Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis

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Objective: **To determine baseline clinical and ultrasonographic plaque factors predictive of progression or regression of asymptomatic carotid stenosis and the predictive value of changes in stenosis severity on risk of first ipsilateral cerebral or retinal ischemic events (including stroke).**

Methods: **A total of 1121 patients with asymptomatic carotid stenosis of 50% to 99% in relation to the bulb diameter (European Carotid Surgery Trial [ECST] method) underwent six monthly clinical assessments and carotid duplexes for up to 8 years (mean follow-up, 4 years). Progression or regression was considered present if there was a change of at least one grade higher or lower, respectively, persisting for at least two consecutive examinations.**

Results: **Regression occurred in 43 (3.8%), no change in 856 (76.4%), and progression in 222 (19.8%) patients. Younger age, high grades of stenosis, absence of discrete white areas in the plaque, and taking lipid lowering therapy were independent baseline predictors of increased incidence of regression. High serum creatinine, male gender, not taking lipid lowering therapy, low grades of stenosis, and increased plaque area were independent baseline predictors of progression.**

One hundred and thirty first ipsilateral cerebral or retinal ischemic events, including 59 strokes, occurred. Forty (67.8%) of the strokes occurred in patients whose stenosis was unchanged, 19 (32.2%) in those with progression, and zero in those with regression. For the entire cohort, the 8-year cumulative ipsilateral cerebral ischemic stroke rate was zero in patients with regression, 9% if the stenosis was unchanged, and 16% if there was progression (average annual stroke rates of 0%, 1.1%, and 2.0%, respectively; log-rank, $P = .05$; relative risk in patients with progression, 1.92; 95% confidence interval, 1.14-3.25).

For patients with baseline stenosis 70% to 99% in relation to the distal internal carotid (North American Symptomatic Carotid Endarterectomy Trial [NASCET] method), in the absence of progression (n = 349), the 8-year cumulative ipsilateral cerebral ischemic stroke rate was 12%. In the presence of progression (n = 77), it was 21% (average annual stroke rates of 1.5% and 2.6%, respectively; log-rank, $P = .34$). Only nine (30%) of the 30 strokes occurred in the progression group.

Conclusions: **Progressive asymptomatic carotid stenosis identified a subgroup with about twice the risk of ipsilateral stroke compared with those without progression. However, the clinical value of screening for progression simply for selecting patients for carotid procedures is limited because of the low frequency of progression and its relatively low associated stroke rate. The cost effectiveness of screening for change in stenosis severity to better direct current optimal medical treatment needs testing. (J Vasc Surg 2014;59:956-67.)**

A number of natural history studies in patients with asymptomatic carotid stenosis have investigated the association between stenosis progression and risk of ipsilateral cerebrovascular events,[1-12] and mostly concluded that progression to >80% stenosis in relation to the diameter of the distal internal carotid (North American Symptomatic Carotid Endarterectomy Trial [NASCET] method) was associated with an increased risk of cerebrovascular events. However, these previous studies had significant limitations such as retrospective design, small sample sizes, short duration of follow-up, suboptimal medical treatment, and often stenosis progression detected after ipsilateral stroke or transient ischemic attack was included in predictive testing. Despite the uncertain clinical significance of progressive asymptomatic carotid stenosis, it remains a common reason for repeated carotid duplex imaging and referral for carotid surgery to reduce stroke risk.

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Table I. Duplex velocity criteria used in the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study[16]

Angiographic diameter stenosis		*Duplex velocity criteria*				
N %	*E %*	PSV_{IC}[18,19]	EDV_{IC}[18-20]	PSV_{IC}/PSV_{CC}[21-23]	PSV_{IC}/EDV_{CC}[24,25]	EDV_{IC}/EDV_{CC}
11	50	<120	<40	<1.5	<7	
30	60					<2.6
47	70	120-150	40-80	1.5-2	7-10	
60	77		80-130	2-3.2		
65	80	150-250				
70	83		>130	3.2-4	10-20	2.6-5.5
82	90	>250		>4	20-30	
90	94				>30	>5.5
95	99			Trickle flow		

CC, Common carotid; *E,* European Carotid Surgery Trial; *EDV,* end-diastolic velocity; *IC,* internal carotid; *N,* North American Symptomatic Carotid Endarterectomy Trial; *PSV,* peak systolic velocity.

The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study was a prospective international cohort study. The primary objective[13,14] was to assess the cerebrovascular risk stratification potential of combinations of patients' baseline clinical and biochemical characteristics, ultrasound-determined degree of stenosis, and plaque morphology. Particularly important were history of contralateral transient ischemic attack or stroke, stenosis severity at baseline, and plaque texture features (grayscale median [GSM], size of plaque area, size of juxtaluminal black area, and presence of discrete white areas [DWAs]), which could stratify stroke risk from less than 1% per year to more than 10% per year.[13,14]

A secondary objective of the ACSRS study was to assess the stroke risk stratification value of stenosis progression or regression using serial (6-monthly) duplex scanning. The aims of the present report were to determine:

1) The incidence of stenosis progression (with or without progression to occlusion) and regression;
2) the association of baseline clinical, biochemical, and plaque features predictive of stenosis progression or regression;
3) the predictive value of changes in the severity of stenosis in terms of ipsilateral cerebral or retinal ischemic (CORI) events including stroke. Associated with this aim, we determined if stenosis progression is a predictor of cerebrovascular events, is independent of baseline stenosis, and investigated any additional predictive value of change in stenosis severity compared with our previously published "ACSRS Best Baseline Risk Stratification Model for Stroke."[13,14]

METHODS

The methodology of the ACSRS study regarding inclusion and exclusion criteria, recruitment sources, clinical and biochemical characteristics, duplex examination, image acquisition of plaques, image normalization and analysis, and primary outcome measures and their use in stroke risk stratification has been previously published.[13-15] Only the most relevant methodology is presented.

Patient recruitment

Inclusion and exclusion criteria. Newly referred (<3 months) patients with 50% to 99% internal carotid artery (ICA) stenosis in relation to the carotid bulb diameter (European Carotid Surgery Trial [ECST] method) without previous ipsilateral CORI events and without neurological abnormality were recruited after written informed consent. Patients who had had contralateral CORI or vertebrobasilar symptoms or signs 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. Patients who could not attend for a 6-monthly neurological assessment and those with a limited life expectancy because of conditions such as severe cardiac failure or disseminated malignancy were excluded.

Baseline clinical and biochemical characteristics

At baseline, all patients had a history taken and a physical examination by the local neurologist, electrocardiographic examination and collection of fasting blood for determination of fibrinogen, fasting lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides), creatinine, and hematocrit, as previously reported.[13]

Duplex examination

Bilateral carotid duplex scanning was performed on admission to the study and every 6 months. Ultrasonographers from all centers were trained at the coordinating center in grading internal carotid stenosis and plaque image capture.[13-15]

Grading of internal carotid stenosis. Velocities were obtained at the point of maximum stenosis in the ICA and the center of the common carotid artery lumen. A combination of velocity measurements and velocity ratios was

Table II. The relationship between the incidence of regression, progression and occlusion in relation to baseline stenosis class

Stenosis class	*Regression, No. (%)*	*No change, No. (%)*	*Progression, No. (%)*	*Occlusion, No. (%)*	*Total, No. (%)*
50%-59%	0	61 (66)	30 (33)	1 (1.1)	92 (100)
60%-69%	3 (3.1)	59 (61)	34 (35)	1 (1.0)	97 (100)
70%-79%	9 (2.8)	262 (81)	50 (15)	1 (0.3)	322 (100)
80%-89%	16 (4.7)	252 (78)	45 (14)	8 (2.5)	321 (100)
90%-95%	15 (5.4)	214 (76)	31 (11)	20 (7.1)	280 (100)
95%-99%	0	8 (89)	0	1 (11)	9 (100)
Total	43 (3.8)	856 (76)	190 (17)	32 (2.9)	1121 (100)
χ^2: $P =$	.031	-	<.001	<.001	

χ^2: χ^2 for trend in comparison to the "No change" group.

used (Table I),[16-24] including the peak systolic velocity (internal carotid)/end diastolic velocity (common carotid) − PSVic/EDVcc − ratio, as indicated by the "Joint Recommendations for Reporting Carotid Ultrasound Investigation in the United Kingdom," allowing grading of stenosis in deciles.[25] 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.[26-29] The degree of contralateral ICA stenosis, if present, and contralateral ICA occlusion were noted.

Progression and regression of stenosis. Using the above criteria, stenoses were graded into six classes: 50% to 59%, 60% to 69%, 70% to 79%, 80% to 89%, 90% to 95%, and 96% to 99% (ECST methodology). Progression or regression was considered to occur if there was a change in at least one class up or down respectively, provided it was found on at least two consecutive visits, in order to minimize any effect related to reproducibility issues. Occlusion was also noted and included in the progression group, unless otherwise stated. Only change in stenosis severity detected prior to CORI events was used.

Outcome measures

The primary outcome measure was the first ipsilateral CORI event, including stroke (fatal or nonfatal).

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, transient ischemic attack, or death associated with carotid endarterectomy/angioplasty or stenting for the still asymptomatic study artery were not included in any of our analyses.

Statistical analysis

Initially, the relationship between the incidence of regression, progression, and occlusion in relation to the baseline severity of stenosis was determined. Subsequently, Kaplan-Meier curves were used to determine overall ipsilateral stenosis progression, occlusion, and regression-free survival. Hazard ratios for clinical, biochemical, and ultrasonic features for progression, occlusion, and regression were determined using unadjusted Cox models. Kaplan-Meier curves were also constructed for risk factors that were significant in the unadjusted models. Risk factors that were significant at $P < .05$ in these unadjusted models for progression, occlusion, and regression were then considered in multivariable Cox proportional hazards models. The ability of each model to predict progression, occlusion, or regression was tested by using the linear predictor score ($x^*\beta$) to construct receiver operating characteristic (ROC) curves. Kaplan-Meier curves were used to determine the ipsilateral CORI event and stroke rates in relation to changes in ipsilateral stenosis.

The IBM SPSS version 20 (SPSS Inc, Chicago, Ill) was used for statistical analysis.

RESULTS

The study included 1121 patients 39 to 89 years old (mean age, 70.0 years; standard deviation, 7.7 years; 61% men), recruited from 1998 to 2002, as previously reported.[13] Baseline characteristics have been previously reported.[13] During follow-up (range, 6 months-8 years; mean, 4 years), 130 first ipsilateral CORI events occurred (59 strokes, of which 12 were fatal; 49 transient ischemic attacks; and 22 amaurosis fugax episodes).

Incidence of stenosis progression, occlusion, and regression

Among the 1121 patients, ipsilateral regression of stenosis by one class or more occurred in 43 (3.8%). There was no change in 856 (76.4%). Progression occurred in 222 (19.8%), of which progression without occlusion was in 190 (16.9%) and progression to occlusion in 32 (2.9%). Progression by more than one class occurred in 26 (2.3%) patients. The incidence of regression, progression, and occlusion in relation to the stenosis at baseline is shown in Table II.

The within-year incidence of progression was 4% in year 1, 10% in year 2, 6% in years 3 and 4, 4% in year 5, 3% in year 6, 2% in year 7, and zero in year 8. The actuarial

Table III. Unadjusted hazard ratios (*HRs*) of risk factors for ipsilateral stenosis progression with or without occlusion, occlusion, and regression

Risk factor	*Progression* HR	*95% CI*	P	*Occlusion* HR	*95% CI*	P	*Regression* HR	*95% CI*	P
Age (10-year increase)	**1.19**	**1.01-1.41**	**.044**	1.18	0.76-1.84	.452	**0.62**	**0.44-0.87**	**.006**
BMI (5 units increase)	1.03	0.82-1.15	.712	0.85	0.53-1.35	.486	1.15	0.81-1.63	.424
SBP (10 units increase)	1.08	0.99-1.16	.051	1.01	0.90-1.33	.351	1.00	0.85-1.19	.968
DBP (10 units increase)	1.07	0.93-1.22	.353	1.26	0.88-1.80	.214	1.37	0.99-1.88	.055
Creatinine (20% increase)	**1.22**	**1.13-1.32**	**<.001**	**1.27**	**1.05-1.53**	**.013**	0.89	0.69-1.15	.386
Ln (GSM+40)	0.78	0.51-1.20	.258	**0.24**	**0.07-0.76**	**.015**	0.74	0.28-1.96	.543
GSM <23	1.21	0.93-1.59	.157	**2.62**	**1.29-5.30**	**.008**	1.01	0.52-1.95	.972
Plaque area$^{1/3}$ (mm^2)	**1.37**	**1.14-1.65**	**.001**	1.46	0.90-2.38	.125	0.82	0.53-1.26	.366
Fibrinogen	1.01	0.87-1.18	.890	1.19	0.82-1.72	.362	1.08	0.75-1.55	.669
Total cholesterol	1.05	0.93-1.18	.419	1.12	0.83-1.50	.463	1.21	0.95-1.56	.124
LDL cholesterol	1.05	0.92-1.20	.436	1.06	0.76-1.50	.721	1.29	0.82-1.45	.572
HDL cholesterol	0.74	0.52-1.05	.095	0.88	0.37-2.89	.770	1.49	0.85-2.64	.164
Triglycerides	1.03	0.90-1.17	.683	0.93	0.62-1.39	.711	1.11	0.84-1.47	.470
Ipsilateral stenosis (10% increase)	**0.84**	**0.76-0.93**	**.001**	**2.58**	**1.69-3.93**	**<.001**	**1.47**	**1.11-1.96**	**.009**
Contralateral stenosis (10% increase)	1.05	0.95-1.16	.341	**1.39**	**1.11-1.74**	**.004**	1.06	0.91-1.23	.440
Plaque type 4+5	1			1			1		
3	1.16	0.77-1.75	.470	1.12	0.32-4.30	.798	0.95	0.40-2.26	.922
2	1.32	0.87-2.03	.195	2.58	0.74-8.97	.137	0.60	0.22-1.65	.322
1	1.57	0.89-2.76	.120	3.93	0.94-16.4	.061	2.36	0.82-6.73	.109
Male	**1.71**	**1.28-2.28**	**.001**	**3.18**	**1.31-7.74**	**.011**	1.56	0.81-3.01	.179
Smoking	0.91	0.64-1.28	.598	0.79	0.30-2.05	.631	1.34	0.66-2.73	.416
Coronary artery disease	**1.36**	**1.04-1.78**	**.023**	1.73	0.87-3.48	.120	1.14	0.60-2.14	.699
Atrial fibrillation	1.20	0.53-2.71	.656	1.36	0.18-10.0	.760	2.44	0.68-10.1	.219
Hypertension	0.86	0.66-1.13	.292	1.21	0.57-2.55	.622	0.61	0.33-1.13	.119
Diabetes	1.23	0.89-1.69	.201	0.61	0.22-1.76	.364	0.68	0.26-1.72	.412
History of contr. TIA or stroke	1.26	0.92-1.72	.146	1.63	0.76-3.53	.211	0.31	0.07-1.29	.109
Antihypertensive therapy	0.87	0.67-1.14	.324	1.02	0.50-2.08	.959	0.74	0.40-1.36	.329
Antiplatelet therapy	0.87	0.60-1.27	.481	1.72	0.52-5.64	.373	0.99	0.39-2.54	.992
Lipid lowering therapy	**0.66**	**0.48-0.91**	**.011**	0.74	0.32-1.73	.494	**2.52**	**1.38-4.02**	**.003**
Contr. carotid occlusion	0.93	0.57-1.52	.774	2.07	0.80-5.36	.136	1.89	0.66-4.32	.269
Presence of DWA (>1)	1.22	0.92-1.63	.165	1.19	0.56-2.52	.642	**0.52**	**0.29-0.96**	**.037**

BMI, Body mass index; *CI,* confidence interval; *DBP,* diastolic blood pressure; *DWA,* discrete white area; *GSM,* grayscale median; *HDL,* high density lipoprotein; *LDL,* low density lipoprotein; *SBP,* systolic blood pressure; *TIA,* transient ischemic attack.
Skewed continuous predictors were transformed to be approximately symmetrically distributed. Significant risk factors are in bold.

progression and regression free rate at 5 years was 72% and 94%, respectively.

Baseline predictors of stenosis progression, occlusion, and regression

Hazard ratios for each individual baseline clinical, biochemical, and ultrasonic risk factors associated with ipsilateral progression of stenosis (with or without occlusion), progression to occlusion, and regression are shown in Table III.

Features associated with progression. Increasing age, male gender, presence of coronary artery disease, elevated plasma creatinine, and increasing plaque area were significant risk factors associated with increased incidence of progression. Systolic blood pressure had a borderline significance ($P = .051$). Increasing severity of baseline ipsilateral stenosis and use of lipid lowering therapy were significant risk factors associated with a decreased incidence of progression (Table III).

In a multivariable Cox proportional hazards model (model 1) with the significant features from Table III as covariates, only male gender, elevated creatinine, not taking lipid lowering therapy, decreasing severity of baseline ipsilateral stenosis, and increasing plaque area were independent predictors of progression (Table IV). On the basis of the model (model 1) shown in Table IV, the linear predictor scores xβ of the model were calculated for each patient. The ROC curve constructed had an area under the curve of 0.637 (95% confidence interval [CI], 0.596-0.677).

The cumulative ipsilateral stenosis progression free Kaplan-Meier curves for each of the independent predictors in the Cox model 1 are shown in Fig 1, *A-E.*

Features associated with occlusion. Male gender, elevated creatinine, increasing baseline ipsilateral stenosis severity, increasing baseline contralateral stenosis severity, and low GSM were significant univariate predictors associated with increased incidence of occlusion (Table III).

In a multivariable Cox proportional hazards model (model 2) with the significant features from Table III as covariates, only male gender, low GSM, and increasing severity of baseline ipsilateral and contralateral stenosis were independent predictors of occlusion (Table IV). On the basis of this model (model 2) shown in Table IV, the linear predictor scores xβ of the model were calculated

Table IV. Proportional hazards models including significant variables from Table III with ipsilateral stenosis progression (model 1) and occlusion (model 2) as the dependent variable

Variable	*β*	*HR*	*95% CI*	P
Model 1: Progression of stenosis as the dependent variable				
Creatinine (20% increase)	.191	1.210	1.114-1.315	<.001
Ipsilateral stenosis (10% increase)	−.193	0.824	0.742-0.916	<.001
Plaque area $^{1/3}$ (mm^2)	.280	1.323	1.095-1.599	.004
Male gender	.357	1.429	1.067-1.914	.017
Lipid lowering therapy	−.375	0.687	0.498-0.948	.022
Model 2: Occlusion as the dependent variable				
Log (GSM+40)	−1.296	0.274	0.084-0.894	.032
Ipsilateral stenosis (10% increase)	.865	2.376	1.565-3.607	<.001
Contralateral stenosis (10% increase)	.192	1.212	1.039-1.414	.014
Male gender	1.130	3.094	1.271-7.534	.013
Model 3: Regression as the dependent variable				
Age (10-year increase)	−.450	0.638	0.450-0.904	.011
Ipsilateral stenosis (10% increase)	.466	1.594	1.179-2.155	.002
Lipid-lowering therapy	.820	2.272	1.232-4.189	.009
DWA	−.693	0.500	0.272-0.920	.026

CI, Confidence interval; *DWA,* discrete white area; *GSM,* grayscale median; *HR,* hazard ratio.
Covariates selected using backward elimination on all variables with 95% CI not overlapping 1.

for each patient. The ROC curve constructed had an area under the curve of 0.793 (95% CI, 0.719-0.867).

The cumulative ipsilateral progression-to-occlusion free Kaplan-Meier curves for each of the independent predictors in the Cox model are shown in Fig 2, *A-D.*

Features associated with regression. Increasing age and presence of DWAs were associated with a decreased incidence of regression. Increasing severity of baseline ipsilateral stenosis and use of lipid lowering therapy were associated with increased incidence of regression (Table III).

In a multivariable Cox proportional hazards model (model 3) with the significant features from Table III as covariates, younger age, use of lipid lowering therapy, increasing severity of ipsilateral stenosis, and absence of DWAs were independent predictors of regression (Table IV). On the basis of this model (model 3) shown in Table IV, the linear predictor scores xβ of the model were calculated for each patient. The ROC curve constructed had an area under the curve of 0.704 (95% CI, 0.620-0.788).

The cumulative ipsilateral regression free Kaplan-Meier curves for each of the independent predictors in the Cox model 3 are shown in Fig 3, *A-D.*

Change in stenosis severity and prediction of ipsilateral CORI events, including stroke

Of the total of 130 ipsilateral CORI events, 88 (67.7%) occurred in the patients whose stenosis was unchanged, 33 (25.4%) in those with progression without occlusion, nine (6.9%) in those that developed occlusion, and zero in those with regression. The incidence of different CORI events in patients with regression, no change, or progression (including progression to occlusion) of stenosis is shown in Table V. The CORI event-free rate in relation to changes in stenosis is shown in Fig 4, *A.* Progression to occlusion was associated with a higher CORI event rate (9/32, 28%) compared with progression without occlusion (33/190, 17%), but the difference was not statistically significant (χ^2, $P = .15$).

Of the total of 59 ipsilateral ischemic strokes, 40 (67.8%) occurred in the patients whose stenosis was unchanged, 15 (25.4%) in those with progression without occlusion, four (6.8%) in those that developed occlusion, and zero in those with regression. The ipsilateral stroke-free rate in relation to changes in stenosis is shown in Fig 4, *B.* Progression to occlusion was associated with a higher stroke rate (4/32; 12.5%) compared with progression without occlusion (15/190; 7.9%), but the difference was not statistically significant (Fisher exact test, $P = .49$).

For the entire cohort, the 8-year cumulative ipsilateral ischemic stroke rate was zero in patients with regression, 9% if the stenosis was unchanged, and 16% if there was progression (average annual stroke rate over 8 years of 0%, 1.1%, and 2.0%, respectively; log-rank, $P = .05$).

Effect of baseline stenosis and progression on risk of subsequent ipsilateral stroke. In the absence of progression, the 8-year cumulative ipsilateral cerebral ischemic stroke rate for patients with baseline stenosis in relation to the bulb (ECST) of 50% to 69%, 70% to 89%, and 90% to 99% was 4%, 8%, and 13%, respectively (average annual stroke rate over 8 years of 0.5%, 1.0%, and 1.6%). In the presence of progression, it was 8%, 15%, and 25% (average annual stroke rate of 1.0%, 1.9%, and 3.1%).

For patients with baseline stenosis 70% to 99% in relation to the distal internal carotid (NASCET method; n = 449), in the absence of progression (n = 349), the 8-year cumulative ipsilateral cerebral ischemic stroke rate was 12%. In the presence of progression (n = 77), it was 21% (average annual stroke rate over 8 years of 1.5% and 2.6%, respectively; log-rank, $P = .34$). However, only nine (30%) of the 30 strokes occurred in the progression group.

For patients with baseline stenosis 80% to 99% (NASCET method; n = 325), in the absence of progression (n = 244), the 8-year cumulative ipsilateral cerebral ischemic stroke rate was 14%. In the presence of progression (n = 61), it was 25% (average annual stroke rate over 8 years of 1.7% and 3.1%, respectively; log-rank, $P = .31$). However, only nine (36%) of the 25 strokes occurred in the progression group.

In a multivariate Cox model with stroke as the dependent variable and with baseline stenosis and progression of stenosis as covariates, both covariates were significant (Table VI). When stenosis was used as the only covariate, the area under the ROC curve of the model output was 0.580 (95% CI, 0.504-0.657). When progression was

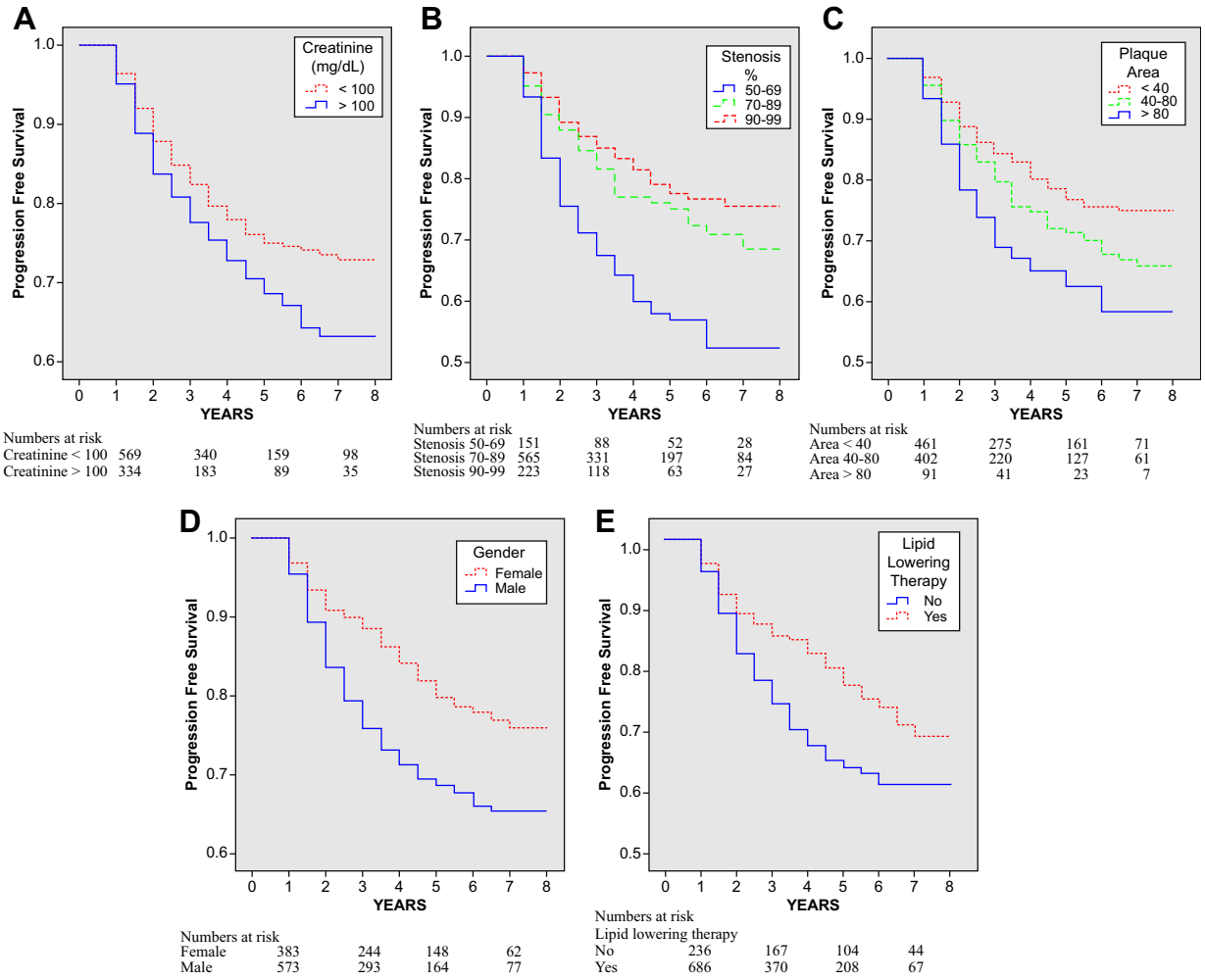

Fig 1. Effect of significant factors in model 1 (Table IV) on progression free survival. **A,** Creatinine (log-rank, $P <$ .001). **B,** Ipsilateral stenosis (log-rank, P overall $<$ .001). **C,** Plaque area (log-rank, $P = .004$). **D,** Gender (log-rank, $P <$ .001). **E,** Lipid-lowering therapy (log-rank, $P = .009$).

added to the model, the area under the ROC curve increased to 0.629 (95% CI, 0.555-0.704; $P > .05$).

Contribution of progression in an established model of stroke risk stratification

In a multivariate model, developed from the same cohort of patients[13] that has been shown to be able to predict the risk of stroke with an area under the ROC curve of 0.80 (95% CI, 0.74-0.87) and stratify patients according to the risk of stroke from 0.1% to 10% per year, we added stenosis progression as a covariate. Progression as a covariate was marginally significant (Table VII). Also, stenosis regression, when added as a covariate, was not significant.

DISCUSSION

The results indicate that a number of factors are associated with plaque progression and regression. The 19.8% incidence of ipsilateral stenosis progression was close to that found in previous studies with a similar duration of follow-up.[2,3,7,10] The annual incidence of progression was high in the first 3 years, decreasing gradually in subsequent years. This suggests that there is a population of patients with plaques that are likely to progress and a population with plaques that in terms of stenosis are stable. Only two previous studies have reported an annual incidence of progression that was the same throughout the follow-up period.[4-7] Regression that occurred in 3.8% of patients is also similar to what most previous studies have reported,[6,9,30-32] although a rate of 16% has been reported in one study.[33]

Previous studies have demonstrated the association of ipsilateral progression with age,[1,11] hypertension,[6,8,10] and coronary artery disease.[5,7] However, this is the first time the incidence of progression is shown to be associated with elevated creatinine, plaque area, and male gender.

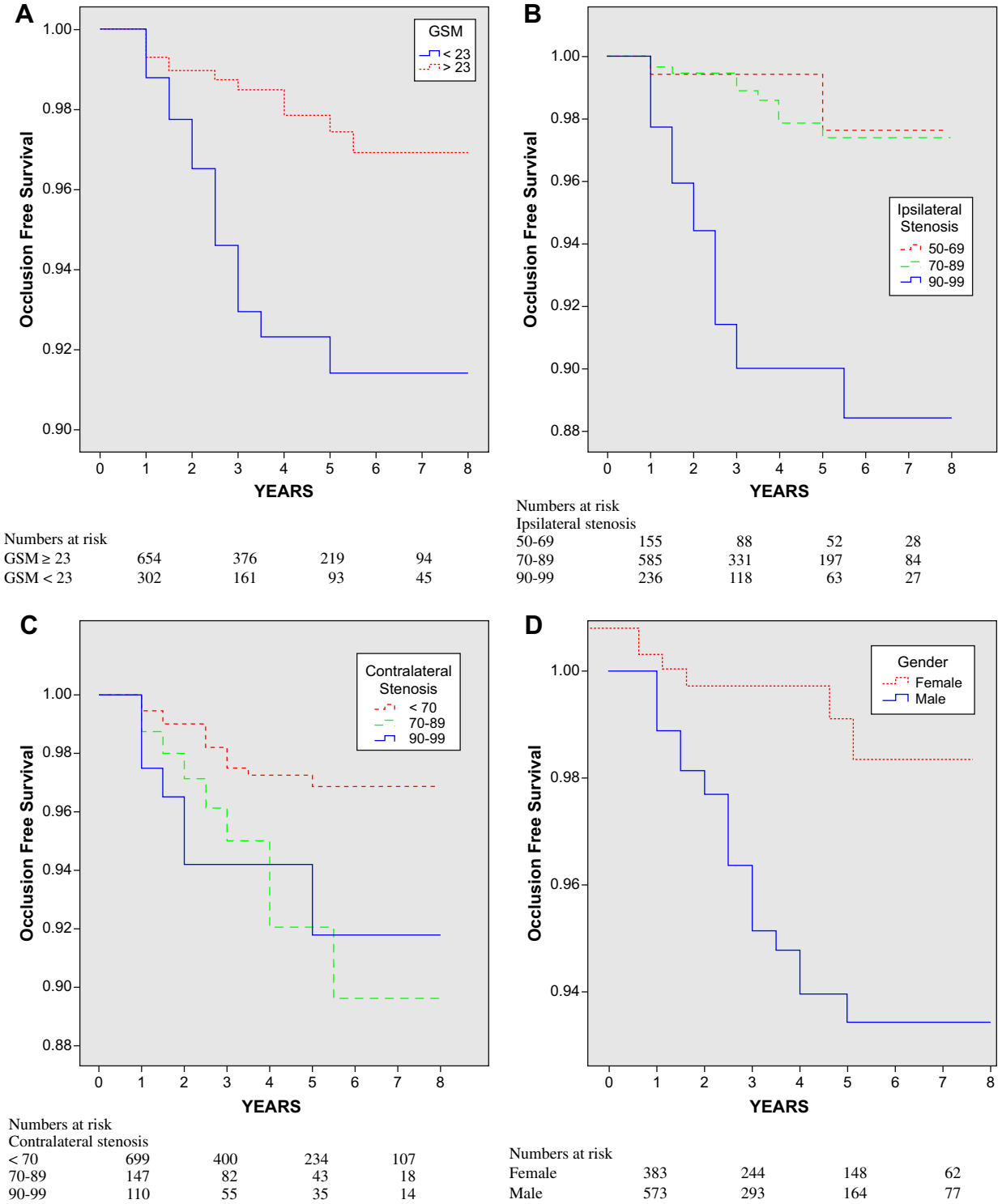

Fig 2. Effect of significant factors in model 2 (Table IV) on occlusion-free survival. **A,** Effect of grayscale median (*GSM*; log-rank, $P = .001$). GSM 23 is the cutoff point between lower and middle tertiles. **B,** Effect of ipsilateral stenosis (log-rank, P overall $< .001$). **C,** Effect of contralateral stenosis (log-rank, P overall $= .008$). **D,** Effect of gender on occlusion-free survival (log-rank, $P = .007$).

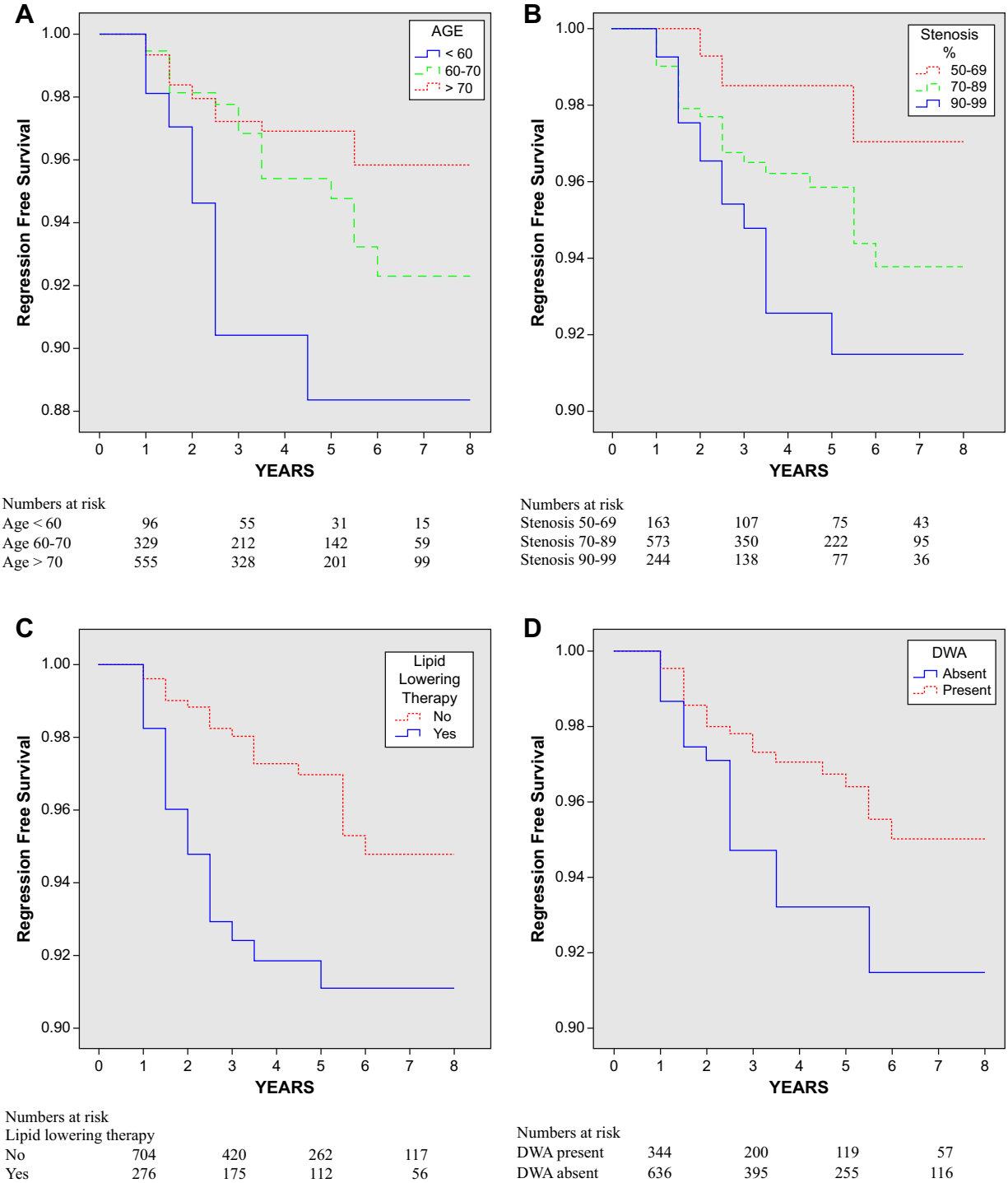

Fig 3. Effect of significant factors in model 3 (Table IV) on regression-free survival. **A,** Age (log-rank, $P = .016$). **B,** Ipsilateral stenosis (log-rank, $P = .081$). **C,** Lipid-lowering therapy (log-rank, $P = .002$). **D,** Presence of discrete white areas (*DWAs*; log-rank, $P = .032$).

Reduced incidence of progression has been seen in patients on lipid-lowering therapy, which is compatible with a previous report of reduction in progression of carotid plaque area.[34]

Elevated creatinine, low GSM indicating a hypoechoic plaque, severe ipsilateral stenosis, contralateral stenosis, and male gender were associated with progression to occlusion. Previous studies have demonstrated the association

Table V. The incidence of ipsilateral cerebral or retinal ischemic (CORI) events in relation to changes in severity of stenosis

Stenosis change	*No events, No. (%)*	*Amaurosis fugax, No. (%)*	*TIA, No. (%)*	*Stroke, No. (%)*	*Total, No. (%)*	*All events, No. (%)*
Regression	43 (100)	0	0	0	43 (100)	0
No change	768 (90)	16 (1.9)	32 (3.7)	40 (4.7)	856 (100)	88 (10)
Progression	180 (81)	6 (2.7)	17 (7.7)	19 (8.6)	222 (100)	42 (19)
Total	991 (88)	22 (2.0)	49 (4.4)	59 (5.3)	1121 (100)	130 (12)
RR	-	1.52	2.15	1.92	-	1.93
95% CI	-	0.60-3.84	1.22-3.80	1.14-3.25	-	1.38-2.71

CI, Confidence interval; *RR*, relative risk; *TIA*, transient ischemic attack.
Progression in this table includes progression to occlusion. RR is the relative risk of events in patients with progression in relation to the rest of the patients.

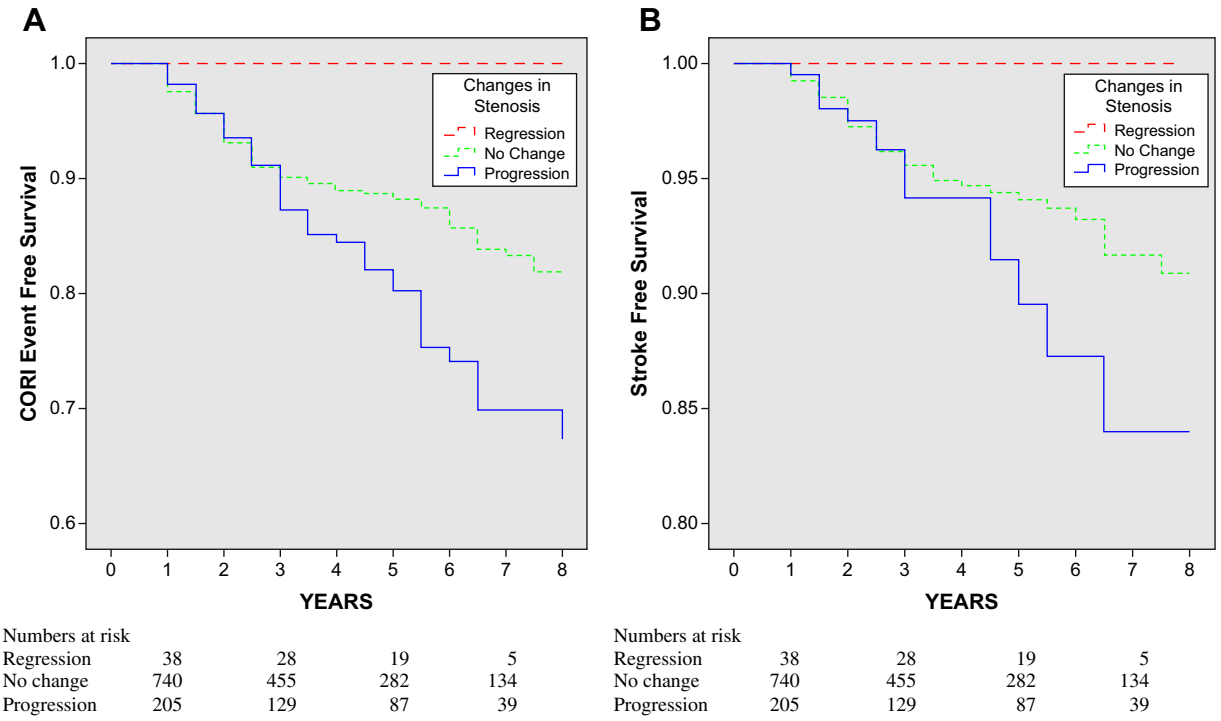

Fig 4. A, Effect of changes in stenosis on ipsilateral cerebrovascular or retinal ischemic (*CORI*) events (log-rank overall, $P < .001$). **B,** Effect of changes in stenosis on ipsilateral hemispheric stroke (log-rank overall, $P = .050$). Note: Only 19 strokes occurred in the group of patients that had progression of stenosis; the remaining 40 strokes occurred in the group that had no change in stenosis.

between ipsilateral progression and type I (hypoechoic) plaque,[7] ipsilateral stenosis,[5,6,11] or contralateral stenosis.[6] However, this is the first time the incidence of progression to occlusion has been shown to be associated with elevated creatinine and male gender. The prediction of progression to occlusion using the significant risk factors (GSM, ipsilateral stenosis, contralateral stenosis, and male gender) in a Cox proportional hazards model (model 2; Table IV) was high as indicated by the area under the ROC curve (0.793), and it may have a clinical application. Future studies need to investigate whether in the presence of the above risk factors patients should receive a more aggressive risk factor modification than what is proposed in current guidelines.

Increasing age and DWAs were associated with a low incidence of regression. Increased age is often associated with a higher incidence of plaque calcification and/or higher collagen content and such plaques are unlikely to remodel and regress. DWAs indicate the presence of plaques that have neovascularization as shown by plaque perfusion studies[35] that may also be resistant to regression. Lipid-lowering therapy was associated with increased incidence of regression. The association between lipid-lowering therapy and plaque regression in patients with asymptomatic carotid stenosis has already been demonstrated,[36] and is a well-established action of statins, reported to occur independently of the baseline cholesterol levels.[36] Our two observations on the reduced likelihood

Table VI. Proportional hazards model with stenosis and progression as covariates and stroke as the dependent variable

Variable	*β*	*HR*	*95% CI*	P
Ipsilateral stenosis (10% increase)	.295	1.343	1.068-1.687	.011
Progression	.616	1.85	1.072-3.202	.027

CI, Confidence interval; *HR,* hazard ratio.

Table VII. Progression of stenosis added as covariate in a proportional hazards model of our previously published report shown to predict the risk of future events

Variable	*β*	*HR*	*95% CI*	P
Ipsilateral stenosis (10% increase)	.017	1.017	1.002-1.032	.023
Log (GSM + 40)	−2.464	0.085	0.042-0.171	<.001
Plaque area$^{1/3}$ (mm^2)	.63	1.878	1.463-2.413	<.001
DWA	.725	2.065	1.292-3.302	.002
History of contralateral TIA or stroke	.661	1.938	1.321-2.842	.001
Progression	.353	1.424	0.980-2.067	.064

CI, Confidence interval; *DWA,* discrete white area; *GSM,* grayscale median; *HR,* hazard ratio; *TIA,* transient ischemic attack.

of progression and increased likelihood of regression in patients on lipid-lowering therapy reiterate the significant role of reducing cholesterol levels in managing patients with asymptomatic carotid artery disease. Additionally, the finding that none of the patients with regression developed a stroke suggests that monitoring plaque changes with ultrasound may be a surrogate endpoint for monitoring the effect of medical therapy.

The ipsilateral ischemic stroke-free survival at 8 years was 100% in the group of patients with regression, 91% in the group without change in stenosis (average annual stroke rate of 1.12%), and 84% in the group with progression of stenosis (average annual stroke rate of 2.0%). Although progression of stenosis identifies a high-risk group, only 19 of all strokes occurred in this group. The remaining 40 strokes were in the group without change in stenosis. Thus, although we have demonstrated that progression of asymptomatic carotid stenosis can identify a subgroup with about twice the risk of stroke compared with those without progression, the clinical value of screening for progression simply for selecting patients for carotid procedures is limited because of the low frequency of progression and the low number of predicted strokes. It appears that plaque progression is a poor indicator of overall plaque instability. This is supported further by the finding that progression was not significant when added to plaque texture features previously shown to be able to stratify patients to an annual risk of stroke from 1% to 10%.[13]

One of the most significant findings in the ACSRS study was the fact that none of the patients with regression developed a stroke. A previous study has reported a low neurological event rate in patients with plaque regression,[30] but no results on stroke were presented. Another study has already demonstrated that in patients with plaque regression, there was a 50% reduction on the incidence of stroke at 5 years,[34] an observation that explains the fall in CORI event rates with medical therapy.[37-40] Future studies should test the efficacy of modern medical interventions such as low density lipoprotein reduction to a target of 70 mg/dL and blood pressure to a target of 130/80 mm Hg in slowing down plaque progression or even induction of regression and the associated stroke risk reduction compared with surgical treatments.

A limitation of the study was that medical therapy was left to the discretion of the physician in charge, and by today's standards, it was not optimal. Additionally, ipsilateral carotid endarterectomy was performed in 129 patients (11.5%) for a still asymptomatic study artery because the clinician in charge or the patient requested it, as previously reported,[13] but it is unlikely that this would have introduced significant bias, given the small percentage of dropouts and the fact that long-term follow-up was performed in most cases. Also, the effect of changes in plaque characteristics during follow-up on incident ipsilateral CORI event and stroke rates, which might improve the otherwise marginal contribution of stenosis progression, should be studied. An advantage of our study was the use of contemporary grading of carotid stenosis in deciles. The standard Strandness groups of stenosis were developed at the time B-mode imaging was very poor. However, during the last 15 years, the use of transverse color flow images and the PSVic/EDVcc ratio as used in our study and now incorporated in the guidelines[25] allow accurate grading of stenosis in deciles.

CONCLUSIONS

Screening to detect progression of stenosis in patients with asymptomatic carotid stenosis may marginally improve the prediction of stroke risk based on stenosis alone, but it is of relatively limited clinical value compared with baseline stenosis severity combined with baseline plaque image analysis and clinical features, which, as shown by previous publications from the ACSRS cohort, can stratify risk of annual stroke from less than 1% to 10%. Patients with an annual stroke risk of less than 2% even when on suboptimal medical therapy as in the ACSRS study should not be entered into randomized controlled trials of medical therapy vs surgery because on optimal medical therapy, their risk may even be lower. They will be introducing "noise" and weaken such studies. Only patients at higher risk should be selected. Ideally, what is now needed is that the ACSRS findings are confirmed in a new cohort on optimal medical therapy, and only those shown to be at high risk despite optimal medical therapy should be considered for randomization.

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Final approval of the article: SK, AN, IC, DT, AG, RN, GG, AA
Statistical analysis: SK, AN
Obtained funding: AN
Overall responsibility: AN

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DISCUSSION

Dr John Ricotta (*Washington, D.C.*). You showed a remarkable ability to discriminate between deciles of stenosis using ultrasound. It's sometimes difficult to do that using angiography. I wonder how confident you are that you can discriminate between a 70% to 80% stenosis and an 80% to 90% stenosis or a 60% to 70% and a 70% to 80%. This would be a very unusual observation. I realize you're quite adept at this, but it's certainly not something we would expect in most labs.

Dr Stavros K. Kakkos. Well, this wasn't the aim of the present study, but it has been shown in the late '90s, when these criteria were published, that there was good correlation with angiography.

Dr Ricotta. But in this study did you correlate your ultrasound measurements with angiographic measurements? There are also a whole series of studies using repeatability and variability of angiographic measurements that suggests that there is about an 8% to 10% variation from one reader to another, and even intereader variability is at the 10% range.

Dr Kakkos. I agree. However, all ultrasound scans were reported centrally. The exam was reviewed carefully by experienced readers and we used, as I said, combinations of velocities and velocity ratios.

Dr Richard Cambria (*Boston, Mass*). Dr Kakkos, congratulations on another ACSRS report. I followed this study in publications very carefully and used some of the material in an address at this Society last year.

But I wonder a little bit about your conclusion. You showed at the beginning, in your background slide, some of the prior data that indicates that plaque progression is a risk factor, so I wonder why your conclusion that says regression, which was a rare event in your study, might be used to monitor or guide therapy. Shouldn't the conclusion be that the observation of progression should be an important factor in clinical decision-making?

Our group has studied this issue of the control of carotid plaque, or lack thereof, with modern medical therapy. And as you showed, a relatively small percentage of your patients were on optimal medical therapy. In a paper to be published next month in the Journal of Vascular Surgery, our data, even in patients with what all would consider to be optimal medical therapy, suggests that this medical therapy fails in a high percentage of patients. So I wouldn't want you to leave the audience with the impression that modern medical therapy is going to be effective in plaque regression.

Dr Kakkos. Unfortunately, progression was relatively rare. And we know from previous studies that its positive predictive value in predicting of future stroke is around 20%.

Additionally, progression wasn't significant in multivariate analysis. So we have to be honest and objective when interpreting our results. The only actual positive finding of our study was regression, so this is why I report it that way.

Dr Ricotta. I don't see anybody else up, so I guess I'm going to get to ask one more question. You only saw regression in your most severe stenosis; is that correct?

Dr Kakkos. This is correct, yes.

Dr Ricotta. So would your recommendation for somebody with a severe stenosis be to monitor them in the hopes that they show regression, or would it be to operate on them because they have the other characteristics that your study has shown are associated with an increased stroke rate?

Dr Kakkos. Regression occurred more often in plaques that were over 80% ECST, which is 60% NASCET, so it was moderate to severe stenosis.

Dr Ricotta. But you didn't get any regression in those patients; you only got regression in the 80% and 90% group.

Dr Kakkos. No, that's where regression was more frequent, in patients with severe stenosis. Now, regarding the reason that happened, to have at the same time occlusion and regression both being more frequent, this might indicate the presence of an unstable plaque that has not only the ability to progress to occlusion but also to regress. That's my interpretation of the findings.

Dr Pierre Karam (*Montreal, Quebec, Canada*). We would like to leave with an idea about the degree of stenosis. You classified stenosis very precisely—50, 60, 70, 80, 90. What are the numbers that worry you? At what time do you worry that this lesion is really severe and you should do something?

Dr Kakkos. We used peak systolic velocity and also peak systolic intrastenotic velocity over the peak systolic velocity of the common carotid; both are well-known criteria. Additionally, we used the peak systolic velocity intrastenotic velocity over the end-diastolic velocity of the common carotid artery. These are all well-known criteria, and as I said, we used the combination for criteria.

Dr Wilhelm Sandmann (*Duisburg, Germany*). Just a practical remark. Several, several years ago when Dr Bonnet from London, Ontario, tried to criticize the surgery on asymptomatic carotid artery stenosis, a lot of studies were set up. And we had also one in Dusseldorf under the leadership of Michael Henrich, who was a very critical neurologist. And at that time, the caseload of carotid endarterectomy was reduced by about 50% per year. But after the study was over, the caseload was more than tripled. And the information from the neurologists around Henrich was that all of them were very glad that the trial was over because they were convinced that the tight stenosis has to be taken away.

So I would take up the comment of Dr Ricotta and ask you, do you think really that in a patient with a significant or, as we better say, critical carotid artery stenosis, the time has come to propose medical treatment, or shouldn't we do medical treatment probably in the beginning with the plaque and when the patient is at risk?

Dr Kakkos. As we have published twice, the main endpoint, the purpose of the ACSRS, was to identify high-risk groups. And if the risk is extremely high, the aim is to operate on. If you're going to replace surgery with best medical therapy, then we need a randomized study. And CREST II, for sure, will try to answer this question.

APPENDIX (online only). The ACSRS Study Group

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T. Schroeder and M. L. Gronholdt (Copenhagen, Denmark)
G. Simoni, C. Finocchi, and G. Rodriguez (Genoa, Italy)
C. Spartera, M. Ventura, and P. Scarpelli (L'Aquila, Italy)
M. Sprynger, B. Sadzot, C. Hottermans, and M. Moonen (Chenee, Belgium)
P. R. Taylor (London, United Kingdom)
A. Tovar-Pardo and J. Negreira (Madrid, Spain)
M. Vayssairat and J. M. Faintuch (Paris, France)
J. Valaikiené (Vilnius, Lithuania)
M. G. Walker (Manchester, United Kingdom)
A. R Wilkinson (Hull, United Kingdom)