Original Paper

Asymptomatic Internal Carotid Artery Stenosis and Cerebrovascular Risk Stratification

Abbreviated Title: Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS)

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Grant Support
Supported by a grant from the European Commission (Biomed II) Program (PL 650629) for the first three years and subsequently by a grant from the CDER Trust (UK), 28 Weymouth street, London W1G 7BZ, UK (Tel/Fax +44 020 8575 7044)

ABSTRACT

Background

The objective was to determine the cerebrovascular risk stratification potential of baseline degree of stenosis, clinical features and ultrasonic plaque characteristics in patients with asymptomatic internal carotid artery (ICA) stenosis.

Methods

This was a prospective, multicentre, cohort study of patients undergoing medical intervention for vascular disease. Hazard ratios for ICA stenosis, clinical features and plaque texture features associated with ipsilateral cerebrovascular or retinal ischemic (CORI) events were calculated using proportional hazards models.

Results

1121 patients with 50-99% asymptomatic ICA stenosis in relation to the bulb (ECST method) were followed-up for 6-96 (mean 48) months. A total of 130 ipsilateral CORI events occurred. Severity of stenosis, age, systolic blood pressure, increased serum creatinine, smoking history of more than 10 pack-years, history of contralateral TIAs or stroke, low gray scale median (GSM), increased plaque area, plaque types 1, 2 and 3 and presence of discrete white areas without acoustic shadowing (DWA) were associated with increased risk.

ROC curves were constructed for predicted risk vs. observed CORI events as a measure of model validity. The area under the ROC curves in a model of stenosis alone, a model of stenosis combined with clinical features and a model of stenosis combined with clinical and plaque features was 0.59 (95% CI 0.54 to 0.64), 0.66 (0.62 to 0.72) and 0.82 (0.78 to 0.86) respectively.

In the last model, stenosis, history of contralateral TIAs or stroke, GSM, plaque area and DWA were independent predictors of ipsilateral CORI events. Combinations of these could stratify patients into different levels of risk for CORI and stroke, with a predicted risk close to the observed. Of the 923 patients with ≥70% stenosis, the predicted five year percentage stroke rate was <5% in 495, 5-9.9% in 202, 10-19.9% in 142 and ≥20% in 84 patients.

Conclusions

Cerebrovascular risk stratification is possible using a combination of clinical and ultrasonic plaque features. These findings need to be validated in additional prospective studies in patients having current medical intervention.

INTRODUCTION

Studies performed in the 1980s and 1990s(1-10) have indicated that the risk of stroke in asymptomatic patients is 0.1-1.6% per year for internal carotid artery (ICA) stenosis <75-80% (NASCET method i.e. in relation to the diameter of the normal distal internal carotid artery) and 2.0-3.3% per year with greater degrees of stenosis.

Two randomized controlled trials, the ACAS in 1995(11) and ACST in 2004(12) reported that in patients with asymptomatic ICA stenosis >60-70% (NASCET) carotid endarterectomy reduced the risk of stroke from 2% to 1% per year(11,12). In these trials carotid endarterectomy was associated with a 2-3% perioperative rate of stroke or death. However, medical intervention which was left to the discretion of the local teams was suboptimal in relation to current practice. Statins and antiplatelet agents were administered to only 25% and 80% of patients respectively(12).

Currently, vascular disease medical intervention includes ongoing risk factor diagnosis, patient education, support of healthy life style practices and medications. Best evidence indicates that the average annual risk of ipsilateral cerebral and any territory stroke among patients with asymptomatic severe ICA stenosis receiving medical intervention alone has fallen to approximately 1%(13,14) making routine carotid endarterectomy unjustified. However, if patient subgroups with sufficiently higher than average risk, despite current optimal medical intervention, could be reliably identified, then carotid surgery may still be justified.

Studies of duplex-determined carotid plaque images have found that hypoechoic (echolucent, mainly black) and heterogenous plaques (plaques with mixed black and white areas) are more often associated with cerebrovascular symptoms than those which are hyperechoic (uniformly white or calcified)(1,2,15-20). Two recent prospective studies have demonstrated that hypoechoic plaques with low gray-scale median (GSM) were associated with a 3-4 fold increase in stroke(21,22). Other duplex-determined plaque features reported to be associated with symptomatic plaques are plaque area and plaque volume(23). However, the potential of such methods when combined in stratifying the risk of ipsilateral stroke/TIA in patients with asymptomatic carotid stenosis has not been investigated. Limitations of previous ultrasound studies of carotid plaque morphology include retrospective design, small samples, lack of subcategorisation of stenosis severity and lack of differentiation between ipsilateral and any territory ischemic symptoms.

The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study, was a multicentre cohort study of patients with asymptomatic ICA stenosis undergoing vascular disease medical intervention alone. The objective was to assess the cerebrovascular risk stratification potential of combinations of patients' clinical and biochemical characteristics, ultrasound-determined degree of stenosis and plaque morphology.

METHODS

Patient Recruitment

Inclusion criteria

Newly referred (<3 months) patients with 50-99% ICA stenosis in relation to the carotid bulb diameter (ECST method) without previous ipsilateral cerebral or retinal ischemic (CORI) symptoms and without neurological abnormality were recruited to the study after written informed consent. Patients who had had contralateral cerebral hemispheric/retinal or vertebrobasilar symptoms or signs of stroke/TIA were included if asymptomatic for at least 6 months prior to recruitment. The ratio of recruited patients with stenosis 50-69% and 70-79% (ECST) from each centre was 1:2. For patients with bilateral asymptomatic carotid atherosclerosis the side with the more severe stenosis was considered ipsilateral (the study artery).

Exclusion criteria

Patients who could not attend for a 6 monthly neurological assessment and those with a life expectancy of less than two years were excluded.

Recruitment sources

The participating centers, their eligibility criteria and quality control procedures have been published previously(24-27) and are summarized in the on line data supplement.

Study Approval

Approval was obtained from the Multicenter Research Ethics Committee (North Thames, London, UK) and local ethics committees.

Clinical and Biochemical Characteristics

At baseline all patients had a history taken and a physical examination by the local neurologist, electrocardiographic (ECG) examination and collection of fasting blood for determination of the following:

- Age, gender, body mass index (BMI), systolic and diastolic blood pressure, smoking history and accrued pack-years.

- Medication usage including antiplatelet, anti-hypertensive and lipid lowering agents.

- Presence of hypertension (antihypertensive medication or BP≥140 mmHg systolic or ≥90 mm Hg diastolic); coronary artery disease (documented myocardial infarction/angina, coronary artery bypass or stenting); diabetes (antihyperglycemic therapy or fasting blood glucose >120 mg/dL) and previous contralateral stroke/TIA or vertebrobasilar symptoms.

- ECG evidence of atrial fibrillation, previous myocardial infarction (MI), myocardial ischemia and left ventricular hypertrophy (LVH) on baseline ECG according to previously published criteria(25). ECGs were reported at the coordinating centre by two cardiologists.

- Fibrinogen, fasting lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), serum creatinine and hematocrit.

Duplex Examination

Bilateral carotid duplex scanning was performed on admission to the study. Ultrasonographers from all centres were trained at the coordinating centre in grading internal carotid stenosis and plaque image capture(24). The entire duplex examination, recorded on S-VHS videotape, was sent to the coordinating centre for quality control.

Grading of internal carotid stenosis

A combination of velocity criteria were used to express the degree of stenosis in terms of both the ECST method and the NASCET method(24,28) (see on line data supplement for duplex criteria). ECST stenosis was used in analysis because of its linear relation to risk of ipsilateral CORI events, unlike NASCET stenosis which has an S-shaped relationship(27). Contralateral ICA occlusion was noted. Bilateral vertebral artery flow was reported as cephalad, reversed or not visualised.

Image normalization, segmentation and analysis

Baseline images from video recordings were digitized off-line on a PC using a video grabber card (Videologic, TV Snap version 1.0.3 c 1994) at a resolution of 640x480 pixels at the coordinating center by two members of the team who were experienced in carotid scanning. Image normalization for gray-scale using linear scaling with “blood” (gray-scale=0) and adventitia (gray-scale=190), and pixel density standardiza-

tion to 20 pixels per mm were performed followed by image analysis. The “Plaque Texture Analysis software” version 3.2 (Iconsoft International Ltd, PO Box 172, Greenford, London UB6 9ZN, UK)(29) was used. Some plaque texture features were automatically calculated using the “Feature Extraction” module of the software (GSM(29), modified Geroulakos plaque classification(18,26) and plaque area), while presence of discrete white areas without acoustic shadowing (DWA) and ulceration were identified visually.

Outcome Measures

Primary outcome measures were (a) ipsilateral CORI events i.e. cerebral or retinal ischemic events which included stroke and (b) ipsilateral cerebral ischemic stroke (fatal or non-fatal). Stroke and TIA were defined as cerebral deficits of most likely vascular origin lasting >24 hours or <24 hours, respectively. When a stroke was reported, details recorded by the local neurologist, a 6-month modified Rankin score(30) and CT or MRI brain scan results were requested. Two coordinating centre members including a neurologist, made the final classification of ipsilateral strokes. Local team members diagnosed TIAs and amaurosis fugax.

Secondary outcome measures were all other strokes and TIAs, contralateral retinal vascular events and all other deaths. Cause of death was determined by local team members, using death certificates, hospital records and family doctor information.

Study Exit Points

Follow-up ceased with the first occurrence of any of the following: the first primary outcome measure, carotid endarterectomy/angioplasty or stenting for the still asymptomatic study artery, death from causes other than ipsilateral stroke or loss to follow-up.

Stroke, TIA or death associated with carotid endarterectomy/angioplasty or stenting for the still asymptomatic study artery were not included in event rate calculations.

Statistical Analysis

Stata® (versions 10.1 and 11; StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA) was used for statistical analysis and production of graphs.

Initially, Kaplan-Meier curves were used for the whole cohort of 1121 patients to determine overall ipsilateral CORI event and stroke free survival over time. Stratified Kaplan-Meier curves were also constructed for % stenosis, history of contralateral TIAs or stroke, discrete white areas, plaque area and GSM. Continuous variables were categorised for stratified Kaplan-Meier plots. For example, stenosis was categorized as mild (<70% ECST/<50% NASCET), moderate (70-89% ECST/50-82 NASCET) or severe (90-99% ECST/ 83-99% NASCET).

Subsequently, hazard ratios for clinical, biochemical and ultrasonic features for ipsilateral CORI events and stroke were determined using an unadjusted Cox model for each variable. Continuous risk factors were transformed to an un-skewed distribution where possible.

Risk factors which were significant at $p<0.05$ in unadjusted models for CORI events or stroke were considered in multivariable proportional hazards models. Flexible parametric models of Royston & Parmar(31) were used because the baseline hazard function at 5 years was of interest, which is erratic in Cox models. Hazard ratios from these models were compared to equivalent Cox models. Model (i) included stenosis and the significant clinical factors to predict time to CORI event; model (ii) included stenosis, the significant clinical factors and plaque features as covariates; model (iii) was formulated identically to (ii) except the dependent variable was time to stroke. Variable selection was not used in model (iii) because of the smaller number of events. Important prognostic variables were selected using backwards elimination, with $p>0.05$ as the condition for a variable to be excluded. To relax the assumption that the effect of covariates on the dependent variable must be linear, multivariable fractional polynomials were used(32).

On the basis of model (iii) ipsilateral cerebral ischemic stroke free survival curves were produced for different combinations of risk factor subgroups from which 5-year stroke rates were calculated.

The assumption of proportional hazards was tested using the Schoenfeld residuals. Harrell's *C*(33) and a pseudo R^2(34) were calculated for models (i-iii). Harrell's *C* is a measure of discrimination which calculates the proportion of time that survival times for pairs of patients can be correctly ordered, on the basis of covariates in the model. Pseudo R^2 is analogous to the standard R^2 (*proportion of explained variation*) adapted to models for censored survival data.

The covariates included in a model were used to calculate the linear predictor score, $\boldsymbol{\beta x}$ (the sum of the product of mean-centred covariate values and corresponding parameter estimates) for each patient. ROC curves were constructed for $\boldsymbol{\beta x}$ against observed 5-year CORI event rates (in the same set of patients). These were compared for the unadjusted ECST stenosis model and models (i) and (ii). This was also done separately for (iii), since comparison of different $\boldsymbol{\beta x}$ for different dependent variables is inappropriate. For model (iii), internal calibration was assessed by comparing predicted risk of stroke at 5 years to the observed proportion experiencing stroke by 5 years.

Role of the Funding Source

Study sponsors had no role in the design, conduct or reporting of this research.

RESULTS

1121 patients between 39 and 89 years (mean age 70.0, SD 7.7, 61% male) were recruited during 1998-2002 with a follow-up of 6-96 months (mean 48 months). 66% of patients were recruited from medical services (vascular internists-28%, neurologists-16%, cardiologists-10%, hypertension clinics-5%, metabolic units-3% and screening programs-4%). 34% of patients were recruited from surgical services (vascular-32%, cardiac surgery-2%). Baseline distribution of patient clinical and biochemical characteristics, degree of stenosis and other plaque features are presented in table 1.

Ipsilateral Cerebrovascular Events

A total of 130 first ipsilateral CORI events occurred (59 strokes of which 12 were fatal, 49 TIAs and 22 amaurosis fugax). For ischemic stroke the modified Rankin scale at 6 months was zero in 4 cases, 1 in 9 cases, 2 in 6 cases, 3 in 8 cases, 4 in 18 cases, 5 in 2 cases and 6 in 12 cases. There were two additional first ipsilateral fatal hemorrhagic strokes.

Other outcome measures

There were 49 first contralateral CORI events (18 ischemic strokes of which 7 were fatal, 22 TIAs and 9 amaurosis fugax). There were 2 vertebrobasilar strokes.

There were a total of 214 deaths (195 non-stroke deaths) of which 157 (73%) were due to cardiovascular causes: myocardial infarction-110, fatal stroke-19 (12 ipsilateral and 7 contralateral already mentioned above), heart failure-17, pulmonary embolism-3, lower limb ischemia/gangrene-3, ruptured abdominal aortic aneurysm-3, renal failure-1 and mesenteric artery thrombosis-1. There were 56 non-vascular deaths; malignancy-37, pneumonia/respiratory failure-12, gastrointestinal hemorrhage-2, dementia-2, road traffic accident-2 and general surgical procedure-1. Cause of death was unknown in one patient.

Ipsilateral carotid endarterectomy was performed in 129 patients with still asymptomatic study artery (stenosis median:85% ECST; interquartile range:75-90) because the clinician in charge or the patient requested it. This occurred soon after publication of the ACST results. Twenty-one patients have been lost to follow up. In these 21 patients contact was lost with 15, 5 declined to re-attend (too old to travel) and 1 emigrated. Thus, 150 patients (13.4%) have been "lost" from the study. They have been included in the analysis up to the last follow-up visit. The remaining 971 (86.6%) have been followed up to a primary event, death or termination of the study in December 2006.

Ipsilateral event rates in relation to stenosis severity

The ipsilateral CORI events and strokes in relation to subgroups of stenosis are shown in table 2. They demonstrate that ipsilateral risk increases with increasing stenosis across mild-severe categories.

Baseline features associated with increased ipsilateral cerebrovascular risk

Hazard ratios for each individual baseline clinical, biochemical and ultrasonic feature associated with patients with ipsilateral CORI events and strokes are shown in table 3. Ipsilateral stenosis, systolic blood pressure, smoking history of more than 10 pack-years, GSM, plaque area, plaque type, history of contralateral TIAs or stroke, and presence of DWA were significant risk factors for CORI events. The hazard ratios for stroke showed a similar pattern, although these were not always statistically significant due to the lower number of events.

Table 4 shows the results of three multivariable proportional hazard models, (i)-(iii). Measures of model performance Harrell's *C* and pseudo R^2 were greatly increased by including plaque features. Powers of continuous covariates remained un-

transformed by multivariable fractional polynomials. Parameter estimates in table 4 were very similar to those obtained using Cox models in each case.

The cumulative ipsilateral CORI event free survival Kaplan-Meier curves for each of the significant risk factors in model (ii) are shown in figure 1 (a-e).

On the basis of the variables shown in table 4 the linear predictor scores $\boldsymbol{x\beta}$ of models (i) and (ii) were calculated for each patient. ROC curves constructed with (a) stenosis (ECST) as a continuous variable, (b) the predictor score from model (i) and (c) the predictor score from model (ii) are shown in figure 2. The predictor score from model (ii) that combined stenosis with clinical and plaque texture features was associated with the largest area under the ROC curve: 0.82 (95% CI 0.77 to 0.85) (Figure 2a). The area under the ROC curve from model (iii) which had stroke as the dependent variable was 0.80 (95% CI 0.74 to 0.87)(Figure 2b).

On the basis of model (iii) ipsilateral cerebral stroke probabilities at five years were produced for different combinations of risk factor subgroups (Table 5). (To calculate individual patient risk, please refer to appendix.) Figure 3 shows calibration for model (iii). At low predicted probabilities the model seems to slightly over-predict. At higher predicted probabilities the model predicts very nicely, with estimates close to the line of agreement and confidence intervals overlapping. The predicted five year percentage stroke rate (observed; 95% CI) was <5% (very low risk) in 654 (1%; 0.2 to 2), 5-9.9% (low risk) in 225 (8%; 5 to 13), 10-19.9% (moderate risk) in 156 (12%; 7 to 18) and ≥20% (high risk) in 86 patients (29%; 14 to 33). Of the 923 patients with ≥70% stenosis, 495 were included in the very low, 202 in the low, 142 in the moderate and 84 in the high risk group.

DISCUSSION

The ACSRS study is the largest prospective study of patients with asymptomatic carotid artery stenosis. The results demonstrate that a number of baseline clinical characteristic s and ultrasonic plaque features are independent predictors of subsequent ipsilateral CORI events. Clinical features added to stenosis improve prediction and the further addition of plaque features improves prediction even more as shown by the increased area under the ROC curves (Fig. 2)

The inclusion criteria in our study provided a wide range of stenosis (50-99% ECST). This allowed classification into subgroups of mild, moderate and severe de-

gree of stenosis and better evaluation of this risk factor in contrast to other published studies that had excluded upper or lower extremes of the range of stenosis(1-8). Because ECST stenosis is linearly related to ipsilateral CORI event and stroke risk and NASCET stenosis is not(27), the ECST measurement has been used in the analysis of our data. Only one previous prospective study has recruited patients within the full range of 50-99% ECST stenosis as used in our study(7) and graded the stenosis as mild (<50%), moderate (50-79%) and severe (80-99%). This study which involved 678 patients with a mean follow-up of 3.6 years showed an increasing ipsilateral CORI event and stroke rate with increasing grades of stenosis.

Smoking is an established risk factor for plaque progression, plaque rupture and ischemic stroke(35,36). The increased risk for ipsilateral stroke in patients with a history of contralateral symptoms has been observed also in the medical arm of the ACST trial. In ACST, at 5 years, there were 56 strokes in 1057 patients without and 39 strokes in 375 patients with a history of contralateral symptoms (OR 2.06 95% CI 1.35 to 3.16)(12).

Mild to moderately raised serum creatinine is an independent predictor of cardiovascular risk and particularly ischemic stroke in asymptomatic individuals and patients with peripheral vascular disease(37,38). In our study creatinine levels higher than 100 µmol/L were associated with hypoechoic plaques (data not shown).

Other established risk factors such as hypertension and hypercholesterolemia were either weakly associated with CORI events or not significant probably because they were present in the majority of the patients.

Carotid plaque area and plaque volume have already been reported to be strong predictors of myocardial infarction and stroke(23) in patients with mild degrees of stenosis. Our results show that plaque area can be used to stratify cerebrovascular risk in patients with plaques producing moderate and severe stenosis (Fig. 1c).

The measurement of GSM after image normalization is now an established reproducible measurement of overall plaque echodensity. Our study confirms the findings of other prospective studies(21,22) that a low GSM is a strong predictor of future strokes.

Plaque heterogeneity is in many plaques the result of presence of DWA without acoustic shadow (i.e. without calcification) in hypoechoic areas. These DWA are often hyperperfused as shown by ultrasonic contrast perfusion agents and correspond to neovascularisation and increased numbers of macrophages on histology(39).

Whether the presence of these areas are responsible for the development of intra-plaque hemorrhage, non uniform plaque stresses promoting plaque rupture or erosion of the fibrous cap merits further investigation.

This study has a number of limitations. Ultrasonic imaging is to a certain extent operator dependent. This has been overcome by training ultrasonographers in equipment presets and image capture; also, by performing image normalization with computerized analysis at the coordinating centre (see on line supplement). The importance of training vascular ultrasonographers in equipment settings and plaque imaging for optimal results cannot be overemphasized.

Another limitation is that the medical management of patients was according to what was considered best medical therapy at each centre – the biggest factor when it comes to the relevance to current clinical practice. At each centre the clinician in charge was free to change therapy according to changing indications. At the beginning of the study only 84% of patients were on antiplatelet therapy and only 25% on lipid lowering therapy reflecting clinical practice at that time. Towards the end of the study these percentages were 95% and 85% respectively. In addition, this “freedom” in management resulted in 129 (11.5%) patients having a carotid endarterectomy in the absence of symptoms soon after the results of the ACST were published. Despite this, follow-up to a CORI event, death or to the end of the study was achieved in 87% of patients.

The clinical implication of our findings is that the combination of clinical and ultrasonic plaque features with stenosis can stratify risk better than stenosis alone and this may lead to refinement of the indications for carotid endarterectomy. Validation of predicted risk in this study was limited since this was done internally, that is for the same group of patients on whom the score was developed. These findings need to be validated in additional prospective observational studies using current medical intervention or in the medical arm of randomized controlled trials comparing carotid endarterectomy plus medical intervention against medical intervention alone.

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Table 1

Baseline clinical, biochemical and ultrasonic features in 1121 patients

Continuous variables (normal distribution; mean±sd)	
Age (years)	70.0 ± 7.7
BMI (kg/m^2)*	25.4 ± 3.7
SBP (mmHg)*	152.3 ± 22.2
DBP (mmHg)*	82.2 ± 10.0
Creatinine (µmol/L)*	100.5 ± 34.1
Fibrinogen (g/L)*	3.56 ± 1.00
Hematocrit (%)*	41.1 ± 4.9
Total Cholesterol (mmol/dL)*	6.01 ± 1.19
LDL Cholesterol (mmol/dL)*	3.90 ± 1.20
HDL Cholesterol (mmol/dL)*	1.30 ± 0.49
Ipsilateral stenosis (%)	78.0 ± 12.8
Contralateral stenosis (%)	45.5 ± 30.0
Continuous variables (skewed distribution; median, interquartile range)	
Pack-years	10 (0, 36)
Triglycerides (mmol/dL)*	1.58 (1.17, 2.19)
Gray scale median (GSM)	32.2 (17.1, 50.6)
Plaque area (mm^2)	41.9 (27.1, 60.2)
Categorical variables	
Gender: female	438 (39%)
Smoking at entry	212 (19%)
Coronary artery disease	379 (34%)
Atrial fibrillation	29 (2.6%)
Hypertension	709 (63%)
Diabetes	231 (21%)
History of contralateral TIAs or stroke	173 (15%)
History of vertebro-basilar symptoms	136 (12%)
Old MI on ECG	201 (18%)
Ischemia on ECG	238 (21%)
LVH on ECG	116 (10%)
Antihypertensive therapy	674 (60%)
Antiplatelet therapy	940 (84%)
Lipid lowering therapy	278 (25%)
Ipsilateral vertebral flow not detected or reversed	90 (8%)
Contralateral internal carotid occlusion	93 (8%)
Ipsilateral ultrasonic ulcer	101 (10%)
Plaque type 4 and 5	186 (17%)
3	509 (45%)
2	341 (30%)
1	85 (8%)
Presence of discrete white areas	718 (64%)

* Percentages of missing values were: BMI 4%, SBP 10%, DBP 10%, creatinine 11%, fibrinogen 23%, hematocrit 12%, total cholesterol 11%, LDL 22%, HDL 22%, triglycerides 12%.

Table 2

Ipsilateral cerebral or retinal ischemic (CORI) events (AF, TIAs and stroke) and ipsilateral ischemic cerebral stroke for all patients and subgroups according to ECST stenosis (*) as used in this paper and NASCET stenosis (**) for comparison with previous publications that have used these methods. Follow-up 6 months to 8 years (mean: 48 months). P values were calculated using chi square test for trend.

ECST stenosis (%)	**NASCET stenosis (%)**	**N**	**CORI events**	**Strokes**
All patients		1121	130 (11.6%)	59 (5.3%)
50-69*	< 50	198	16 (8.1%)	5 (2.5%)
70-89*	50-79	598	65 (10.9%)	29 (4.8%)
90-99*	80-99	325	49 (15.1%)	25 (7.7%)
			P = 0.01	P = 0.008
< 80	< 70**	514	50 (9.7%)	21 (4.1%)
80-99	70-99**	607	80 (13.2%)	38 (6.3%)
			P = 0.07	P = 0.10

Table 3

Unadjusted hazard ratios (HR) of risk factors for ipsilateral CORI events and ipsilateral cerebral stroke. (Skewed continuous predictors were transformed to be approximately symmetrically distributed). HR with P<0.05 are in bold

Risk factor	CORI HR	95% CI	Stroke HR	95% CI
Age (10 yr increase)	1.10	(0.88 to 1.38)	**1.42**	**(1.00 to 2.02)**
BMI (5 unit increase)*	0.86	(0.65 to 1.14)	0.85	(0.57 to 1.28)
Systolic blood pressure (10 unit increase)*	**1.11**	**(1.07 to 1.22)**	1.07	(0.94 to 1.22)
Diastolic blood pressure (10 unit increase)*	1.21	(0.99 to 1.47)	1.14	(0.86 to 1.50)
Creatinine (20% increase)*	1.10	(0.96 to 1.25)	**1.28**	**(1.09 to 1.50)**
ln(GSM+40)	**0.08**	**(0.04 to 0.15)**	**0.06**	**(0.02 to 0.15)**
Fibrinogen*	1.03	(0.85 to 1.26)	1.17	(0.84 to 1.48)
Haematocrit (10 unit in-crease)*	1.18	(0.83 to 1.66)	1.13	(0.07 to 1.85)
Total cholesterol*	1.08	(0.92 to 1.26)	1.02	(0.80 to 1.28)
LDL cholesterol*	1.03	(0.86 to 1.23)	0.97	(0.74 to 1.27)
HDL cholesterol*	1.12	(0.75 to 1.69)	1.34	(0.80 to 2.24)
Triglyceride (doubling)*	1.18	(0.80 to 1.74)	1.73	(0.99 to 3.05)
Ipsilateral. Stenosis (10% increase)	**1.02**	**(1.01 to 1.04)**	**1.04**	**(1.01 to 1.06)**
Contralateral stenosis (10% increase)	1.03	(0.98 to 1.10)	1.05	(0.96 to 1.14)
Plaque area (mm^2) $^{1/3}$	**2.51**	**(2.01 to 3.12)**	**2.45**	**(1.76 to 3.40)**
Plaque type 4&5	**1**	**-**	**1**	**-**
3 .	**6.31**	**(1.52 to 26.19)**	4.41	(0.58 to 33.74)
2 .	**19.66**	**(4.83 to 80.06)**	**18.79**	**(2.58 to 137.03)**
1 .	**18.28**	**(4.20 to 79.52)**	**20.74**	**(2.63 to 163.70)**
Male	0.92	(0.65 to 1.30)	1.10	(0.65 to 1.86)
Smoking	1.10	(0.72 to 1.70)	1.51	(0.84 to 2.71)
≥10 smoking pack-years	**1.65**	**(1.16 to 2.34)**	1.52	(0.90 to 2.56)
Coronary artery disease	1.19	(0.84 to 1.70)	1.32	(0.78 to 2.21)
Atrial fibrillation	1.36	(0.50 to 3.68)	1.55	(0.38 to 6.36)
Hypertension	0.98	(0.68 to 1.40)	1.00	(0.59 to 1.70)
Diabetes	0.77	(0.48 to 1.25)	0.88	(0.45 to 1.74)
History of vertebro-basilar symptoms	1.48	(0.92 to 2.38)	1.48	(0.73 to 3.00)
History of contralateral TIAs or stroke	**2.35**	**(1.60 to 3.43)**	**3.03**	**(1.77 to 5.20)**
Old MI on ECG	1.31	(0.87 to 1.97)	1.62	(0.91 to 2.87)
Ischaemia on ECG	1.41	(0.95 to 2.08)	1.36	(0.76 to 2.45)
LVH on ECG	1.03	(0.59 to 1.80)	1.15	(0.52 to 2.53)
Antihypertensive therapy	0.94	(0.66 to 1.34)	0.94	(0.56 to 1.59)
Antiplatelet therapy	0.98	(0.60 to 1.59)	1.05	(0.50 to 2.20)
Lipid lowering therapy	0.87	(0.58 to 1.29)	0.81	(0.45 to 1.48)
Ipsilateral vertebral flow	1.74	(0.88 to 3.42)	3.72	(0.91 to 15.24)
Contralateral internal carotid occlusion	1.27	(0.71 to 2.25)	1.05	(0.42 to 2.62)
Ipsilateral ultrasonic ulcer	0.52	(0.24 to 1.11)	0.48	(0.15 to 1.55)

Presence of DWAs (>1)	**2.32**	**(1.49 to 3.6)**	1.68	(0.92 to 3.06)

* Percentages of missing values were: BMI 4%, SBP 10%, DBP 10%, creatinine 11%, fibrinogen 23%, hematocrit 12%, total cholesterol 11%, LDL 22%, HDL 22%, triglycerides 12%.

Table 4

Flexible parametric proportional hazards models including significant variables from table 3 with ipsilateral CORI events as the dependent variable. (GSM = Gray Scale Median; DWA = Discrete White Areas; HR = Hazard Ratio). Selected using backwards elimination on all variables with 95% CI not overlapping 1 in table 2.

(i) Clinical factors only. Ipsilateral CORI events as the dependent variable.
5-year baseline hazard estimated as .886; Harrell's C = .66; Pseudo R^2 = .17

Variable	*β*	**HR**	**95% CI**	**P**
Stenosis (% ECST)	0.028	1.03	1.01 to 1.04	<0.001
Pack-years (<10, ≥10)	0.429	1.53	1.07 to 2.18	0.018
History of contralateral TIAs and/or stroke	0.858	2.36	1.61 to 3.46	< 0.001

(ii) Clinical factors with plaque features. Ipsilateral CORI events as the dependent variable
5-year baseline hazard estimated as .949; Harrell's C = .79; Pseudo R^2 = .55

Variable	*β*	**HR**	**95% CI**	**P**
Stenosis (% ECST)	0.01696	1.02	1.00 to 1.03	0.027
Log(GSM + 40)	-2.4519	0.09	0.04 to 0.17	<0.001
Plaque area^{⅓} (mm^2)	0.6539	1.92	1.50 to 2.46	<0.001
DWA (Present vs. absent)	0.7417	2.10	1.32 to 3.35	0.002
History of contralateral TIAs and/or stroke (Yes vs no)	0.6901	1.99	1.32 to 2.92	0.001

(iii) Clinical factors with plaque features. Ipsilateral hemispheric stroke as the dependent variable. Note no variable selection was performed here because of too few events. Variables were identical to those used in (ii).
5-year baseline hazard estimated as .972; Harrell's C = .80; Pseudo R^2 = .61

Variable	*β*	**HR**	**95% CI**	**P**
Stenosis (% ECST)	0.026	1.03	1.00 to 1.05	0.024
Log(GSM + 40)	-2.672	0.07	0.02 to 0.20	<0.0001
Plaque area^{⅓} (mm^2)	0.629	1.88	1.28 to 2.75	<0.0001
DWA (Present vs. absent)	0.429	1.54	0.81 to 2.92	0.18
History of contralateral TIAs and/or stroke (Yes vs. no)	0.973	2.65	1.54 to 4.54	<0.0001

Table 5. Estimated % risk of ipsilateral cerebral stroke within 5 years (for patients with ≥ 70% ECST stenosis)

– denotes a covariate combination which did not occur in observed data

* denotes a covariate combination which occurred less than five times in observed data

Stenosis	History of contralateral TIAs or stroke	DWA present	Plaque area (mm²)	GSM >30	GSM 15-30	GSM <15
90-99% ECST (83-99% NASCET)	Present	Yes	>80	20.3*	52.8*	–
			40-80	13.8	35.8	70.0*
			<40	7.8*	20.1*	–
		No	>80	13.3*	34.5*	–
			40-80	9.0*	–	45.7*
			<40	5.1*	13.1*	25.7*
	Absent	Yes	>80	7.7*	20.0	39.1*
			40-80	5.2	13.5	26.5
			<40	2.9	7.6	14.9*
		No	>80	5.0*	13.0*	25.5*
			40-80	3.4*	–	17.3
			<40	1.9	5.0	9.7*
70-89% ECST (50-82% NASCET)	Present	Yes	>80	13.8*	35.0*	70.4*
			40-80	9.4	24.4*	47.7
			<40	5.3	13.7*	26.8
		No	>80	9.0*	23.5*	–
			40-80	6.1*	15.9*	31.1*
			<40	3.4	8.9*	17.4*
	Absent	Yes	>80	5.2	13.6	26.6
			40-80	3.5	9.2	18.0
			<40	2.0	5.2	10.1
		No	>80	3.4*	–	17.4
			40-80	2.3	6.0	11.8
			<40	1.3	3.4	6.6

Appendix – Calculation of predicted 5 year stroke free survival

The hazard ratios for covariates presented in table 4 (iii) can be combined with the baseline survival function to predict 5-year stroke free survival probabilities for a patient with a given set of covariates.

For an individual with baseline covariate values (close to mean covariates) as listed in table 6 the stroke free survival at 5 years, $S_0(5y)$ is estimated as 0.972.

Table 6 Baseline covariates and transformed values in an individual

Covariate	Baseline value	Corresponding transformations
Stenosis, %	80	None
GSM	30	ln(GSM+40) = 4.248
Plaque area, mm^2	40mm^2	(Plaque area)^{⅓} = 3.420
DWA	Absent	0
History of contralateral TIAs and/or stroke	Absent	0

Predicted 5-year stroke free survival for a patient with different values of the covariates in table 6 can be calculated as follows.

1. Transform continuous covariates using the formulae given in table 6, third column.
2. Using these (possibly transformed) values, calculate the differences, *x*, between the value you are interested in and the values used in $S_0(5y)$ (Table 7, second column).
3. Multiply each of these differences by the corresponding log-hazard ratio, β, from table 4(iii) to obtain βx as shown in table 7 column 4.
4. Sum the values obtained in step 3 above to denote this as $\boldsymbol{\beta x}$.
5. Calculate exp($\boldsymbol{\beta x}$)
6. Compute predicted survival probability as a percentage for a patient using 100 x $0.972^{\exp(\boldsymbol{\beta x})}$.

Following this calculation for a patient with 90% stenosis, GSM = 10, plaque area = 80 mm^2, DWA present and history of contralateral TIAs and/or stroke absent:

1. ln(GSM+40) = 3.912. (Plaque area)^{⅓} = 4.309

Table 7 Steps 2 and 3 in the calculation of 5 year predicted stroke free survival

Variable	Calculation	2. *x*	β	3. βx
Stenosis	90 – 80	10	0.026	0.2600
ln(GSM+40)	3.912 – 4.248	-0.336	-2.672	0.8978
(Plaque area)$^{1/3}$	4.309 – 3.4200	0.889	0.629	0.5592
DWA	1 – 0	1	0.429	0.4290
History of contralateral TIAs and/or stroke	0 – 0	0	0.973	0

4. Sum of βx = $\boldsymbol{\beta x}$ = 0.2600 + 0.8978 + 0.5592 + 0.4290 + 0 = 2.1460

5. exp(2.146) = 8.551

6. Predicted 5-year stroke free survival 100 x $0.972^{exp(2.146)}$ = 78.4%

CAPTIONS FOR FIGURES

Figure 1

Kaplan-Meier plots showing ipsilateral CORI event free survival stratified by:

(a)ECST stenosis: Log rank test: P for trend = 0.002

(b) GSM: Log rank test: P for trend < 0.0001

(c) Plaque area (mm^2): Log rank test: P for trend < 0.0001

(d) DWA: Log rank test: P < 0.0001

(e) History of contralateral TIAs or stroke: Log rank test: P < 0.0001

Figure 2

(A) ROC curves for CORI events using (a) stenosis as continuous variable, (b) the linear predictor score from the proportional hazards model (model i) that included stenosis and significant clinical features only (recruitment, pack-years, history of contralateral TIAs or stroke) and (c) the proportional hazards model (model ii) that included stenosis, significant clinical and plaque characteristics (GSM, plaque area, DWA and history of contralateral TIAs or stroke) for predicting ipsilateral CORI events. Corresponding areas under curve are (a) 0.59 (95% CI 0.54 to 0.64), (b) 0.66 (95% CI 0.62 to 0.72) and (c) 0.82 (95% CI 0.78 to 0.86). P < 0.003 for all pairwise comparisons.
(B) ROC curve for stroke using the linear predictor score of the proportional hazards model (model iii). Area under curve is 0.80 (95% CI 0.74 to 0.86).

Figure 3

Calibration plot for model (iii), based on all 1121 patients.

– – – shows the line of perfect agreement between predicted and observed 5-year stroke risk.

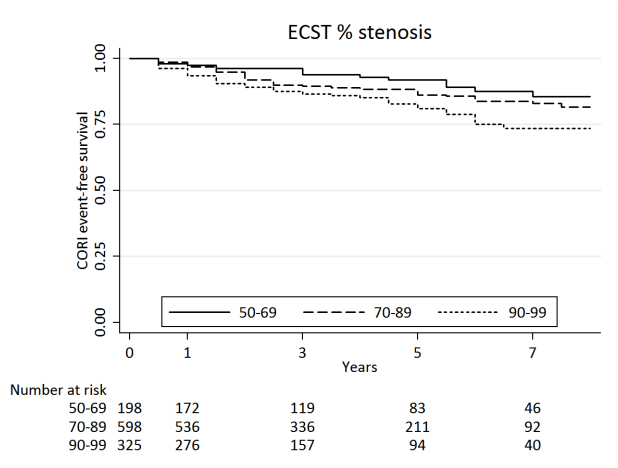

Figure 1a

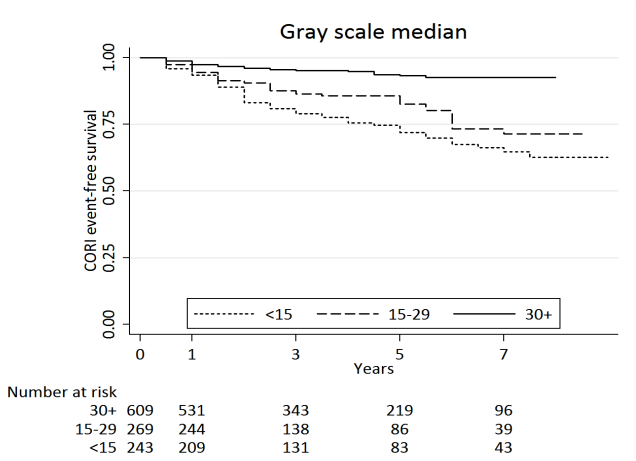

Figure 1b

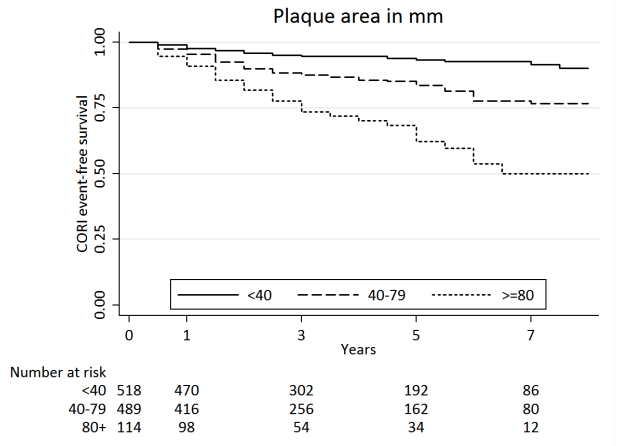

Figure 1c

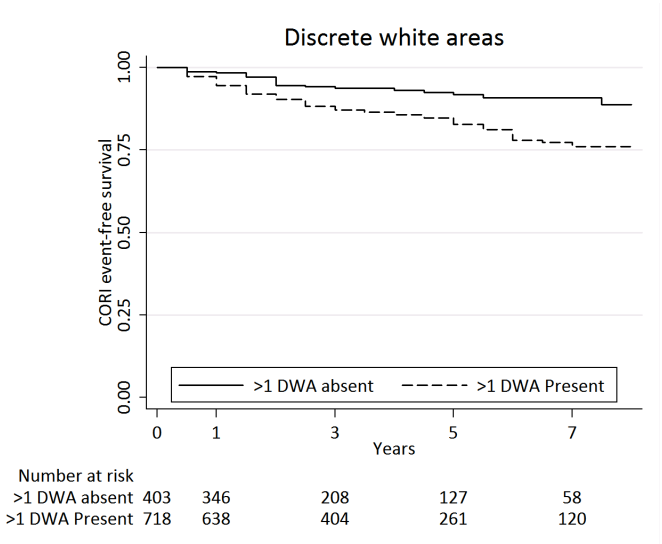

Figure 1d

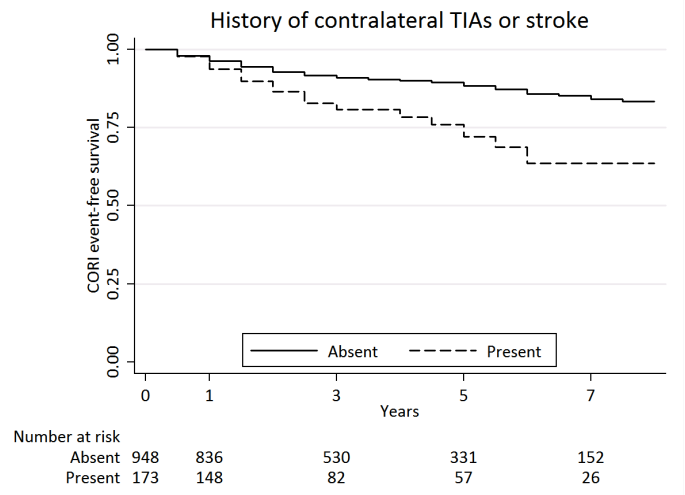

Figure 1e

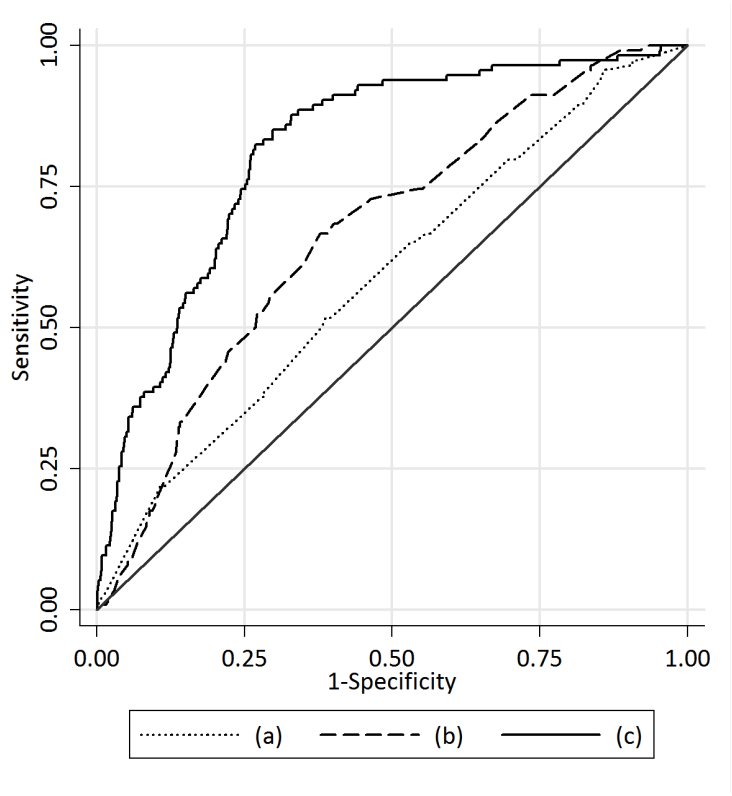

Figure 2 (a)

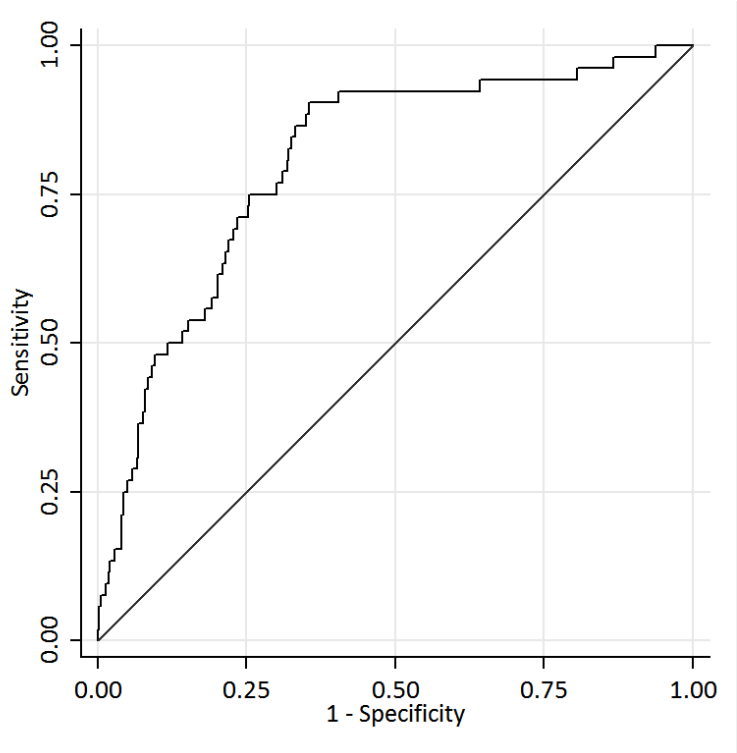

Figure 2 (b)

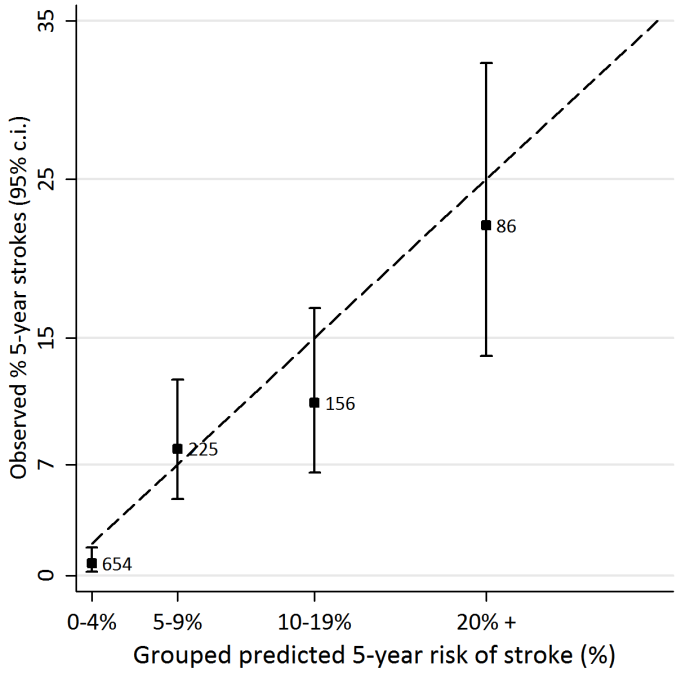
Observed % 5-year strokes (95% c.i.)
0
7
15
25
35
654
225
156
86
0-4%
5-9%
10-19%
20% +
Grouped predicted 5-year risk of stroke (%)

Fig. 3