arch atheroma or arch origin disease	0.80 (0.76–0.84)	<0.001
Access		0.76 (0.72–0.80)	<0.001
diseased CCA	Atheroma CCA		
ECA problem	Diseased and/or occluded ECA		
Type arch		0.84 (0.80–0.87)	<0.001
bovine	Conjoint origin of left CCA and brachiocephalic trunk		
type III	2 cm between highest point of arch and origin of brachiocephalic trunk		
Angulated distal ICA	Angulated distal ICA ≥90 degrees	0.77 (0.73–0.81)	<0.001
Pinpoint stenosis	90-99% stenosis ICA with flow beyond lesion	0.79 (0.75–0.83)	<0.001

Abbreviations: CCA = common carotid artery, CI = confidence interval, ECA = external carotid artery, ICA = internal carotid artery.

Table 2. Baseline patient characteristics of 275 patients included in the analyses, and of 853 patients included in ICSS as a whole.

BASELINE CHARACTERISTICS		
	CAS (current study, n=275)	**CAS (ICSS,[5] n=853)**
Sex		
Male	194 (71)	601 (70)
Age at intervention		
Age (years)	70 ± 9	70 ± 9
< 70	141 (51)	unknown
≥ 70	134 (49)	unknown
Vascular risk factors (*) *		
Treated hypertension	183 (66)	587 (69)
Treated hyperlipidaemia	173 (64)	522 (61)
Any diabetes mellitus	62 (23)	184 (24)
Cardiac failure	7 (3)	23 (3)
Atrial fibrillation	21 (8)	57 (7)
Angina in past 6 months	22 (8)	83 (10)
Previous myocardial infarction	48 (18)	151 (18)
Previous CABG	40 (15)	109 (13)
Current smoker	83 (31)	205 (24)
Ex-smoker	122 (45)	408 (48)
Peripheral arterial disease	48 (18)	139 (16)
Ipsilateral carotid stenosis		
50 – 69%	29 (11)	92 (11)
70 – 99%	246 (89)	761 (89)
Contralateral carotid stenosis		
< 50%	166 (61)	565 (66)
50 – 69%	42 (15)	128 (15)
70 – 99%	45 (17)	105 (12)
Occlusion	18 (7)	49 (6)
Procedural outcome		
30-day stroke rate	16 (6)	58 (7)

Values are mean ± SD, or number (%).

Abbreviations: CABG = coronary artery bypass graft, SD = standard deviation.

~~(*)~~ * For vascular risk factors information was available for 271 patients.

Table 3. Number (%) of patients with anatomical risk factors for the total cohort. *Chi-square analysis and two-sample t-test comparing presence of risk factors and the mean DAR score between both age groups.*

PRESENCE OF ANATOMICAL RISK FACTORS AND THE DAR SCORE				
	Total cohort (n=275)	**<70 years (n=141)**	**≥70 years (n=134)**	***P*-value**
Arch atheroma				**<0.001**
No atheroma	188 (68)	113 (80)	75 (56)	
Atheroma	87 (32)	28 (20)	59 (44)	
Access				0.15
Normal	199 (72)	109 (77)	90 (67)	
Diseased CCA	50 (18)	20 (14)	30 (23)	
ECA problem	26 (9)	12 (9)	14 (11)	
Type arch				0.77
Normal arch	190 (69)	99 (70)	91 (68)	
Bovine arch	31 (11)	17 (12)	14 (10)	
Type III arch	47 (17)	21 (15)	26 (20)	
Bovine & type III arch	7 (3)	4 (3)	3 (2)	
Target vessel				0.11
Normal	201 (73)	109 (77)	92 (69)	
Angulated ICA	74 (27)	32 (23)	42 (31)	
Type lesion				0.77
Normal	183 (67)	95 (67)	88 (66)	
Pinpoint stenosis	92 (33)	46 (33)	46 (34)	
DAR score				**0.003**
< 5.0	180 (65)	107 (76)	73 (55)	
5.0 – 5.9	58 (21)	20 (14)	38 (28)	
6.0 – 6.9	26 (9)	10 (7)	16 (12)	
≥ 7.0	11 (4)	4 (3)	7 (5)	
Mean score ± SD	4.3 ± 1.4	3.9 ± 1.4	4.6 ± 1.5	**<0.001**

Abbreviations: CCA = common carotid artery, ECA = external carotid artery, ICA = internal carotid artery, SD = standard deviation.

Table 4. Procedural risk of any stroke following CAS according to the Delphi anatomical risk (DAR) score for the total cohort. *Binomial logistic regression was used to give odds ratios (ORs) per anatomical risk group where possible. 'Low-risk' anatomy (DAR score < 5.0) was used as reference category.*

PROCEDURAL ANY STROKE RISK ACCORDING TO THE DAR SCORE				
	N patients	**N strokes (%)**	**Unadjusted OR (95% CI)**	***P*-value**
DAR score				
< 5.0	180	8 (4)	1.00	
5.0 – 5.9	58	4 (7)	1.59 (0.46 – 5.50)	0.46
6.0 – 6.9	26	3 (12)	2.80 (0.69 – 11.33)	0.15
≥ 7.0	11	1 (9)	2.15 (0.24 – 18.91)	0.49

Table 5. Procedural risk of any stroke following CAS for the total cohort. *Binomial logistic regression was used to give odds ratios (ORs) per anatomical risk factor where possible. 'Normal' anatomy was used as reference category.*

PROCEDURAL RISK OF ANY STROKE ACCORDING TO INDIVIDUAL RISK FACTORS				
	N patients	**N strokes (%)**	**Unadjusted OR (95% CI)**	***P*-value**
Arch atheroma				
Not present	188	10 (5)	1.00	
Present	87	6 (7)	1.32 (0.46 – 3.75)	0.61
Access				
Normal	199	12 (6)	1.00	
ECA problem	50	2 (4)	0.65 (0.14 – 3.00)	0.58
Diseased CCA	26	2 (8)	1.30 (0.27 – 6.16)	0.74
Type arch				
Normal arch	190	8 (4)	1.00	
Bovine arch	31	2 (7)	1.57 (0.32 – 7.76)	0.58
Type III arch	47	5 (11)	2.71 (0.84 – 8.30)	0.09
Bovine & type III arch	7	1 (14)	3.79 (0.41 – 35.34)	0.24
Target vessel				
Normal	201	13 (7)	1.00	
Angulated ICA	74	3 (4)	0.61 (0.17 – 2.21)	0.45
Type lesion				
Normal	183	9 (5)	1.00	
Pinhole stenosis	92	7 (8)	1.59 (0.57 – 4.42)	0.37

Abbreviations: CCA = common carotid artery, ECA = external carotid artery, ICA = internal carotid artery, SD = standard deviation.

A clinical validation study of anatomical risk scoring for procedural stroke in patients treated by carotid artery stenting in the International Carotid Stenting Study

Short title: A validation of anatomical risk scoring for CAS.

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Key Words: Carotid artery stenting; vascular anatomy; procedural stroke; risk score

Submission category: original research

Declarations of interest: none

Word Count: 2509 (introduction – discussion)

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WHAT THIS PAPER ADDS

Although several anatomical risk factors have been suggested to influence procedural difficulty of carotid artery stenting (CAS), no validated risk score is available to help select suitable patients for CAS. The Delphi anatomical risk (DAR) score was developed to predict difficulty of CAS in relation to procedural stroke risk, and hereby aid in patient selection. This is the first attempt to clinically validate the DAR score within this post-hoc analysis of ICSS. No significant association between the DAR score and procedural stroke risk was found. However, the small sample size potentially rendered the study underpowered and our results should be replicated in the future.

ABSTRACT

BACKGROUND: Vascular anatomy of aortic arch and supra-aortic arteries has been suggested as influencing the risk of carotid artery stenting (CAS). The expert opinion-based Delphi anatomical risk (DAR) score was developed to predict difficulty of CAS in relation to procedural stroke risk, and hereby aid in patient selection.

OBJECTIVES: We aimed to validate the DAR score in the context of a randomised clinical trial.

METHODS: In this post-hoc analysis of the International Carotid Stenting Study (ICSS), we included only patients treated by CAS with available pre-procedural CT angiography (CTA). Patients with tortuous anatomy unsuitable for stenting were excluded from ICSS. CTA-based vascular anatomy was rated by two independent observers. Every possible combination of anatomy resulted in a risk score, divided in four categories of expected risk (low:<5.0; low-intermediate:5.0–5.9; high-intermediate: 6.0–6.9; high:≥7.0). Binomial logistic regression was used to assess the relation between anatomical risk scoring, and procedural risk of any stroke. We also assessed differences between predefined age groups.

RESULTS: 275 patients were included. Interobserver reliability for all anatomical risk factors was high (κ 0.76-0.84). In total, 16 strokes (6%) occurred in the procedural period. We observed no significant relationship between the DAR score and risk of procedural stroke, with the risk of stroke being 9% in the high-risk versus 4% in the low-risk categories (*P*=0.49). A higher mean DAR score was observed in patients ≥70 years compared to younger patients (4.6±1.5 vs 3.9±1.4, *P*<0.001), which was mainly explained by higher rates of arch atheroma (44% vs 20%, *P*<0.001). A prolonged duration of the intervention was significantly associated with increased stroke risk (11% vs 4%, *P*=0.04), but not with the DAR score.

CONCLUSION: We found no statistically significant association between anatomical difficulty, as defined in the DAR score, and procedural stroke risk. However, our small sample size potentially

rendered the study underpowered to detect group differences, and confirmation with a larger sample is essential.

INTRODUCTION

Extracranial atherosclerotic carotid disease is an important risk factor for stroke. Carotid artery stenting (CAS) has gained popularity in the past decade as an alternative to carotid endarterectomy (CEA) for treatment of significant carotid stenosis, and has been shown equally effective in long-term stroke prevention.[1,2] However, most large randomised trials comparing CEA with CAS have shown a higher risk of procedural stroke in patients treated by stenting.[3–6] Thus, the reduction of these procedural strokes is pivotal in treatment optimization. As the majority of procedural strokes occur on the day of stenting,[7,8] a reduction is likely to be achieved through optimal selection of patients with favourable characteristics for CAS. As transfemoral CAS requires guidewire navigation through the aortic arch up to the carotid bifurcation, any difficulty with arterial navigation could increase the risks of arterial damage and subsequent thrombo-embolism. Consequently, several features of vascular anatomy have been suggested to influence the procedural risks of CAS.[9–14]

The Delphi anatomical risk (DAR) score is an expert opinion-based scoring system that grades expected difficulty of CAS based on seven individual anatomical features of the aortic arch and supra-aortic arteries, developed by Macdonald et al as an aid to case selection.[15] The assumption underlying the DAR score is that a higher score predicts the risk of procedural stroke during CAS. A recent substudy from the International Carotid Stenting Study (ICSS) showed that the DAR score predicted the risk of ischaemic lesions on magnetic resonance diffusion weighted imaging (DWI) following CAS, although not after correction for age.[16] To the best of our knowledge, up to now the DAR score has not been validated for the clinically relevant outcome of procedural stroke related to CAS.

We aimed to clinically validate the DAR score criteria within this post-hoc analysis of the ICSS, a large randomised controlled trial that compared CAS and CEA in recently symptomatic patients. Individual anatomical features as well as the DAR score were related to the risk of any procedural stroke up to 30 days in patients undergoing CAS.

MATERIALS AND METHODS

Trial protocol and patient selection

The ICSS trial protocol (ISRCTN 25337470) has been published previously.[17] In summary, patients with recently symptomatic moderate or severe carotid stenosis (>50%) who were eligible for both surgery and stenting were randomly assigned to CEA or CAS. Patients were excluded from ICCS if they had a stenosis known to be unsuitable for stenting because of tortuous anatomy proximal or distal to the stenosis, the presence of visible thrombus, proximal common carotid artery stenotic disease, or pseudo-occlusion ('string sign'). All procedures were performed by interventionists approved by a credentialing committee as having appropriate training and experience of carotid stenting. Individual interventionists who were not able to satisfy the credentialing requirements were identified as probationary investigators. Stenting procedures carried out by probationary investigators were proctored by an experienced carotid interventionist, until the proctor was satisfied that the interventionist could carry out procedures without supervision.

For the purpose of this study, ICSS patients were included only if they had been randomised to CAS, the CAS procedure was completed, and pre-procedural computed tomography angiography (CTA) images were available for analysis (i.e. centrally stored in the ICSS archive). In order to calculate DAR score, imaging had to include the aortic arch and supra-aortic arteries up to the base of skull.

Anatomical risk scoring

The DAR score is a scoring system of carotid anatomy, based on expert consensus, developed to categorise expected difficulty of CAS. The final DAR score is calculated according to the flow chart in the original expert consensus paper.[15] **Table 1** shows seven anatomical risk factors and their definitions as included in the DAR score. Every possible combination of anatomy results in a risk score between 2.4 and 8.5, and has been divided in 4 categories of expected risk (low: <5.0; low-intermediate: 5.0–5.9; high-intermediate: 6.0–6.9; high: ≥7.0).

Two trained independent observers (DdW, EdV) assessed available pre-operative vascular CTAs in order to grade anatomical difficulty and the DAR score. In case of disagreement, consensus was achieved through discussion with a third independent observer (AH).

Procedural stroke (ipsi- and contralateral)

In ICSS, major events were adjudicated by an independent endpoint committee that was unaware of treatment allocation. Stroke was defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. We analysed only procedural stroke, defined as any stroke occurring within 30 days of the stenting procedure, irrespective of the vascular territory of the event.

Duration of procedure

In ICSS, investigators were asked to complete technical data forms for all interventions, which allowed us to study exact duration of the stenting procedure. A prolonged duration of a stenting procedure was arbitrarily defined as any procedure lasting ≥75 minutes.

Statistical analysis

A power analysis was performed using Rstudio (version 1.0.143, RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA; URL http://www.rstudio.com/). Total 30-day stroke risk in ICSS was 7.0%. Assuming a procedural stroke risk of 10% in the highest DAR score group versus 4% in the lowest DAR score group, 566 patients would be needed for the analysis (confirming to a power of 0.8 at an alpha level of 0.05 and a confidence interval of 95%).

We compared the presence of anatomical risk factors in two predefined age groups (<70 years and ≥70 years) using a chi square test. Binomial logistic regression analysis was used to test procedural risk of stroke according to individual anatomical risk factors and the DAR score. Comparison between the reference group and risk factor under consideration was expressed in an odds ratio with Wald 95% confidence interval. Similarly, we analysed an association between anatomical difficulty and a prolonged duration of the intervention. All analyses were performed for the total cohort and divided by the predefined age groups.

We performed an interobserver reliability analysis for each anatomical risk factor in the DAR score. A Kappa statistic (κ) was used to determine consistency among observers (DdW, EdV). A κ-value of less than 0.20 indicates poor; 0.20-0.39, fair; 0.40-0.59, moderate; 0.60-0.79, good; and 0.80-1.00 i outstanding agreement between observers.[18] Statistical analyses were conducted using SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). We considered a *P*-value of <0.05 statistically significant for all analyses. Data are presented as mean ± standard deviation, unless otherwise specified.

RESULTS

Study population

A total of 1713 patients were enrolled in ICSS, of whom 855 were randomly allocated to CAS. Pre-procedural CTA was available for 275/855 patients (33%), of which 97% had been performed within three months of the procedure. Baseline characteristics are presented in **Table 2**. Mean age at intervention was 70±9 years and the majority were male (71%). **Table 2** also shows the baseline characteristics of all patients included in ICSS as a whole, which confirms representativeness of the selected sample.

Anatomical risk scoring

The overall interobserver reliability for the seven anatomical risk factors was high with all kappa values between 0.76 and 0.84 (**Table 1**). The third observer was consulted in 94/275 patients (34%), in 69/94 patients the disagreement concerned merely one factor. The presence of anatomical risk factors and the DAR score is shown in **Table 3**. The mean DAR score was 4.3 in the total cohort and only 11 (4%) of patients were scored as high difficulty (DAR score ≥7.0). Patients aged 70 years and above had a significantly higher DAR score when compared to younger patients (4.6±1.5 vs 3.9±1.4, $P<0.001$), which was mainly attributable to higher rates of arch atheroma (44% vs 20%, $P<0.001$).

Procedural stroke risk (ipsi- and contralateral)

A total of 16/275 (6%) of patients had a stroke during the procedural period, with a higher risk of stroke in patients ≥70 years compared to younger patients (9% vs 3%, $P=0.03$). All strokes were ischaemic and 7/275 (3%) patients had a stroke that was fatal or disabling.

The risk of stroke according to the DAR score is presented in **Table 4**. Univariate logistic regression showed that the DAR score did not accurately predict procedural stroke, although the low-risk group

(DAR score <5.0) had the lowest risk of stroke in the overall cohort. The risk of stroke in the high-risk group (DAR score ≥7.0) was doubled when compared to the low-risk group but this difference was not statistically significant (9% vs 4%; OR 2.15, 95% CI 0.24-18.91, *P*=0.49).

We performed several additional analyses. A separate analysis for age groups <70 years vs ≥70 years showed a significantly increased risk of stroke in the high-intermediate group (DAR score 6.0-6.9) when compared to the low risk group in patients <70 years (OR 13.13, 95% CI 1.62-105.86, *P*=0.02; data not shown). However, this was based on solely four strokes in the age group <70 years, which is reflected in the wide confidence interval. Furthermore, we grouped the DAR score into two categories of expected risk instead of four (low risk: <6.0, high risk: ≥6.0), which did not result in any statistical significance (stroke risk 11% vs 5%; OR 2.28, 95% CI 0.70 – 7.50, *P*=0.17; data not shown).

Table 5 presents the risk of stroke according to the individual anatomical risk factors. None of the evaluated anatomical features showed a significant association with procedural stroke when analysed separately. Arch atheroma, the anatomical feature that was overexpressed in patients over 70 years of age, did not increase the risk of stroke in the total cohort. A separate analysis for the two predefined age groups showed a significantly higher risk of stroke in the patients <70 years with bovine and type III arch (25% vs 1%; OR 32.67, 95% CI 1.63-656.41, *P*=0.02; data not shown). However, this was based on solely one stroke in the four patients <70 years with bovine and type III arch, also reflected in the wide confidence interval.

Duration of intervention

Duration of intervention was available for 242/275 (88%) patients and in these patients the median procedure duration was 65 (range 15-400) minutes. According to our pre-defined definition, a total of 76/242 (31%) CAS interventions were prolonged for 75 minutes or more. A prolonged duration of the intervention was significantly associated with increased risk of stroke (11% vs 4%; OR 3.14, 95%

CI 1.05-9.39, *P*=0.04; data not shown). However, no association was found between higher DAR score and prolonged CAS intervention (data not shown).

DISCUSSION

Several features of vascular anatomy have been proposed to predict difficulty of CAS, and are suggested to increase the risk of procedural stroke after CAS. In the current study, we attempted to validate the anatomical risk score as a substudy of ICSS, and demonstrated that the DAR score can be reliably assessed with good interobserver agreements. As our sample size was too small to reach adequate power, no definite conclusions could be drawn on the relationship between the DAR score and procedural risk of stroke after CAS. Of note, as our analysis was confined to CAS patients, no conclusions can be drawn regarding comparisons with carotid endarterectomy.

Perhaps now more than ever, patient selection for carotid interventions is a topic of broad interest, and guidelines pay careful attention to optimizing the selection of suitable patients for CAS.[19] If we had shown that vascular anatomy predicted procedural stroke after CAS, assessment of anatomy could be used to identify high-risk patients, and thereby reduce the periprocedural complication risk. In a recent substudy of ICSS, it was suggested that the DAR score was able to predict the occurrence of new postprocedural DWI lesions after CAS, although not after correction for age.[16] To our knowledge, this is the first study to validate the DAR score for the clinically relevant outcome of procedural stroke after CAS. Unfortunately, with only 275 patients our study was insufficiently powered to allow final conclusions. However, some interesting findings could be observed. A doubling of stroke risk was seen in the high-risk compared to the low-risk DAR categories. Second, a prolonged duration of intervention was significantly associated with increased risk of stroke. This might reflect the degree of difficulty of the intervention, which is likely to be associated with anatomical difficulty, although not statistically significant in our study. Lastly, we did demonstrate that patients over 70 years of age had a significantly higher DAR score compared to younger patients, and strokes were over three times as common in this elderly patient group. The higher degree of anatomical difficulty in older patients was largely explained by a higher incidence of aortic arch atheroma. This is in line with previous studies in which octogenarians were shown to have increased incidence of aortic arch calcifications and innominate stenosis.[20,21] Consequently, it has been suggested that the observation of increased procedural risk in elderly patients is related to increased anatomical complexity.[22] In the current study, elderly patients had both a higher procedural risk and a higher DAR score. However, although twice as many strokes were seen in the high anatomical risk patients, this did not reach statistical significance.

The only relevant anatomical exclusion criteria from ICSS were the presence of a stenosis thought to be unsuitable for stenting because of tortuous anatomy proximal or distal to the stenosis and pseudo-occlusion. These criteria might be thought to correspond to the factors included in the DAR score of angulated distal ICA and pinpoint stenosis. However, it is notable that although 166 patients in the current study were included in ICSS with one or more of these two factors, they did not have a significantly higher rate of procedural stroke. Thus, our results support excluding such patients only if the anatomy is considered unfavourable for stenting by an experienced interventionist.

Our findings need to be interpreted in the light of the following limitations of our study. Firstly, only a third of ICSS CAS patients had the required baseline CTA available, resulting in a representative but relatively small cohort. We deliberately excluded patients in whom only digital subtraction angiography and/or magnetic resonance angiography had been performed, in order to achieve a dataset as homogenous as possible. It is notable that there were only small numbers of patients in the high-risk groups. This might be a reflection of patient selection in ICSS, and the ICSS CAS population included likely reflected DAR intermediate to low-risk patients in everyday practice. Second, although stroke rate was high in our cohort, the absolute number of strokes was small. The limited power made it less likely to find more modest contributors to risk of procedural strokes. Thirdly, in accordance with the DAR score, only anatomical factors were studied. Plaque characteristics may also be an important predictor of stroke, especially in patients with challenging anatomy.[23–25] In this study we limited analysis to anatomical risk factors included in the DAR score. A tortuous CCA was rated most difficult in the DAR score expert consensus study, and was excluded from the final risk score because it would rate too difficult in combination with other anatomical risk factors.[15] In addition, several other anatomical factors like severe (circumferential) lesion calcification[26,27] or lesion length,[10,28] might also contribute to procedural hazard, but had not been included in the final DAR score.

Finally, it is notable that among the anatomical factors included in the DAR score, only pinpoint stenosis might be expected to influence risk during stent deployment. The others would be expected only to increase the risk of stroke resulting from carotid cannulation. The latter causes stroke in only a minority of stented cases. In ICSS as a whole, an analysis of the mechanisms of procedural stroke only identified 4 non-ipsilateral strokes out of 55 stented patients with procedural ischaemic stroke that could be related to cannulation and only one case that could be attributed to technical difficulties related to anatomical factors.[7] We were unable to determine whether the DAR score would have predicted stroke in these cases because of the very small number of events.

Conclusions and recommendations

This is the first clinical validation analysis of the Delphi anatomical risk score for procedural stroke after CAS. We showed no statistically significant association between anatomical difficulty, as defined in the DAR score, and procedural stroke risk, in this recently symptomatic patient group. However, the small sample size potentially rendered the study underpowered to give firm conclusions, and a trend towards higher stroke rate in high anatomical risk categories could be noted. Nonetheless, we have shown that the DAR score is a feasible and consistently reported instrument when based on CTA imaging. Furthermore, because only small numbers of stroke can be expected to be associated with anatomical risk factors, our study should be replicated in the future. In order to obtain a sufficient number of baseline CTAs and events, it is important that currently running trials, as well as trials still to be designed, and registries, include these imaging work-up in their study protocols.

CONFLICT OF INTEREST: none.

FUNDING: none.

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TABLES

Table 1. The seven anatomical risk factors that comprise the Delphi anatomical risk (DAR) score, their definitions, and interobserver reliability per risk factor.

Anatomical risk factor	Definition	Kappa (95% CI)	*P*-value
Arch atheroma	Severe arch atheroma or arch origin disease	0.80 (0.76–0.84)	<0.001
Access		0.76 (0.72–0.80)	<0.001
diseased CCA	Atheroma CCA		
ECA problem	Diseased and/or occluded ECA		
Type arch		0.84 (0.80–0.87)	<0.001
bovine	Conjoint origin of left CCA and brachiocephalic trunk		
type III	2 cm between highest point of arch and origin of brachiocephalic trunk		
Angulated distal ICA	Angulated distal ICA ≥90 degrees	0.77 (0.73–0.81)	<0.001
Pinpoint stenosis	90-99% stenosis ICA with flow beyond lesion	0.79 (0.75–0.83)	<0.001

Abbreviations: CCA = common carotid artery, CI = confidence interval, ECA = external carotid artery, ICA = internal carotid artery.

Table 2. Baseline patient characteristics of 275 patients included in the analyses, and of 853 patients included in ICSS as a whole.

BASELINE CHARACTERISTICS		
	CAS (current study, n=275)	**CAS (ICSS,[5] n=853)**
Sex		
Male	194 (71)	601 (70)
Age at intervention		
Age (years)	70 ± 9	70 ± 9
< 70	141 (51)	unknown
≥ 70	134 (49)	unknown
Vascular risk factors*		
Treated hypertension	183 (66)	587 (69)
Treated hyperlipidaemia	173 (64)	522 (61)
Any diabetes mellitus	62 (23)	184 (24)
Cardiac failure	7 (3)	23 (3)
Atrial fibrillation	21 (8)	57 (7)
Angina in past 6 months	22 (8)	83 (10)
Previous myocardial infarction	48 (18)	151 (18)
Previous CABG	40 (15)	109 (13)
Current smoker	83 (31)	205 (24)
Ex-smoker	122 (45)	408 (48)
Peripheral arterial disease	48 (18)	139 (16)
Ipsilateral carotid stenosis		
50 – 69%	29 (11)	92 (11)
70 – 99%	246 (89)	761 (89)
Contralateral carotid stenosis		
< 50%	166 (61)	565 (66)
50 – 69%	42 (15)	128 (15)
70 – 99%	45 (17)	105 (12)
Occlusion	18 (7)	49 (6)
Procedural outcome		
30-day stroke rate	16 (6)	58 (7)

Values are mean ± SD, or number (%).

Abbreviations: CABG = coronary artery bypass graft, SD = standard deviation.

* For vascular risk factors information was available for 271 patients.

Table 3. Number (%) of patients with anatomical risk factors for the total cohort. *Chi-square analysis and two-sample t-test comparing presence of risk factors and the mean DAR score between both age groups.*

PRESENCE OF ANATOMICAL RISK FACTORS AND THE DAR SCORE				
	Total cohort (n=275)	**<70 years (n=141)**	**≥70 years (n=134)**	***P*-value**
Arch atheroma				**<0.001**
No atheroma	188 (68)	113 (80)	75 (56)	
Atheroma	87 (32)	28 (20)	59 (44)	
Access				0.15
Normal	199 (72)	109 (77)	90 (67)	
Diseased CCA	50 (18)	20 (14)	30 (23)	
ECA problem	26 (9)	12 (9)	14 (11)	
Type arch				0.77
Normal arch	190 (69)	99 (70)	91 (68)	
Bovine arch	31 (11)	17 (12)	14 (10)	
Type III arch	47 (17)	21 (15)	26 (20)	
Bovine & type III arch	7 (3)	4 (3)	3 (2)	
Target vessel				0.11
Normal	201 (73)	109 (77)	92 (69)	
Angulated ICA	74 (27)	32 (23)	42 (31)	
Type lesion				0.77
Normal	183 (67)	95 (67)	88 (66)	
Pinpoint stenosis	92 (33)	46 (33)	46 (34)	
DAR score				**0.003**
< 5.0	180 (65)	107 (76)	73 (55)	
5.0 – 5.9	58 (21)	20 (14)	38 (28)	
6.0 – 6.9	26 (9)	10 (7)	16 (12)	
≥ 7.0	11 (4)	4 (3)	7 (5)	
Mean score ± SD	4.3 ± 1.4	3.9 ± 1.4	4.6 ± 1.5	**<0.001**

Abbreviations: CCA = common carotid artery, ECA = external carotid artery, ICA = internal carotid artery, SD = standard deviation.

Table 4. Procedural risk of any stroke following CAS according to the Delphi anatomical risk (DAR) score for the total cohort. *Binomial logistic regression was used to give odds ratios (ORs) per anatomical risk group where possible. 'Low-risk' anatomy (DAR score < 5.0) was used as reference category.*

PROCEDURAL ANY STROKE RISK ACCORDING TO THE DAR SCORE				
	N patients	**N strokes (%)**	**Unadjusted OR (95% CI)**	***P*-value**
DAR score				
< 5.0	180	8 (4)	1.00	
5.0 – 5.9	58	4 (7)	1.59 (0.46 – 5.50)	0.46
6.0 – 6.9	26	3 (12)	2.80 (0.69 – 11.33)	0.15
≥ 7.0	11	1 (9)	2.15 (0.24 – 18.91)	0.49

Table 5. Procedural risk of any stroke following CAS for the total cohort. *Binomial logistic regression was used to give odds ratios (ORs) per anatomical risk factor where possible. 'Normal' anatomy was used as reference category.*

PROCEDURAL RISK OF ANY STROKE ACCORDING TO INDIVIDUAL RISK FACTORS				
	N patients	**N strokes (%)**	**Unadjusted OR (95% CI)**	***P*-value**
Arch atheroma				
Not present	188	10 (5)	1.00	
Present	87	6 (7)	1.32 (0.46 – 3.75)	0.61
Access				
Normal	199	12 (6)	1.00	
ECA problem	50	2 (4)	0.65 (0.14 – 3.00)	0.58
Diseased CCA	26	2 (8)	1.30 (0.27 – 6.16)	0.74
Type arch				
Normal arch	190	8 (4)	1.00	
Bovine arch	31	2 (7)	1.57 (0.32 – 7.76)	0.58
Type III arch	47	5 (11)	2.71 (0.84 – 8.30)	0.09
Bovine & type III arch	7	1 (14)	3.79 (0.41 – 35.34)	0.24
Target vessel				
Normal	201	13 (7)	1.00	
Angulated ICA	74	3 (4)	0.61 (0.17 – 2.21)	0.45
Type lesion				
Normal	183	9 (5)	1.00	
Pinhole stenosis	92	7 (8)	1.59 (0.57 – 4.42)	0.37

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