Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification

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Background: The purpose of this study 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, multicenter, 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: A total of 1121 patients with 50% to 99% asymptomatic ICA stenosis in relation to the bulb (European Carotid Surgery Trial [ECST] method) were followed-up for 6 to 96 months (mean, 48). 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 transient ischemic attacks (TIAs) or stroke, low grayscale median (GSM), increased plaque area, plaque types 1, 2, and 3, and the presence of discrete white areas (DWAs) without acoustic shadowing were associated with increased risk. Receiver operating characteristic (ROC) curves were constructed for predicted risk versus observed CORI events as a measure of model validity. The areas under the ROC curves for a model of stenosis alone, a model of stenosis combined with clinical features and a model of stenosis combined with clinical, and plaque features were 0.59 (95% confidence interval [CI] 0.54-0.64), 0.66 (0.62-0.72), and 0.82 (0.78-0.86), respectively. In the last model, stenosis, history of contralateral TIAs or stroke, GSM, plaque area, and DWAs were independent predictors of ipsilateral CORI events. Combinations of these could stratify patients into different levels of risk for ipsilateral CORI and stroke, with predicted risk close to observed risk. Of the 923 patients with ≥70% stenosis, the predicted cumulative 5-year stroke rate was <5% in 495, 5% to 9.9% in 202, 10% to 19.9% in 142, and ≥20% in 84 patients.
Conclusion: Cerebrovascular risk stratification is possible using a combination of clinical and ultrasonic plaque features. These findings need to be validated in additional prospective studies of patients receiving optimal medical intervention alone. (J Vasc Surg 2010;52:1486-96.)

Studies performed in the 1980s and 1990s[1-10] have indicated that the risk of stroke in asymptomatic patients is 0.1% to 1.6% per year for internal carotid artery (ICA) stenosis <75% to 80% (North American Symptomatic Carotid Endarterectomy Trial [NASCET] method; ie, in relation to the diameter of the normal distal internal carotid artery) and 2.0% to 3.3% per year with greater degrees of stenosis.

Two randomized controlled trials, the Asymptomatic Carotid Atherosclerosis Study (ACAS) in 1995[11] and Asymptomatic Carotid Surgery Trial (ACST) in 2004,[12] reported that in patients with asymptomatic ICA stenosis >60% to 70% (NASCET) carotid endarterectomy reduced the risk of stroke from 2% to 1% per year. In these trials, carotid endarterectomy was associated with a 2% to 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. For example, in the ACST, 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 lifestyle practices, and medications. Best

evidence indicates that the average annual risk of ipsilateral cerebral stroke among patients with asymptomatic moderate-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 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 grayscale median (GSM) were associated with a threefold to fourfold increase in stroke.[21,22] Other duplex-determined plaque features reported to be associated with symptomatic plaques are plaque area,[23] and plaque heterogeneity as indicated by the presence of noncalcified (absence of acoustic shadow) discrete white areas (DWAs) within black areas.[24] However, the potential of combinations of such methods for stratifying the risk of ipsilateral stroke/transient ischemic attack (TIA) in patients with asymptomatic carotid stenosis has not been investigated. Limitations of previous ultrasound scan studies of carotid plaque morphology include retrospective design, small samples, lack of subcategorization 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 multicenter 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, and the ultrasound scan-determined degree of stenosis and plaque morphology.

METHODS

Patient recruitment

Inclusion criteria. Newly referred (<3 months) patients with 50% to 99% ICA stenosis in relation to the carotid bulb diameter (European Carotid Surgery Trial [ECST] method) without previous ipsilateral cerebral or retinal ischemic (CORI) symptoms and without neurological abnormality were recruited to the study after they provided written informed consent. Patients who 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. 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 6 monthly neurological assessments, and those with a limited life expectancy because of conditions such as severe cardiac failure or disseminated malignancy, were excluded from this study.

Recruitment sources. The participating centers, their eligibility criteria, and quality control procedures have been published previously[25-28] and are summarized in the online 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, antihypertensive, and lipid lowering agents.
- Presence of hypertension (antihypertensive medication or BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic), coronary artery disease (documented myocardial infarction [MI]/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 MI, myocardial ischemia, and left ventricular hypertrophy (LVH) on baseline ECG according to previously published criteria.[25] ECGs were reported at the coordinating center 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 centers were trained at the coordinating center in grading internal carotid stenosis and plaque image capture.[25] The entire duplex examination, recorded on S-VHS videotape, was sent to the coordinating center for quality control.

Grading of internal carotid stenosis. A combination of velocity criteria was used to express the degree of stenosis in terms of both the ECST method and the NASCET method[25,29] (see online data supplement). ECST stenosis was used in analysis because of its linear relationship to risk of ipsilateral CORI events, unlike NASCET stenosis which has an S-shaped relationship.[28] Contralateral ICA occlusion was noted. Bilateral vertebral artery flow was reported as cephalad, reversed, or not visualized.

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 640 × 480 pixels at the coordinating center by two members of the team who were experienced in carotid scanning. Image

Table I. Baseline clinical, biochemical, and ultrasonic features in 1121 patients

Continuous variables (normal distribution; mean $\pm$ SD)	
Age, year	70.0 $\pm$ 7.7
BMI (kg/m^2)[a]	25.4 $\pm$ 3.7
SBP (mm Hg)[a]	152.3 $\pm$ 22.2
DBP (mm Hg)[a]	82.2 $\pm$ 10.0
Creatinine (μmol/L)[a]	100.5 $\pm$ 34.1
Fibrinogen (g/L)[a]	3.56 $\pm$ 1.00
Hematocrit (%)[a]	41.1 $\pm$ 4.9
Total cholesterol (mmol/dL)[a]	6.01 $\pm$ 1.19
LDL cholesterol (mmol/dL)[a]	3.90 $\pm$ 1.20
HDL cholesterol (mmol/dL)[a]	1.30 $\pm$ 0.49
Ipsilateral stenosis (%)	78.0 $\pm$ 12.8
Contralateral stenosis (%)	45.5 $\pm$ 30.0
Continuous variables (skewed distribution; median, interquartile range)	
Pack-years	10 (0, 36)
Triglycerides (mmol/dL)[a]	1.58 (1.17, 2.19)
Grayscale 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 vertebrobasilar 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 types 4 and 5	186 (17%)
Plaque type 3	509 (45%)
Plaque type 2	341 (30%)
Plaque type 1	85 (8%)
Presence of discrete white areas	718 (64%)

BMI, Body mass index; *DBP,* diastolic blood pressure; *ECG,* electrocardiogram; *LVH,* left ventricular hypertrophy; *MI,* myocardial infarction; *SBP,* systolic blood pressure; *TIAs,* transient ischemic attacks.
[a]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%.

normalization for grayscale using linear scaling with "blood" (grayscale = 0) and adventitia (grayscale = 190), and pixel density standardization to 20 pixels per mm were performed followed by image analysis. The "Plaque Texture Analysis software" version 3.2 (Iconsoft International Ltd, Greenford, London, UK)[30] was used. Some plaque texture features were automatically calculated using the "Feature Extraction" module of the software: GSM,[30] modified Geroulakos plaque classification[18,27] and plaque area. Presence of DWAs without acoustic shadowing and ulceration were identified visually (see online data supplement).

Table II. 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[a] as used in this paper and NASCET stenosis[b] for comparison with previous publications that have used these methods.

ECST stenosis (%)	NASCET stenosis (%)	No.	CORI events	Strokes
All patients		1121	130 (11.6%)	59 (5.3%)
50-69[a]	<50	198	16 (8.1%)	5 (2.5%)
70-89[a]	50-82	598	65 (10.9%)	29 (4.8%)
90-99[a]	83-99	325	49 (15.1%)	25 (7.7%)
			$P = .01$	$P = .008$
<80	<70[b]	514	50 (9.7%)	21 (4.1%)
80-99	70-99[b]	607	80 (13.2%)	38 (6.3%)
			$P = .07$	$P = .10$

AF, Atrial fibrillation; *CORI,* cerebrovascular or retinal ischemic; *ECST,* European Carotid Surgery Trial; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *TIAs,* transient ischemic attacks.
Follow-up 6 months to 8 years (mean, 48 months). *P* values were calculated using chi-square test for trend.

Outcome measures. Primary outcome measures were (1) ipsilateral CORI events (ie, cerebral or retinal ischemic events that included stroke) and (2) ipsilateral cerebral ischemic stroke (fatal or nonfatal). Stroke and TIA were defined as cerebral deficits most likely of vascular origin lasting >24 hours or <24 hours, respectively. For each stroke, details recorded by the local neurologist, a 6-month modified Rankin score,[31] and computed tomography (CT) or magnetic resonance imaging (MRI) brain scan results were requested. Two coordinating center members including a neurologist, made the final classification of ipsilateral strokes. Local team members diagnosed amaurosis fugax TIAs and vertebrobasilar strokes.

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, College Station, Tex) 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 percentage of stenosis, history of contralateral TIAs or stroke, DWAs,

Table III. Unadjusted hazard ratios (*HRs*) of risk factors for ipsilateral CORI events and ipsilateral cerebral stroke. (Skewed continuous predictors were transformed to be approximately symmetrically distributed.)

Risk factor	CORI HR	95% CI	Stroke HR	95% CI
Age (10 year increase)	1.10	(0.88-1.38)	**1.42**	**(1.00-2.02)**
BMI (5 unit increase)[a]	0.86	(0.65-1.14)	0.85	(0.57-1.28)
Systolic blood pressure (10 unit increase)[a]	**1.11**	**(1.07-1.22)**	1.07	(0.94-1.22)
Diastolic blood pressure (10 unit increase)[a]	1.21	(0.99-1.47)	1.14	(0.86-1.50)
Creatinine (20% increase)[a]	1.10	(0.96-1.25)	**1.28**	**(1.09-1.50)**
ln (GSM+40)	**0.08**	**(0.04-0.15)**	**0.06**	**(0.02-0.15)**
Fibrinogen[a]	1.03	(0.85-1.26)	1.17	(0.84-1.48)
Hematocrit (10 unit increase)[a]	1.18	(0.83-1.66)	1.13	(0.07-1.85)
Total cholesterol[a]	1.08	(0.92-1.26)	1.02	(0.80-1.28)
LDL cholesterol[a]	1.03	(0.86-1.23)	0.97	(0.74-1.27)
HDL cholesterol[a]	1.12	(0.75-1.69)	1.34	(0.80-2.24)
Triglyceride (doubling)[a]	1.18	(0.80-1.74)	1.73	(0.99-3.05)
Ipsilateral stenosis (10% increase)	**1.02**	**(1.01-1.04)**	**1.04**	**(1.01-1.06)**
Contralateral stenosis (10% increase)	1.03	(0.98-1.10)	1.05	(0.96-1.14)
Plaque area $(mm^2)^{1/3}$	**2.51**	**(2.01-3.12)**	**2.45**	**(1.76-3.40)**
Plaque types 4 & 5	1	—	1	—
3.	**6.31**	**(1.52-26.19)**	4.41	(0.58-33.74)
2.	**19.66**	**(4.83-80.06)**	**18.79**	**(2.58-137.03)**
1.	**18.28**	**(4.20-79.52)**	**20.74**	**(2.63-163.70)**
Male	0.92	(0.65-1.30)	1.10	(0.65-1.86)
Smoking	1.10	(0.72-1.70)	1.51	(0.84-2.71)
≥10 smoking pack-years	**1.65**	**(1.16-2.34)**	1.52	(0.90-2.56)
Coronary artery disease	1.19	(0.84-1.70)	1.32	(0.78-2.21)
Atrial fibrillation	1.36	(0.50-3.68)	1.55	(0.38-6.36)
Hypertension	0.98	(0.68-1.40)	1.00	(0.59-1.70)
Diabetes	0.77	(0.48-1.25)	0.88	(0.45-1.74)
History of vertebrobasilar symptoms	1.48	(0.92-2.38)	1.48	(0.73-3.00)
History of contralateral TIAs or stroke	**2.35**	**(1.60-3.43)**	**3.03**	**(1.77-5.20)**
Old MI on ECG	1.31	(0.87-1.97)	1.62	(0.91-2.87)
Ischemia on ECG	1.41	(0.95-2.08)	1.36	(0.76-2.45)
LVH on ECG	1.03	(0.59-1.80)	1.15	(0.52-2.53)
Antihypertensive therapy	0.94	(0.66-1.34)	0.94	(0.56-1.59)
Antiplatelet therapy	0.98	(0.60-1.59)	1.05	(0.50-2.20)
Lipid lowering therapy	0.87	(0.58-1.29)	0.81	(0.45-1.48)
Ipsilateral vertebral flow	1.74	(0.88-3.42)	3.72	(0.91-15.24)
Contralateral internal carotid occlusion	1.27	(0.71-2.25)	1.05	(0.42-2.62)
Ipsilateral ultrasonic ulcer	0.52	(0.24-1.11)	0.48	(0.15-1.55)
Presence of DWAs (>1)	**2.32**	**(1.49-3.6)**	1.68	(0.92-3.06)

BMI, Body mass index; *CI,* confidence interval; *CORI,* cerebrovascular or retinal ischemic; *DWAs,* discrete white areas; *ECG,* electrocardiogram; *GSM,* grayscale median; *LVH,* left ventricular hypertrophy; *MI,* myocardial infarction.
HR with $P < .05$ are in bold.
[a]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%.

plaque area, and GSM. Continuous variables were categorized for stratified Kaplan-Meier plots. For example, stenosis was categorized as mild (<70% ECST/<50% NASCET), moderate (70% to 89% ECST/50% to 82% NASCET) or severe (90% to 99% ECST/83% to 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 unskewed distribution where possible.

Risk factors which were significant at $P < .05$ in unadjusted models for CORI events or stroke were considered in multivariable proportional hazards models. Flexible parametric models of Royston & Parmar[32] 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 $P > .05$ 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.[33]

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.

Table IV. Flexible parametric proportional hazards models including significant variables from Table III with ipsilateral CORI events as the dependent variable. Selected using backward elimination on all variables with 95% CI not overlapping 1 in Table III

Variable	β	HR	95% CI	P value
(i) Clinical factors only. Ipsilateral CORI events as the dependent variable. Five-year baseline hazard estimated as .886; Harrell's $C = .66$; Pseudo $R^2 = .17$				
Stenosis (% ECST)	0.028	1.03	1.01-1.04	<.001
Pack-years (<10, ≥10)	0.429	1.53	1.07-2.18	.018
History of contralateral TIAs and/or stroke (Yes vs no)	0.858	2.36	1.61-3.46	<.001
(ii) Clinical factors with plaque features. Ipsilateral CORI events as the dependent variable. Five-year baseline hazard estimated as .949; Harrell's $C = .79$; Pseudo $R^2 = .55$				
Stenosis (% ECST)	0.01696	1.02	1.00-1.03	.027
Log (GSM + 40)	−2.4519	0.09	0.04-0.17	<.001
Plaque area$^{1/3}$ (mm^2)	0.6539	1.92	1.50-2.46	<.001
DWAs (Present vs absent)	0.7417	2.10	1.32-3.35	.002
History of contralateral TIAs and/or stroke (Yes vs no)	0.6901	1.99	1.32-2.92	.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). Five-year baseline hazard estimated as .972; Harrell's $C = .80$; Pseudo $R^2 = .61$				
Stenosis (% ECST)	0.026	1.03	1.00-1.05	.024
Log (GSM + 40)	−2.672	0.07	0.02-0.20	<.0001
Plaque area$^{1/3}$ (mm^2)	0.629	1.88	1.28-2.75	<.0001
DWAs (Present vs absent)	0.429	1.54	0.81-2.92	.18
History of contralateral TIAs and/or stroke (Yes vs no)	0.973	2.65	1.54-4.54	<.0001

CI, Confidence interval; *CORI*, cerebrovascular or retinal ischemic; *DWAs*, discrete white areas; *ECST*, European Carotid Surgery Trial; *GSM*, grayscale median; *HR*, hazard ratio; *TIAs*, transient ischemic attacks.

The assumption of proportional hazards was tested using the Schoenfeld residuals. Harrell's C[34] and a pseudo R^2 were calculated[35] 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, βx (the sum of the product of mean-centered covariate values and corresponding parameter estimates) for each patient. Receiver operating characteristic (ROC) curves were constructed for βx 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 model (iii), since comparison of different βx 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

A total of 1121 patients aged 39 to 89 years (mean age 70.0; SD 7.7; 61% men) were recruited during 1998 to 2002 with a follow-up of 6 to 96 months (mean, 48 months). There was 66% of patients recruited from medical services (vascular internists, 28%; neurologists, 16%; cardi-

ologists, 10%; hypertension clinics, 5%; metabolic units, 3%; and screening programs, 4%). Thirty-four percent 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 I.

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.

Severe and fatal ipsilateral strokes (n = 14; Rankin scores 5 and 6) occurred exclusively in plaque types 1 and 2 (10 in type 2 and 4 in type 1); also exclusively in plaques with GSM <30 (4 in plaques with GSM 15-30, and 10 in plaques with GSM <15). Seven of these strokes occurred in the 231 patients with diabetes with the other 7 in the remaining 890 patients (P = .006; odds ratio [OR], 3.94; 95% confidence interval [CI], 1.37-11.35). Five of these strokes occurred in the 173 patients with a history of contralateral TIA or stroke (P = .035; OR, 3.10; 95% CI, 1.03-9.38).

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 two vertebrobasilar strokes. Of the 18 contralateral strokes, 4 occurred in the 125 patients with plaques producing 90% to 99% stenosis, 1 in the 170 producing 70% to 89% stenosis, and the remaining 13 in the 826 producing less than 70% stenosis. Plaque
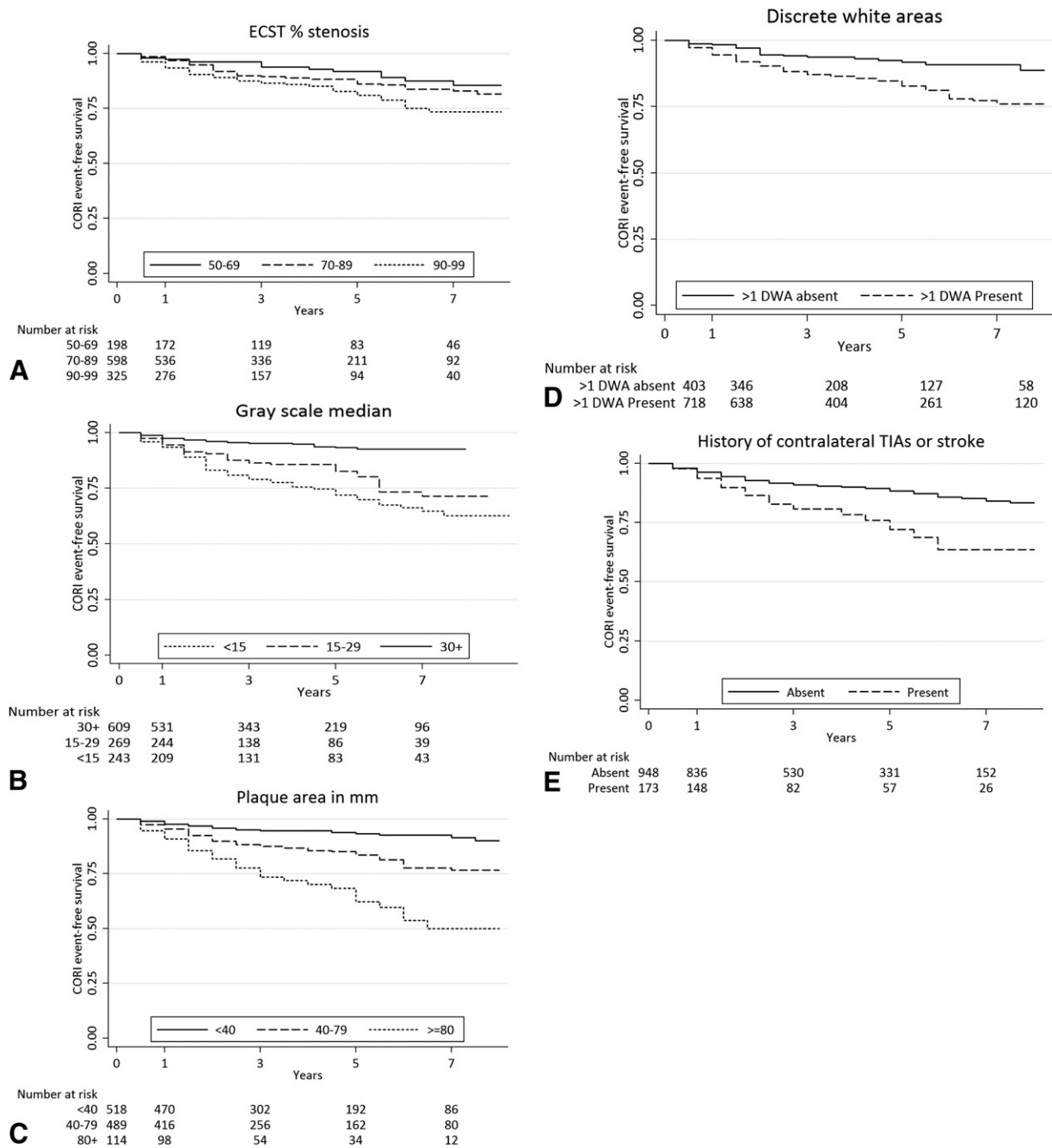
Fig 1. Kaplan-Meier plots showing ipsilateral cerebrovascular or retinal ischemic (*CORI*) event-free survival stratified by: **(A)** European Carotid Surgery Trial (*ECST*) stenosis: log-rank test: *P* for trend = .002; **(B)** grayscale median (*GSM*): log-rank test: *P* for trend < .0001; **(C)** plaque area (mm^2): log-rank test: *P* for trend < .0001; **(D)** discrete white areas (*DWA*): log-rank test: *P* < .0001; **(E)** history of contralateral transient ischemic attacks (*TIAs*) or stroke: log-rank test: *P* < .0001.

characterization was not performed on the contralateral side. The only factor associated with contralateral stroke was the presence of atrial fibrillation (OR, 8.28; 95% CI, 2.26-30).

There was a total of 214 deaths (195 non-stroke deaths) of which 157 (73%) were due to vascular causes:

MI, 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 nonvascular
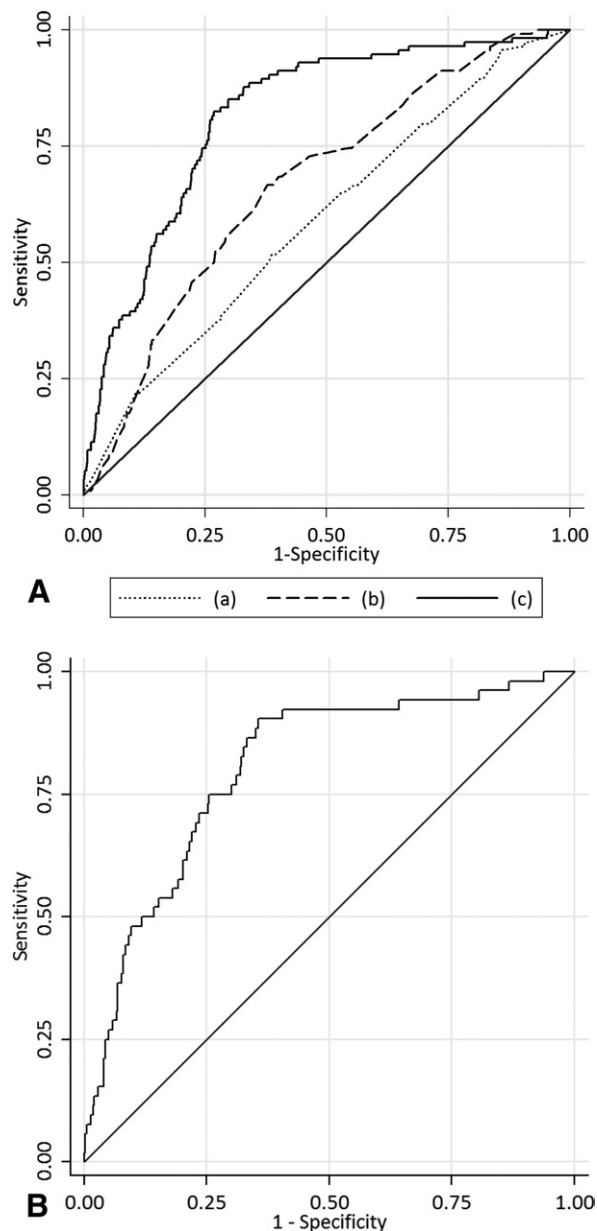
Fig 2. Receiver operating characteristic (ROC) curves **(A)** for cerebrovascular or retinal ischemic (CORI) events using **(a)** stenosis as continuous variable, **(b)** the linear predictor score from the proportional hazards model (model i) that included stenosis and significant clinical features only (pack-years, history of contralateral transient ischemic attacks [TIAs] or stroke), and **(c)** the proportional hazards model (model ii) that included stenosis, significant clinical and plaque characteristics (grayscale median [GSM], plaque area, discrete white areas [DWAs], and history of contralateral TIAs or stroke) for predicting ipsilateral CORI events. Corresponding areas under curve are **(a)** 0.59 (95% confidence interval [CI], 0.54-0.64), **(b)** 0.66 (95% CI, 0.62-0.72), and **(c)** 0.82 (95% CI, 0.78-0.86). $P < .003$ for all pairwise comparisons. ROC curve for stroke **(B)** using the linear predictor score of the proportional hazards model (model iii). Area under curve is 0.80 (95% CI, 0.74-0.86).

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 1 patient.

Ipsilateral carotid endarterectomy was performed in 129 patients for a 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. Of these 129 patients, 11 (5.6%) were in the group of 198 with less than 70% stenosis, 77 (12.9%) in the group of 598 with 70% to 89% stenosis, and 40 (12.3%) in the group of 325 with 90% to 99% stenosis. Twenty-one patients were lost to follow-up. In these, contact was lost with 15 patients, 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 patients (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 II. 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 III. 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 DWAs 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 IV 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 untransformed by multivariable fractional polynomials. Parameter estimates in Table IV 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 Fig 1, *A-E*.

On the basis of the variables shown in Table IV, the linear predictor scores *x*β 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 Fig 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, 0.77-0.85; Fig 2, *A*). The area under the ROC curve from model (iii) which had stroke as the dependent variable was 0.80 (95% CI, 0.74-0.87; Fig 2, *B*).

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

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

DWAs, Discrete white areas; *ECST,* European Carotid Surgery Trial; *GSM,* grayscale median; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *TIAs,* transient ischemic attacks.

—Denotes a covariate combination which did not occur in observed data.

[a]Denotes a covariate combination which occurred less than five times in observed data.

On the basis of model (iii) predicted cumulative 5-year rates for ipsilateral cerebral stroke were estimated for different combinations of risk factor subgroups (Table V). (To calculate individual patient risk, see appendix in the online data supplement). Fig 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 CIs overlapping. The predicted 5-year percentage stroke rate (observed; 95% CI) was <5% (very low risk) in 654 (1%; 0.2-2), 5% to 9.9% (low risk) in 225 (8%; 5-13), 10% to 19.9% (moderate risk) in 156 (12%; 7-18), and ≥20% (high risk) in 86 patients (29%; 14-33). 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 undergoing medical intervention alone. The results demonstrate that a number of baseline clinical characteristics 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. The results also emphasize the high mortality mainly from MI in patients with asymptomatic carotid stenosis.

Smoking is an established risk factor for plaque progression, plaque rupture, and ischemic stroke.[36,37] The increased risk for ipsilateral stroke in patients with a history of contralateral symptoms has been observed also in the med-
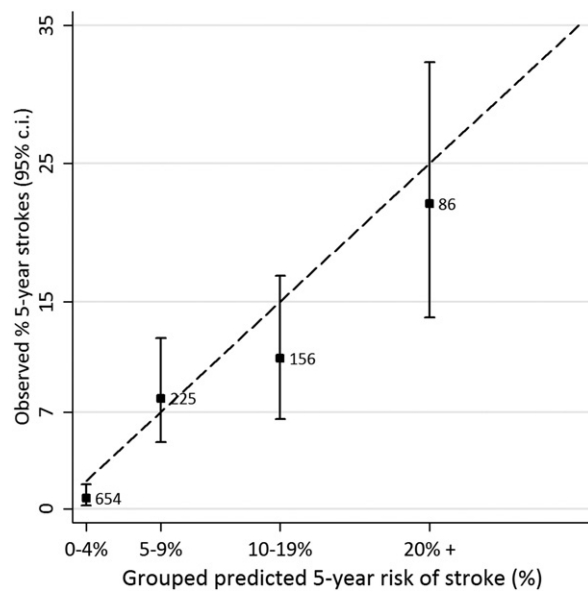
Fig 3. Calibration plot for model (iii), based on all 1121 patients (– – – shows the line of perfect agreement between predicted and observed 5-year stroke risk).

ical 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, 1.35-3.16).[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.[38,39] 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.

The inclusion criteria in our study provided a wide range of stenosis (50% to 99% ECST). This allowed classification into subgroups of mild, moderate, and severe degree 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,[28] 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% to 99% ECST stenosis as used in our study[7] and graded the stenosis as mild (<50%), moderate (50% to 79%), and severe (80% to 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.

The carotid plaque area has already been reported to be a strong predictor of MI and stroke[23] in patients with mild

degrees of stenosis. Our results show that the plaque area can be used to stratify cerebrovascular risk in patients with plaques producing moderate and severe stenosis (Fig 1, C).

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 has already been shown to be associated with symptomatic plaques.[24] With the exception of calcified plaques, it is the result of presence of DWAs without acoustic shadow in hypoechoic areas. These DWAs are often hyperperfused as shown by ultrasonic contrast perfusion agents and correspond to neovascularization and increased numbers of macrophages on histology.[40] Whether the presence of these areas are responsible for the development of intraplaque hemorrhage, non uniform plaque stresses promoting plaque rupture or erosion of the fibrous cap merits further investigation.

This study is unique not only because of the relatively large number of patients studied, but also because, in contrast to previous studies that had concentrated on one feature only, it shows how plaque characteristics add significantly to the risk stratification potential of stenosis and clinical features. It also provides a method that allows estimation of risk for any patient.

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 center (see online supplement). The importance of training vascular ultrasonographers in equipment settings and plaque imaging for optimal results cannot be overemphasized.

A limitation of this study is that the medical management of patients was according to what was considered best medical therapy at each center – the biggest factor when it comes to the relevance to current clinical practice. At each center, 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. Toward the end of the study, these percentages were 95% and 85%, respectively. However, the intensity of the treatment varied and, unlike current guidelines, very few patients were treated to target cholesterol level. In addition, this "freedom" in management resulted in 129 patients (11.5%) 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 clinical and ultrasonic plaque features can be used to stratify risk and may lead to refinement of the indications for carotid endarterectomy. The availability of user-friendly software for image analysis and automatic calculation of risk can make the method part of routine practice in the vascular laboratory.

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. The findings need to be validated in additional prospective studies using current optimal medical intervention.

AUTHOR CONTRIBUTIONS

Conception and design: AN, DT, NL, CD

Analysis and interpretation: AN, SK, EK, MG, MS, TT, GG, NL, CD, TM, AA

Data collection: AN, SK, MG, MS, DT, TT, GG, RN, AA

Writing the article: AN, NL, CD, TM, AA

Critical revision of the article: AN, SK, EK, MG, MS, DT, TT, GG, NL, CD, TM, RN, AA

Final approval of the article: AN, SK, EK, MG, MS, DT, TT, GG, NL, CD, TM, RN, AA

Statistical analysis: AN, EK, CD, TM

Obtained funding: AN

Overall responsibility: AN

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COLLECTIONS OF PAPERS

On the Web version of the Journal, selected articles have been grouped together for the convenience of the readers. The current collections include the following:

American Board of Vascular Surgery	Basic Science Reviews
Editorial Comments	Guidelines
History	Lifeline Research Meeting Abstracts
Reporting Standards	Reviews
Technical Notes	

ONLINE DATA SUPPLEMENT

Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification

Participating centers. Participating centers had an active noninvasive vascular laboratory with color duplex facility, a volume of patients of at least 500 per year, and staff experienced in the investigation of patients with extracranial cerebrovascular disease: a neurologist, a vascular physician or surgeon, and a radiologist. In addition, they were able to identify on average 15 individuals or patients with asymptomatic atherosclerotic carotid bifurcation disease that could be recruited to the study by screening new attendees (within 3 months) to their practice using ultrasound scan.

Quality control. The ultrasound methodology in the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study included a set of procedures designed to control quality and monitor key components of measurements. These include instrumentation settings, method of recording data, standardization of the method of scanning, and personnel training at the coordinating center. Throughout the study, performance was compared to the set standards. Results of the quality control, already published,[1] indicate that the goal of prospectively controlling quality in the ACSRS study had been achieved.

Grading of internal carotid stenosis. Velocities were obtained at the point of maximum stenosis in the internal carotid artery and the center of the common carotid artery lumen with the beam of ultrasound at 60° to the direction of flow. Because absolute velocity measurements could underestimate stenosis (eg, in the presence of cardiac arrhythmia) or overestimate stenosis (eg, in the presence of severe contralateral disease), ultrasonographers at each center were trained to use a combination of absolute velocity measurements and velocity ratios (Table I).[2-11] In plaques that were not calcified, anatomical criteria using color flow or power Doppler imaging of the artery in transverse section (percent diameter stenosis from measurements of vessel and residual lumen diameter at the site of maximum stenosis) were used to supplement velocity criteria.[12-15]

The entire duplex examination was recorded on S-VHS videotape and sent to the coordinating center as part of the quality control. Contralateral internal carotid artery (ICA) occlusion was noted.

Bilateral vertebral artery flow was reported as cephalad, reversed, or not visualized.

Recording of plaque images. A high frequency linear array transducer was used and the following technical ultrasound settings were observed to ensure optimum image quality for plaque type classification and texture analyses.

1. Maximum dynamic range was used which ensured the greatest possible display of grayscale values.
2. Persistence was set on low and frame rate on high, the latter ensuring good temporal scale values.
3. The time gain compensation curve (TGC) was sloping through the tissues but was positioned vertically through the lumen of the vessel because there was little attenuation of the ultrasound beam as it passed through blood. This ensured that the brightness of the adventitia of the anterior and posterior walls was similar.
4. The overall gain was adjusted to give optimum image quality. This was achieved by adjustment of the gain control to minimize but not abolish noise.
5. The most linear post-processing available curve was used.
6. The ultrasound beam was at 90° to the arterial wall.
7. The minimum depth was used so that the plaque occupied a large part of the image.

The above settings were essential prerequisites for plaque texture analysis, which was performed at the coordinating center. Ultrasonographers from participating centers attended for 2-day training at the coordinating center. They were trained, not only on equipment settings and method of image recording, but also on the method of image normalization. Although they were not expected to perform image normalization, it was felt that knowledge of how it was done would ensure that all prerequisites for image analysis described above would be included. A specially prepared video recording with instructions on how to perform the examination was provided. Video recordings of the examination and frozen images of plaques were sent to the coordinating center for image analysis. Continuous feedback ensured quality.[1]

Determination of baseline plaque characteristics

Image normalization and segmentation. Images that were recorded on videotapes 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 640×480 pixels at the coordinating center by two members of the team who were experienced in carotid scanning. Image normalization, standardization, and analysis were performed by the same members of the team.

The "Plaque Texture Analysis software" version 3.2 (Iconsoft International Ltd, Greenford, London, UK)[16] which is a dedicated research software package was used. Normalization was performed with the "Image Normalization" module using linear scaling with blood (grayscale value assigned: 0) and adventitia (grayscale value assigned: 190) as reference points as previously described.[16,17] First, a sample of "blood" was selected from the vessel lumen avoiding areas of "noise." Next, using the zoom facility, the brightest part of adventitia adjacent to the plaque was magnified at least four times and the middle two-fourths were selected (Fig 1). The normalized image appeared automatically in the window next to the original image and was saved as a separate file with "n" added as the last letter to the original name. The normalized image was then standardized to a pixel density of 20 pixels per millimeter using the bicubic method available in the "Pixel Density Normalization" module and saved in the database as a

Table I. Duplex velocity criteria used in the ACSRS study* (from Nicolaides et al,[3] 1996)

Angiographic diameter stenosis		Duplex velocity criteria				
N %	E %	PSV_{IC}[4,5]	EDV_{IC}[4-6]	PSV_{IC}/PSV_{CC}[7-9]	PSV_{IC}/EDV_{CC}[10,11]	EDV_{IC}/EDV_{CC}
12	50	<120	<40	<1.5	<7	<2.6
30	60				7-10	
47	70	120-150	40-80	1.5-2		
60	77	150-250	80-130	2-3.2		
65	80			3.2-4	10-20	2.6-5.5
70	83		>130			
82	90	>250		>4	20-30	
90	95				>30	>5.5
99	99			Trickle flow		

ACSRS, Asymptomatic Carotid Stenosis and Risk of Stroke; *CC,* common carotid; *E,* European Carotid Surgery Trial; *EDV,* end-diastolic velocity; *IC,* internal carotid; *N,* North American Symptomatic Carotid Endarterectomy Trial (NASCET).
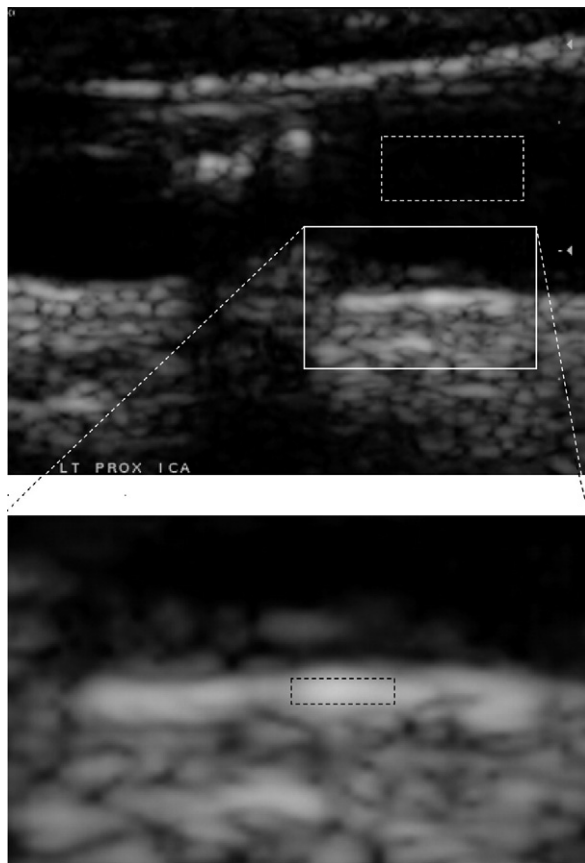

Fig 1. For image normalization a sample of "blood" free of noise and a sample from the inner two-fourths of the brightest part of the adventitia adjacent to the plaque are obtained.

separate file. The "Image Scaling" module was subsequently used to register the scale distance (usually 10 mm) as shown on the side of the image. The "Image Crop" module was then used. This had two windows, one for the normalized black and white image and the other for the color flow image for guidance. Visualization of the color

flow or power Doppler images as recorded by the ultrasonographers enabled the operator to identify the dark areas of plaque adjacent to the lumen (absence of color) and the areas of ulceration (presence of color). The "Log Image" facility that allowed a temporary logarithmic transformation of the image producing a better definition of the plaque outline was subsequently used. The plaque outline was then traced with the mouse and the plaque area within this outline was saved as a separate plaque image file with the same name and extension ".plq". Care was taken not to include adventitia. Both components of a plaque (anterior and posterior wall) could be selected. For plaques with a calcified cap, both the calcified area and the area of the plaque adjacent to the calcification that was outside the acoustic shadow were included.

Using the "Feature Extraction" module produced a variety of texture features that were automatically calculated including plaque type, grayscale median (GSM), and plaque area. These features were automatically saved in a text database that could be opened by "Microsoft Office Excel" (Microsoft Inc, Redmond, Wash) or SPSS for subsequent statistical analysis. Plaque images were automatically contoured and color-coded. Pixels with gray values 0 to 24 were colored black, 25 to 49 in blue, 50 to 74 in green, 75 to 99 in yellow, 100 to 124 in orange, and pixels greater than 124 in red (Fig 2).

The definitions and reproducibility of texture features used in this study are given below.

GSM. This was the median of the gray values of all the pixels in the plaque image.[16-19] In a reproducibility study of 35 plaques measured by two observers, the interobserver mean difference of GSM was 3.6, the within-subject SD was 13.6, and the intra-class correlation coefficient was 0.93.[16]

Plaque type. Plaques were classified automatically by the software into the following types according to a modified Geroulakos classification[20,21] as defined below.

Type 1. Uniformly echolucent (black): <15% of the pixels in the plaque area were occupied by pixels with grayscale values >25.
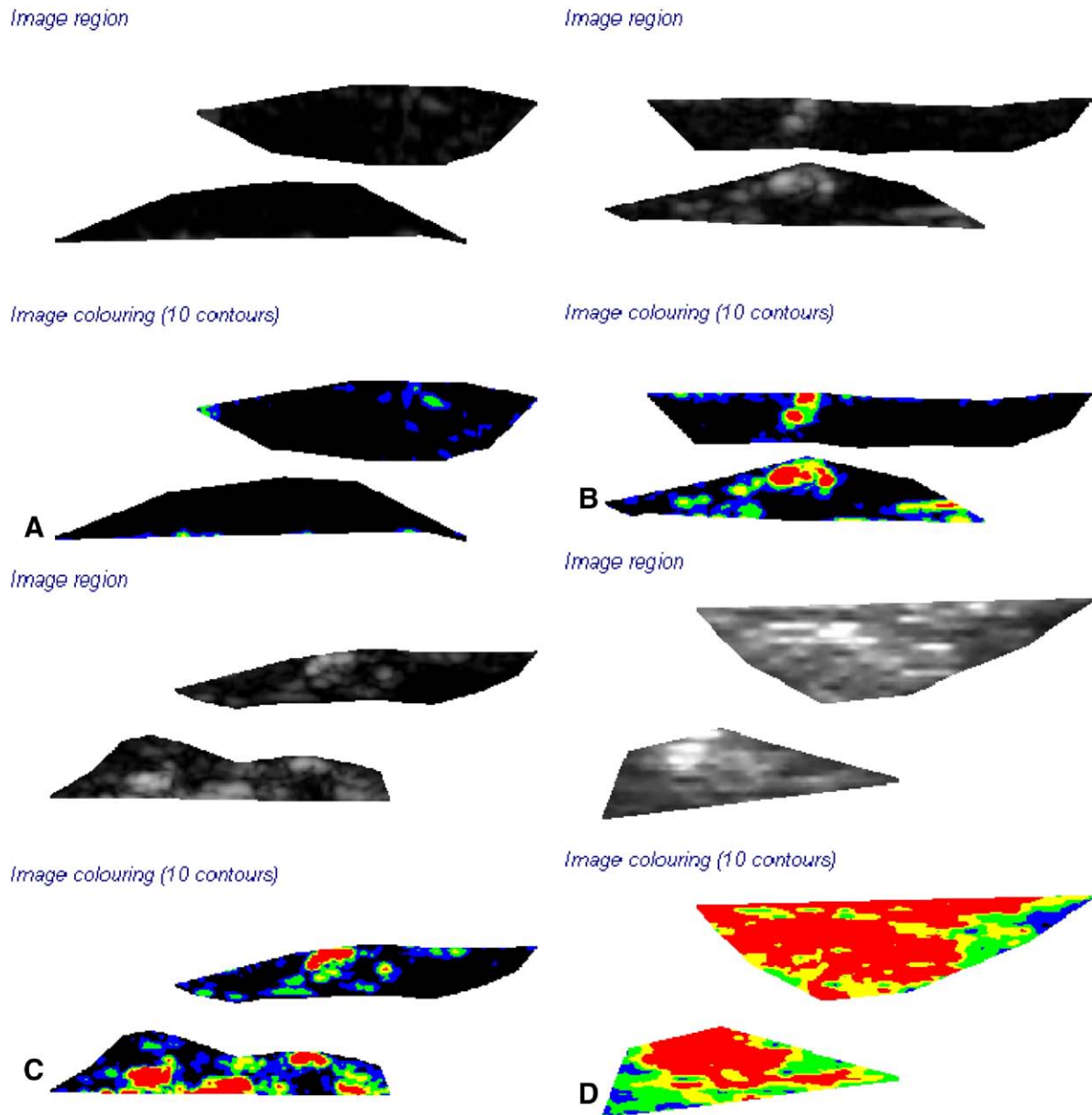
Fig 2. Examples of normalized grayscale and color contoured images of "cut" plaques. **(A)** Type 1, GSM 2, DWA absent; **(B)** Type 2, GSM 18, DWA present; **(C)** Type 3, GSM 28, DWA present; **(D)** Type 4, GSM 98, DWA n/a.

Type 2. Mainly echolucent: pixels with grayscale values >25 occupy 15% to 50% of the plaque area.

Type 3. Mainly echogenic: pixels with grayscale values >25 occupy 50% to 85% of the plaque area.

Type 4 or 5. Uniformly echogenic: pixels with grayscale values >25 occupy >85% of the plaque area.

Examples of type 1 to 4 plaques are shown in Fig 2, *A-D*.

A reproducibility study involving 1062 plaques classified visually by one observer after image normalization and automatically by the software had a kappa statistic of 0.61 ($P < .001$). Because of the low event rate in plaque types 4

and 5 as previously demonstrated,[21] and because the software cannot distinguish between them, these plaque types have been grouped together.

Plaque area. This was calculated by the software using the distance scale on the side of the image frame for calibration and the plaque area outlined by the operator. It was expressed in mm².[16,22] In a reproducibility study involving 50 plaques, the interobserver intraclass correlation coefficient was 0.73.

Discrete white areas. The presence of discrete white areas (DWAs) defined as areas with pixels having grayscale

Table II. 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	40 mm^2	(Plaque area)$^{1/3}$ = 3.420
DWAs	Absent	0
History of contralateral TIAs and/or stroke	Absent	0

DWAs, Discrete white area; *GSM,* grayscale median; *TIAs,* transient ischemic attacks.

Table III. Steps 2 and 3 in the calculation of 5-year predicted stroke-free survival

Variable	Calculation	χ	β	βχ
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
DWAs	1-0	1	0.429	0.4290
History of contralateral TIAs and/or stroke	0-0	0	0.973	0

DWAs, Discrete white area; *GSM,* grayscale median; *TIAs,* transient ischemic attacks.

values >124 (colored red by the software for easy visual identification) not producing acoustic shadowing in plaque types 1 to 3 was noted (Fig. 2, *B* and *C*). A reproducibility study involving 80 plaques classified visually after image normalization by two observers for presence or absence of DWAs had a kappa statistic of 0.83 (*P* < .01).

Plaque ulceration. This was defined as a defect >2 × 2 mm on the surface of the plaque shown by color flow or power Doppler to be communicating with the vessel lumen. It was reported by the ultrasonographers from each partner center.[23]

Calculation of predicted 5-year stroke-free survival. The hazard ratios for covariates presented in Table IV (iii) in the printed article 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 II above, the stroke-free survival at 5 years S$_0$ (5y) is estimated as 0.972.

Predicted 5-year stroke-free survival for a patient with different values of the covariates than those in Table II can be calculated as follows:

1. Transform continuous covariates using the formulae given in Table II, 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 III, second column).
3. Multiply each of these differences by the corresponding log-hazard ratio, β, from Table IV (iii) in the printed article to obtain β*x* as shown in Table III, column 5.

4. Sum the values obtained in step 3 above to denote this as **β*x***.
5. Calculate exp (**β*x***).
6. Compute predicted survival probability as a percentage for a patient using $100 \times 0.972^{\,\exp\,(\beta x)}$.

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

1. ln (GSM+40) = 3.912; (Plaque area)$^{1/3}$ = 4.309.
4. Sum of β*x* = **β*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 $100 \times 0.972^{\exp\,(2.146)}$ = 78.4%.

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