Brief Report

One-Year Progression of Moderate Asymptomatic Carotid Stenosis Predicts the Risk of Vascular Events

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Background and Purpose—This study aimed at evaluating whether ultrasound monitoring of moderate asymptomatic carotid stenosis may help in identifying subjects at high risk for vascular events.

Methods—We included 523 subjects with unilateral asymptomatic carotid stenosis of 50% to 69%. Follow-up carotid ultrasound was performed within 12 months from inclusion to detect the frequency and degree of stenosis progression. Subjects were prospectively evaluated for a median period of 42 months (interquartile range, 38–45) after a second ultrasound evaluation. Outcome measures were any stroke and transient ischemic attack, myocardial infarction, and death.

Results—Carotid stenosis progression was associated with the occurrence of vascular events (hazard ratio, 21.57; 95% confidence interval, 11.81–39.39; $P<0.001$). During follow-up, 96.7% of subjects without progressive carotid stenosis remained free from vascular events. Among patients with progressive stenosis, 53.7% experienced a vascular event and 27.1% experienced an ipsilateral stroke.

Conclusions—One-year moderate asymptomatic carotid stenosis progression is related to higher risk of vascular events, including ipsilateral stroke. **(*Stroke*. 2013;44:XXX-XXX.)**

Key Words: carotid stenosis ■ cerebrovascular disease ■ risk factors ■ ultrasound

The most appropriate treatment for asymptomatic carotid stenosis (ACS) remains controversial.[1] Subjects with ACS are usually considered to be at low risk for ipsilateral neurological events, but they present a potentially unstable clinical condition.[2] Clear strategies for monitoring disease progression and for helping to guide physicians in making therapeutic decisions are not available.

We aimed at prospectively evaluating whether ultrasound monitoring of moderate ACS can provide markers able to identify subjects at the highest risk for development of vascular events.

Methods

This prospective study was conducted from January 2004 to December 2009, at our ultrasound outpatient clinic (Marche Polytechnic University, Ancona, Italy). Subjects with ultrasound evidence of moderate (50%–69%) stenosis of the internal carotid artery (ICA)[3] were considered for enrollment.

Exclusion criteria were previous ipsilateral carotid revascularization, coexisting severe medical conditions preventing follow-up completion, contralateral carotid stenosis ≥50% to avoid interference in the assessment of strokes related to ipsilateral stenosis, and embolizing cardiopathies. Hypertension, diabetes mellitus, smoking, hyperlipidemia, and coronary artery disease were diagnosed on the basis of medical history and clinical, instrumental, and hematologic evaluations. Subjects received the best treatment available for each vascular risk condition and education about lifestyle modifications.[4]

Carotid arteries were assessed and defined by continuous wave Doppler and color flow B-mode Doppler ultrasound (Philips iU22; Bothell). Quantification of stenosis was performed according to validated criteria.

Within 12 months from enrollment, each patient underwent a follow-up carotid ultrasound evaluation to assess the frequency and degree of progression of ICA stenosis defined as an increase in the stenosis by at least 1 category: ≥70 to near occlusion, near occlusion, and occlusion. Patients who had any vascular event in the time span between baseline and second ultrasound evaluation were excluded from the study. After the second Doppler evaluation, patients were followed-up clinically every 3 months during the first year and then by telephone interviews every 6 months by 1 designated investigator who was blind to the clinical and ultrasound data. As per the study protocol, subjects' adherence to pharmacological treatments and lifestyle modifications was assessed. Outcome measures were occurrence of transient ischemic attacks (TIAs), ischemic stroke, myocardial infarction (MI), and death.

In the case of events not directly observed at our hospital, clinical records were acquired. Stroke or TIA diagnoses were verified by a brain computed tomography or magnetic resonance imaging.[5] The diagnosis of primary events was performed by 2 expert physicians (M.S. and F.V.) who were blind to ultrasound findings. Patients who had TIA or stroke ipsilateral to the carotid stenosis were referred to the Vascular Surgery Department. The study was approved by the Ethics Committee of the Marche Polytechnic University. All participants gave their informed written consent according to the Declaration of Helsinki.

Statistical Analysis

Comparison of basal characteristics was performed with 2-sample *t* test with equal variances and Pearson χ^2. After testing each factor in

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a univariate Cox regression model, a multivariable model was used to examine the association between progressive carotid stenosis and occurrence of combined vascular events, adjusting for variables that emerged as significant ($P<0.20$) in the univariate models. Results of the Cox models are presented as hazard ratio and 95% confidence interval (CI). The proportional hazard assumption of the model was assessed by plotting the scaled Schoenfeld residuals against time for each selected variable in the model. The variable age did not fulfil the assumption; hence, we included the interaction term age and analysis time in the final multivariable model. For accuracy purposes, Cox-Snell residuals were calculated. Finally, we fitted a competing risk model considering only ipsilateral ischemic stroke as the first adverse outcome and all other vascular events as the competing events. Results of this model are presented as the subhazard ratio and 95% CI. Data analysis was performed using Stata/IC 11.1 Statistical package.

Results

Of 616 consecutive subjects screened, 93 were excluded: 60 for contralateral ICA stenosis ≥50%, 22 for severe medical conditions or embolizing cardiopathies, and 11 for carotid revascularization. Of these 11 patients, in 6 cases the decision to perform revascularization treatment was due to the occurrence of an ipsilateral TIA or minor stroke after the first ultrasound evaluation. We enrolled 523 subjects with moderate ACS. Median time for the second ultrasound evaluation was 9 months (interquartile range, 8–12). Progression of ICA stenosis was detected in 129 subjects (24.7%). The median clinical follow-up period was 42 months (interquartile range, 38–45). Demographics and clinical characteristics of subjects with progressive and nonprogressive ICA stenosis are reported in Table 1.

Eighty-one subjects (15.5%) had clinical events: 42 strokes, 38 ipsilateral to the carotid stenosis, 22 TIAs, 14 MIs, and 3 deaths (related annual incidence rate was 2.35% for overall strokes, 2.12% for ipsilateral strokes, 1.23% for TIAs, 0.78% for MIs, and 0.17% for deaths). Among the 394 subjects without progressive carotid disease, 3 (0.8%) had an ipsilateral stroke, 2 (0.5%) had a contralateral stroke, 6 (1.5%) had MI, and 2 (0.5%) subjects died. Regarding subjects with progressive carotid disease, 35 (27.1%) had an ipsilateral stroke, 22 (17.0%) had TIA, 2 (1.6%) had contralateral stroke, 8 (6.2%) had MI, and 1 (0.8%) died. Progression of carotid stenosis was significantly associated with the occurrence of vascular events. Table 2 presents univariate analyses with all potential predictors of combined vascular events. A further subgroup analysis for different levels of stenosis progression was not performed given the low number of subjects with progression by 2 or 3 categories (5.4% and 0%, respectively).

In the multivariable Cox model, risk for combined events was predicted by progressive ICA stenosis (hazard ratio, 21.57; 95% CI, 11.81–39.39; $P<0.001$) after adjusting the model for age, smoking, diabetes mellitus, hypertension, antidiabetics, and the interaction term age and analysis time. Finally, in the competing risks regression analysis, ICA stenosis progression significantly predicted the risk of ipsilateral stroke (subhazard ratio, 31.97; 95% CI, 9.83–103.91; $P<0.001$) after adjusting the model for the same covariates (Figure).

Table 2. Univariate Cox Regression Analyses Considering as Outcome Variable the Incidence of Combined Vascular Events

Variables	Hazard Ratio	SE	95% Confidence Interval
Age	1.03	0.02	0.995–1.055
Sex	1.22	0.27	0.783–1.893
Smoking	1.52	0.36	0.959–2.416
Diabetes mellitus	1.36	0.32	0.856–2.170
Dyslipidemia	0.92	0.21	0.595–1.428
Hypertension	1.64	0.45	0.959–2.797
CAD	0.87	0.24	0.503–1.502
Antihypertensives	1.33	0.32	0.824–2.139
Antidiabetics	1.38	0.34	0.854–2.218
Statins	0.81	0.19	0.516–1.272
Antiplatelets	1.33	0.31	0.845–2.083
Progressive carotid stenosis	20.90	6.34	12.535–37.880

CAD indicates coronary artery disease.

Table 1. Demographic and Clinical Characteristics

	Progressive Stenosis (n=129)	Nonprogressive Stenosis (n=394)	Difference (Test) *P*
Age, mean (SD)	74 (8)	73 (8)	0.069*
Women, n (%)	56 (43.4)	185 (47.0)	0.483†
Hypertension, n (%)	102 (79.1)	267 (67.8)	0.014†
Dyslidipemia, n (%)	62 (48.1)	236 (59.9)	0.018†
Diabetes mellitus, n (%)	43 (33.3)	93 (23.6)	0.070†
Smoking, n (%)	28 (21.7)	104 (26.4)	0.287†
CAD, n (%)	21 (16.3)	95 (24.1)	0.063†
Antihypertensives, n (%)	91 (70.5)	246 (62.4)	0.095†
Antidiabetics, n (%)	40 (31.0)	88 (22.3)	0.047†
Statins, n (%)	53 (41.1)	163 (41.4)	0.954†
Antiplatelets, n (%)	75 (58.1)	214 (54.3)	0.448†

CAD indicates coronary artery disease; and SD, standard deviation.
*Two-sample *t* test.
†Pearson χ^2 test.

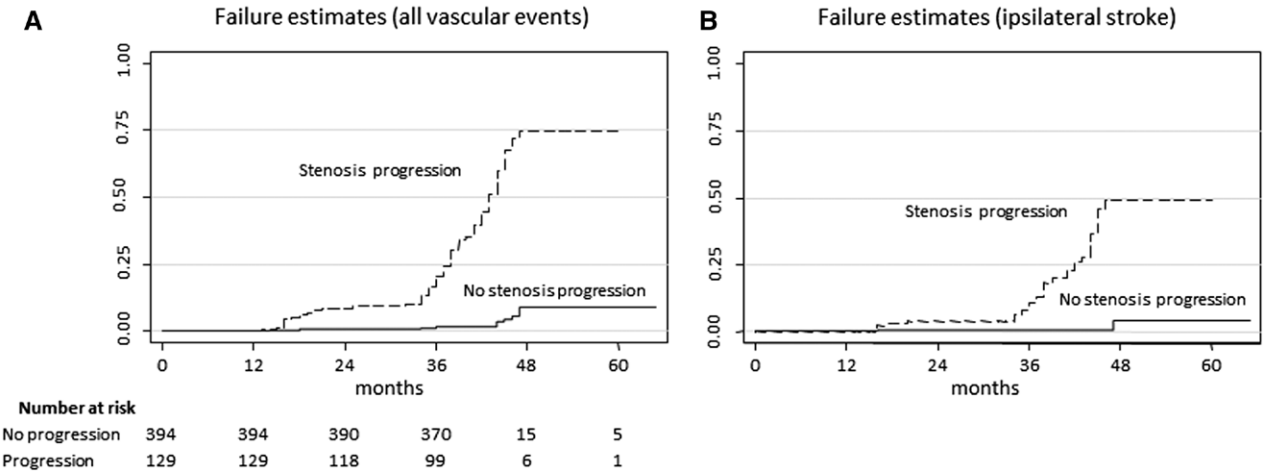

Figure. **A**, Failure estimates for combined vascular events. **B**, Failure estimates for ipsilateral strokes.

Discussion

Our study shows that 1-year ultrasound monitoring of moderate ACS can help in identifying subjects at higher vascular risk. Progressive lumen narrowing is significantly associated with the risk of ipsilateral stroke, contralateral stroke, MI, and death. This finding suggests that carotid stenosis should be considered as part of a generalized atherosclerosis process involved in the pathogenesis of vascular accidents at different organic levels. For this reason, the need for more aggressive treatment strategies in these subgroups of subjects with ACS should be stressed. Additional ultrasound follow-up evaluations might have allowed a more comprehensive assessment of carotid plaque characteristics.[6] We attempted to obtain reliable prognostic information without overburdening health service resources; therefore, we performed 2 ultrasound evaluations during a short time interval to avoid patient dropouts. Moreover, among measures potentially able to provide information about plaque-associated risk, we considered the degree of stenosis, which may be evaluated in a relatively simple and reproducible way.

Our results may have implications for disease monitoring and treatment strategies in the clinical practice. Faster rates of progression of moderate ACS as evidenced by a short-term ultrasound monitoring should be considered a marker of increased risk for vascular events.

Disclosures

None.

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