Progression of Carotid Stenosis Detected by Duplex Ultrasonography Predicts Adverse Outcomes in Cardiovascular High-Risk Patients

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Background and Purpose—The progression of carotid stenosis reflects the activity of atherosclerotic disease and may indicate a risk for systemic atherothrombotic complications. We investigated whether progressive carotid stenosis determined by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients.

Methods—We prospectively studied 1065 of 1268 consecutive patients initially asymptomatic with respect to carotid disease. Carotid ultrasound investigations at baseline and after a median of 7.5 months (range, 6 to 9 months) were performed to identify patients with progressive stenosis as defined by Doppler velocity criteria. Patients were then followed up clinically for a median of 3.2 years for the occurrence of major adverse cardiovascular events (composite MACEs: myocardial infarction, percutaneous coronary or peripheral interventions, coronary or vascular surgery, amputation, stroke, and all-cause mortality).

Results—We found progressive carotid stenosis in 93 patients (9%) by ultrasound and thereafter recorded 495 MACEs in 421 patients (40%) during clinical follow-up. Patients with progressive carotid stenosis had a significantly increased risk for cardiovascular events compared with patients with nonprogressive disease: adjusted hazard ratios and confidence intervals were 2.01 for composite MACEs (95% CI, 1.48 to 2.67, $P<0.001$), 2.38 for myocardial infarction (95% CI, 1.07 to 5.35, $P=0.044$), 1.59 for any coronary event (95% CI, 1.10 to 2.28, $P=0.011$), 2.00 for stroke (95% CI, 1.02 to 4.11, $P=0.035$), 2.42 for any peripheral vascular event (95% CI, 1.61 to 3.62, $P<0.001$), and 1.75 for cardiovascular death (95% CI, 1.03 to 2.97, $P=0.039$).

Conclusion—Progression of carotid stenosis within a 6- to 9-month interval detected by duplex ultrasound predicts midterm clinical adverse events of atherosclerosis in high-risk patients affecting the coronary, cerebrovascular, and peripheral circulations. **(*Stroke*. 2007;38:2887-2894.)**

Key Words: carotid artery ■ carotid stenosis ■ stroke ■ ultrasound

Atherosclerosis is a systemic disease that frequently affects extensive parts of the arterial tree.[1,2] The coincidence of clinical sequelae of coronary, cerebrovascular, and peripheral artery disease therefore is encountered in a considerable proportion of patients.[3] Unstable atherosclerotic plaques in any vascular segment are associated with a markedly increased risk for clinical complications, and it has been demonstrated that patients with atherothrombotic complications in 1 vessel area frequently also show unstable plaques in other vascular segments.[4] Based on these observations, the concept of "vulnerable patients" emerged,[4,5] ie, patients exhibiting active atherosclerotic disease in multiple vascular locations with a high likelihood of experiencing adverse events in the near future. Scientific efforts to identify these cardiovascular highest-risk patients early are numerous, but concepts ready for implementation in clinical routine remain scarce.

With continuous expansion of the scope of preventive cardiovascular therapies, there is a growing interest in cardiovascular risk stratification strategies. In this context, several large-scale studies investigated the utility of carotid ultrasound scanning.[6–10] Carotid plaque burden is associated with the extent of coronary and peripheral artery disease and increases the risk for stroke.[6,7] Progression of carotid stenosis reflects the activity of atherosclerotic disease[11] and is associated with incident stroke.[12,13] However, it remains unclear whether progressive carotid stenosis also indicates a risk for complications of atherosclerosis affecting other parts of the

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Table 1. Criteria for Quantification of the Degree of Carotid Stenosis by Duplex Ultrasound

	0% to 29%	30% to 49%	50% to 69%	70% to 89%	90% to 99%	100%
PSV_{ICA}/PSV_{CCA}	<1.4	1.5 to 1.9	2.0 to 3.9	>4.0	Trickle flow	No flow
PSV_{ICA}	<120	120 to 149	150 to 249	>250		

PSV indicates peak systolic velocity; ICA, internal carotid artery; and CCA, common carotid artery. Flow velocities are given in cm/s.

circulation. We hypothesized that progressive carotid stenosis identifies patients at high risk for future clinical events of atherosclerosis in the coronary, cerebrovascular, and peripheral circulations and investigated whether the progression of carotid stenosis, as measured by duplex ultrasound, is associated with adverse outcomes in cardiovascular high-risk patients.

Methods

Study Design

We prospectively enrolled all consecutive patients who underwent duplex ultrasound investigations of the extracranial carotid arteries from March 2002 until March 2003 at our institution and who were neurologically asymptomatic in the Inflammation in Carotid Arteries Risk for Atherosclerosis Study.[11,13,14] Patients underwent a baseline carotid ultrasound investigation and a second ultrasound examination after a period of 6 to 9 months to identify those with progressive stenosis. We aimed to assess progression of carotid stenosis rather than the progression of intima-media thickness because we assumed that stenosis progression directly reflects progression of advanced atherosclerosis, and detection has immediate clinical implications, particularly in cases of high-grade stenoses. After the second ultrasound examination, patients were followed up clinically for the occurrence of cardiovascular end points.

Patient Selection

We intended to include cardiovascular high-risk patients with a high likelihood for progressive carotid disease and therefore chose a hospital referral–based approach. Our ultrasound laboratory serves the Departments of Internal Medicine of a 2200-bed university hospital. The main indications for performing carotid ultrasound were carotid bruits, multiple cardiovascular risk factors, and known atherosclerotic disease in other vessel areas (coronary or peripheral artery disease).

Inclusion and Exclusion Criteria

Patients who were initially asymptomatic with respect to carotid artery disease were eligible, defined by a neurologist as the absence of transient ischemic attacks, amaurosis fugax, or stroke in each patient's recent 12-month history. Exclusion criteria were symptomatic carotid artery disease necessitating revascularization therapy, current infectious or inflammatory diseases, recent operations or endovascular interventions (within 14 days), the presence of bilateral carotid occlusions, or previous bilateral stent implantation or bilateral carotid endarterectomy. In patients with a degree of stenosis >70% at baseline, carotid revascularization was offered to the patient after discussion of the case with an independent neurologist. Patients with planned carotid revascularization at the baseline visit were not included in the study. The study was approved by the local review board and institutional ethics committee, and all patients provided informed consent.

We enrolled 1363 eligible patients in the study. Of these, 95 (7%) had to be excluded owing to missing duplex ultrasound follow-up data after the initial 6- to 9-month period (28 deaths; 67 refused the repeated duplex ultrasound investigation) and another 203 patients (15%) who were thereafter lost to clinical follow-up, leaving 1065 patients for the final analysis. Clinical characteristics and mortality of the 298 patients with missing follow-up data were not significantly different compared with the current study sample (data not shown).

Study End Points

The primary study end point was the occurrence of a first major adverse cardiovascular event (MACE), a composite of myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stroke, peripheral percutaneous angioplasty (PTA), peripheral vascular surgery, amputation due to critical limb ischemia, and all-cause mortality. Surgical or endovascular procedures on the carotid arteries were not included as a study end point, as these procedures might have been directly related to the qualifying carotid ultrasound investigation at study entry or during follow-up. Secondary end points were the occurrence of (1) MI; (2) any coronary event, including MI, PCI, or CABG; (3) any stroke; (4) any peripheral vascular event, including amputation, lower-limb PTA, or lower-limb vascular surgery; and (5) cardiovascular death.

We intended to predict cardiovascular events by repeated carotid ultrasound investigations. Therefore, the occurrence of study end points was assessed during a time interval starting after the second carotid ultrasound investigation. Cardiovascular events occurring between the first and second carotid ultrasound investigation were not considered study end points, as these events could not have been predicted by the findings from the repeated ultrasound investigations.

Color-Coded Duplex Sonography and Grading of Stenoses

Duplex examinations at baseline and during follow-up were performed on an Acuson 128 XP10 machine with a 7-MHz linear-array probe (Acuson, Mountain View, Calif) by experienced technical assistants who were supervised by 2 of the authors. Duplex operators were blinded with respect to the patients' clinical data, laboratory findings, and previous ultrasound investigations. Duplex grading of carotid stenoses was done as described previously[15–17] (Table 1). Progression of atherosclerotic disease was defined as an increase of the degree stenosis by at least 1 category; progression of stenosis in either 1 or both carotid arteries was considered indicative of progressive disease.[11] We previously reported acceptable agreement between duplex ultrasound and angiography.[17] In the present study, we found an excellent interobserver agreement for identifying progressive disease in a subgroup of 100 patients investigated by 2 blinded observers in parallel at baseline and follow-up (κ=0.90, 95% CI, 0.84 to 0.96).

Surveillance Protocol

After inclusion in the study and a baseline ultrasound examination, patients were scheduled for a follow-up visit 6 to 9 months after the initial presentation for clinical reevaluation and repeated duplex scanning. Thereafter, patients were clinically reevaluated every 6 months at the outpatient ward of our department until December 2005. A follow-up questionnaire was then sent to each patient during January 2006 to reevaluate the occurrence of MACEs. Information from the follow-up questionnaire was validated by reviewing the original hospital discharge reports of corresponding readmissions due to MACEs. If the follow-up questionnaire was not returned, personal telephone contact to the patients or to the treating physicians was established. Further information was obtained by reviewing the hospital discharge reports of any other readmission during the follow-up period. The performance of PCI, PTA, CABG, peripheral vascular surgery, and amputation was validated by review of the

Table 2. Demographic Data and Clinical Characteristics of 1065 Patients With Progressive vs Nonprogressive Carotid Stenosis After a Follow-Up Period of a Median 7.5 Months (Range, 6 to 9 Months)

	Nonprogressive Disease (n=972, 91%)	Progressive Disease (n=93, 9%)	*P* Value
Age, y	69 (61 to 76)	71 (65 to 78)	0.019
Men/women	607 (62%)/365 (38%)	61 (66%)/32 (34%)	0.63
Body mass index, kg/m^2	26.2 (24.0 to 28.7)	25.7 (23.8 to 28.4)	0.41
Smoking status at study entry			0.026
Nonsmokers	716 (73)	62 (66%)	
1 to 10 cigarettes daily	99 (10%)	12 (13%)	
11 to 20 cigarettes daily	74 (8%)	15 (16%)	
>20 cigarettes daily	83 (9%)	4 (5%)	
Arterial hypertension	660 (68%)	71 (76%)	0.12
Total cholesterol, mg/dL	205 (175 to 238)	201 (175 to 225)	0.14
LDL cholesterol, mg/dL	118 (94 to 148)	117 (87 to 137)	0.14
HDL cholesterol, mg/dL	50 (42 to 60)	49 (40 to 61)	0.57
History of diabetes mellitus	215 (22%)	27 (29%)	0.16
Glycated hemoglobin A1, %	5.9 (5.6 to 6.5)	6.2 (5.7 to 7.0)	0.023
Family history of atherosclerosis	536 (55%)	54 (58%)	0.67
History of peripheral artery disease			0.020
None	567 (58%)	42 (45%)	
Asymptomatic	232 (24%)	24 (25%)	
Intermittent claudication	173 (18%)	27 (29%)	
History of coronary artery disease (CCS stage)			0.94
None	457 (47%)	40 (43%)	
I	302 (31%)	30 (32%)	
II	183 (19%)	20 (22%)	
III	30 (3%)	3 (3%)	
History of MI	230 (24%)	27 (29%)	0.30
History of stroke	153 (16%)	23 (25%)	0.037
Baseline degree of stenosis, worse side			<0.001
0% to 29%	549 (57%)	19 (20%)	
30% to 49%	103 (11%)	18 (19%)	
50% to 69%	220 (23%)	35 (38%)	
70% to 89%	72 (7%)	20 (22%)	
90% to 99%	28 (3%)	1 (1%)	
Serum creatinine, mg/dL	1.1 (0.93 to 1.23)	1.0 (0.94 to 1.19)	0.42
Statin treatment	557 (57%)	63 (68%)	0.066
Aspirin treatment	546 (56%)	56 (60%)	0.51
Clopidogrel treatment	232 (23%)	29 (31%)	0.096
Angiotensin-converting enzyme inhibitor/angiotensin blocker	698 (72%)	73 (79%)	0.18
High-sensitivity C-reactive protein, mg/dL	0.28 (0.13 to 0.61)	0.54 (0.22 o 0.80)	<0.001

original procedure protocols. End points were adjudicated by 2 independent observers who were blinded to the patients' baseline clinical and ultrasound data.

Definitions

MI and stroke were defined according to published guidelines.[18,19] For stroke, cranial computed tomography or magnetic resonance imaging was used for confirmation of the diagnosis. Definitions of traditional cardiovascular risk factors are given elsewhere.[11]

Statistical Methods

Continuous data are presented as the median and interquartile range (from the 25th to the 75th percentile), or the total range. Discrete data are given as counts and percentages. We used Yates' corrected χ^2 tests, Mann-Whitney *U* tests, exact tests, and Spearman's correlation coefficients for univariate analyses, as appropriate. Multivariable Cox proportional-hazards models were applied to assess the association between progressive carotid stenosis and a first MACE occurring after the second carotid

ultrasound investigation. Baseline variables that were unbalanced between patients with and without progressive carotid stenosis indicated by a value of $P<0.2$ were entered into multivariable models to adjust for potentially confounding effects. Additionally, we adjusted for established risk factors for MACEs. Results of the Cox models are presented as the hazard ratio (HR) and 95% CI. We investigated the association between progressive carotid stenosis and the risk for the composite end point MACE in predefined subgroups. Assessment of model fit was done according to standard procedures. A 2-sided value of $P<0.05$ was considered statistically significant. Calculations were performed with Stata (release 8.0, Stata, College Station, Tex) and SPSS for Windows (version 12.0, SPSS Inc, Chicago, Ill).

Results

Patient Characteristics and Progressive Disease

The median age of the study population was 69 years (interquartile range, 61 to 76 years) and 668 patients (63%) were male. In 17% of the patients (176/1065), a history of stroke was found without residual or recurrent symptoms. In these patients, the median time interval between prior stroke and inclusion in the study was 5.0 years (range, 2.1 to 12.0 years).

During the initial study period of a median 7.5 months (range, 6 to 9 months), progression of carotid lesions was found in 93 of 1065 patients (9%) by ultrasound. Six patients had progressive lesions in both carotid arteries. Another 6 patients developed a de novo occlusion of a carotid artery, all having an ipsilateral subocclusive stenosis (90% to 99%) at baseline. Progression by 1 category of the degree of stenosis was found in 81 of 93 patients (87%), progression by 2 categories in 11 of 93 patients (12%), and progression by 3 categories in 1 of 93 patients (1%). In 9 of 1065 patients (0.8%), plaque regression by 1 category was recorded; these patients were analyzed in the group of patients with nonprogressive disease.

Patients with progressive disease were older, were more frequently smokers, had higher levels of glycohemoglobin, had a higher degree of carotid stenosis at baseline, more frequently had coincident peripheral arterial disease, and had a history of stroke compared with patients with nonprogressive disease (Table 2).

Follow-Up for MACEs

We recorded 495 MACEs in 421 patients (40%) during a median 3.2 years (interquartile range, 2.9 to 3.5 years) of clinical follow-up starting at the time of the second carotid ultrasound investigation. Events included 42 MIs (3.9%), 64 PCIs (6%), 47 CABGs (5%), 56 strokes (5%), 22 peripheral vascular surgical operations (2%), 98 peripheral PTAs (9%), 9 amputations (0.8%), and 157 deaths (15%). Of 56 strokes, 53 were ischemic and 3 were hemorrhagic; clinically, 36 strokes were considered minor and 20 were major. According to the ipsilateral baseline degree of carotid stenosis, 18 strokes occurred in patients with a degree <30%, 10 in degrees of 30% to 49%, 17 in degrees of 50% to 69%, and 11 with a degree of stenosis of ≥70%. Nine of 56 strokes occurred in patients with progressive carotid disease, and 7 of these strokes were ipsilateral to the progressive stenosis. All peripheral vascular interventions were done in symptomatic patients due to either severe claudication or critical limb ischemia. Of 157 deaths, 112 (71%) were cardiovascular. Cumulative event-free survival rates for a first MACE at 1, 2, and 3 years were 86% (95% CI, 0.84 to 0.88), 76% (95% CI, 0.73 to 0.79), and 65% (95% CI, 0.62 to 0.68), respectively.

Table 3. Multivariable Cox Proportional-Hazards Models Assessing the Association Between Progressive Carotid Artery Disease Within 6 to 9 Months, Measured by Duplex Ultrasound, and the Risk for MACEs

	HR	95% CI	*P* Value
Progressive carotid stenosis	2.01	1.48 to 2.67	<0.001
Age, y	1.00	0.99 to 1.02	0.49
Female	0.95	0.76 to 1.18	0.63
Current smoking	0.97	0.76 to 1.22	0.77
Hypertension	1.26	0.99 to 1.60	0.053
Glycated hemoglobin A1, %	1.00	0.97 to 1.04	0.73
LDL cholesterol, mg/dL	0.99	0.98 to 1.01	0.50
High-sensitivity C-reactive protein, mg/dL	1.29	1.14 to 1.45	<0.001
History of MI	1.43	1.14 to 1.80	0.002
History of stroke	0.94	0.71 to 1.24	0.65
History of peripheral artery disease	1.42	1.15 to 1.75	0.001
Statin treatment	0.88	0.71 to 1.09	0.24
Baseline degree of stenosis			
<50%	1.0	...	...
50% to 70%	1.76	0.95 to 2.41	0.070
>70%	1.81	1.04 to 3.44	0.039

Progressive Carotid Disease and Risk for MACEs

Patients with progressive carotid stenosis during the initial 6- to 9-month period had a significantly increased risk for the occurrence of clinical adverse events in the coronary, cerebrovascular, and peripheral circulations (Table 3): adjusted HRs and 95% CIs for patients with progressive compared with nonprogressive carotid disease were 2.01 for composite MACEs (95% CI, 1.48 to 2.67, $P<0.001$), 2.38 for MI (95% CI, 1.07 to 5.35, $P=0.044$), 1.59 for any coronary event (95% CI, 1.10 to 2.28, $P=0.011$), 2.00 for stroke (95% CI, 1.02 to 4.11, $P=0.035$), 2.42 for any peripheral vascular event (95% CI, 1.61 to 3.62, $P<0.001$), and 1.75 for cardiovascular death (95% CI, 1.03 to 2.97, $P=0.039$) (Figure 1). All 6 patients with bilateral progression experienced an MACE during follow-up.

Investigating the risk for the composite end point MACE in predefined subgroups (Figure 2), we observed that progressive carotid stenosis predicted an adverse outcome irrespective of the patients' traditional cardiovascular risk factors, prevalent comorbidities, or baseline degree of carotid stenosis. Patients with progressive carotid disease without statin therapy at baseline exhibited a higher risk for an MACE (HR=3.53; 95% CI, 2.18 to 5.42) compared with patients with statin therapy (HR=1.66; 95% CI, 1.11 to 2.28), showing a significant interaction (log-likelihood ratio test $P=0.039$).

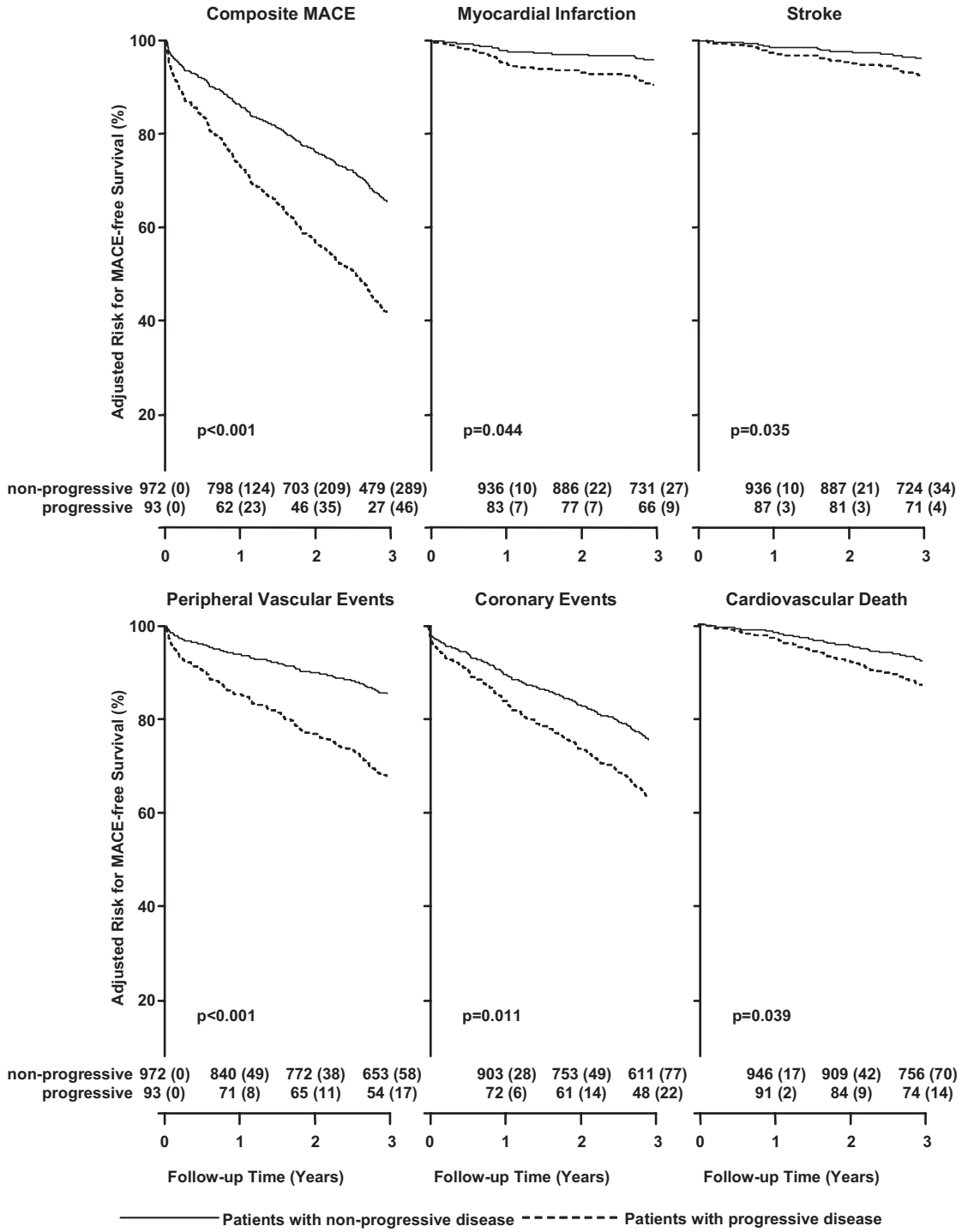

Figure 1. Association between progressive carotid artery disease within 6 to 9 months measured by Doppler ultrasound criteria (as indicated in Table 1) and risk for MACEs (composite of MI, PCI/PTA, coronary or peripheral vascular surgery, amputation, stroke, and death). Coronary events included MI, PCI/PTA, and CABG; peripheral vascular events included amputation, peripheral PTA, and peripheral vascular surgery. Risk estimates were calculated by multivariable Cox proportional-hazards analysis adjusted for risk factors listed in Table 3.

Discussion

We have demonstrated that progressive carotid disease during a short-term interval predicts medium-term clinical adverse events of atherosclerosis in the coronary, cerebrovascular, and peripheral circulations in cardiovascular high-risk patients. These findings suggest that disease progression in the carotid arteries indicates a systemic risk for complications of atherosclerosis. Ultrasound scanning of the carotid arteries in a 6- to 9-month interval identifies patients at particularly high risk at an early stage.

Prior studies have linked progressive carotid stenosis exclusively to stroke rather than to complications of cardiovascular disease in general.[12,13] A study by Rothwell et al,[5] however, suggested a possible link between carotid

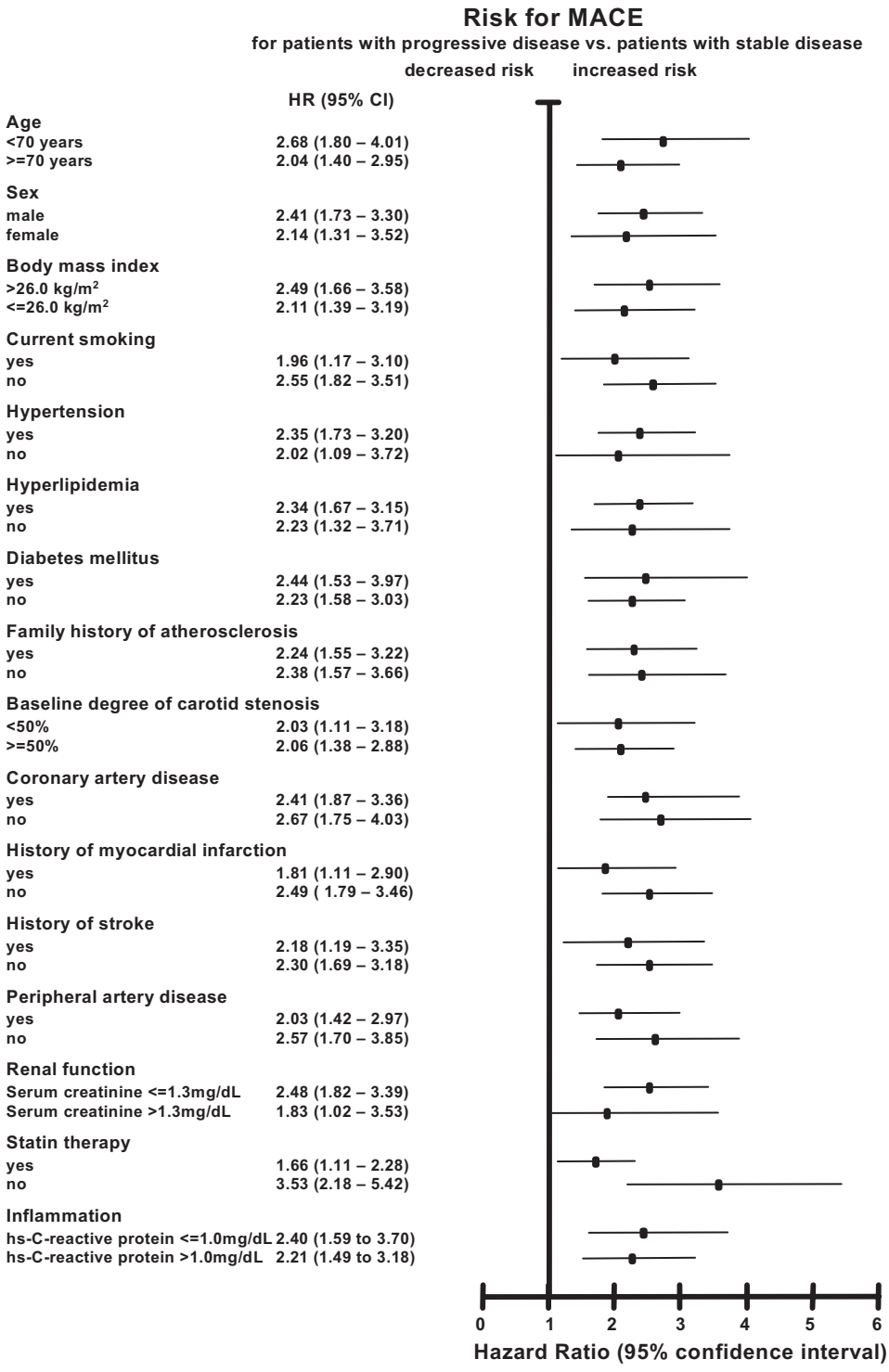

Figure 2. Risk for MACEs (composite of MI, PCI/PTA, coronary or peripheral vascular surgery, amputation, stroke, and death) of patients with progressive carotid stenosis defined by Doppler ultrasound criteria (listed in Table 1) compared with patients with nonprogressive disease (referent) according to demographic data, cardiovascular risk factors, and comorbidities. HRs and 95% CIs were calculated by multivariable Cox proportional-hazards analyses.

plaque and nonstroke vascular death, without further delineating the cardiovascular outcomes. There is also evidence from small studies of an association between high-risk carotid plaques and complex coronary lesions and coronary adverse events.[20,21] The present investigation has demonstrated that progressive carotid stenosis indicates an increased risk for clinical adverse events of atherosclerosis in the coronary and peripheral as well as in the cerebrovascular circulation. In other vascular territories, particularly the coronary arteries, rupture is the predominant cause of atherothrombotic events. Our findings therefore suggest that examination of progressive

carotid disease may identify patients with multiple rupture-prone plaques in the vasculature.

It seems important to note that progressive carotid disease was confirmed as a robust marker of cardiovascular risk in virtually all investigated subgroups and added to the risk prediction of traditional risk factors. This observation supports the view that progressive carotid atherosclerosis, irrespective of a patient's cardiovascular risk profile or the baseline degree of stenosis, serves as a powerful prognostic marker for incident clinical complications. As yet, repeated ultrasound investigations are advocated only in patients with advanced-grade stenoses. Our data suggest that repeated ultrasound also should be done in patients with plaques and moderate stenoses to look for progressive disease.

Interpreting the findings among different subgroups, we observed that patients with progressive carotid disease who received statin therapy exhibited a lower risk for future MACEs than did patients with progressive disease without statins. This may reflect the pleiotropic effects of statins in the vasculature.[22] Besides cholesterol lowering, stabilization of the atherosclerotic plaque, reduction of oxidative stress, improvement of endothelial function, and potent inhibition of vascular inflammation have been attributed to the use of statins.[22,23] It thus seems mandatory to advocate high-dose statin treatment for patients with progressive carotid disease, targeting an LDL cholesterol level to $<$100 mg/dL.[24]

With respect to the underlying mechanisms for our observation, unrecognized systemic factors seem to determine the association between progressive carotid atherosclerosis and complications of atherosclerosis in other vessel areas. Several investigators have noted the presence of multiple vulnerable plaques in patients at risk for cardiovascular events and reiterated the importance of evaluating the entire arterial tree in all patients with an atherothrombotic event.[25,26] Inflammation affecting multiple segments of the arterial tree seems to be an important pathophysiologic substrate in the process of generalized atherosclerosis. Inflammation is a trigger for endothelial dysfunction and plaque growth and has been demonstrated to predict progression of atherosclerosis.[11] Nevertheless, in the present study, progressive carotid stenosis predicted MACEs irrespective of the patients' inflammatory status, suggesting that additional pathophysiologic factors must be considered. Aside from inflammation, arteriosclerosis and subsequent arterial stiffening result in an environment fostering atherosclerosis progression and are also known to predict cardiovascular events.[27] Finally, vascular remodeling should be considered a potentially important determinant for progression of vascular stenosis. Remodelling is not directly related to atheroma burden and may occur in patients with both stable and unstable plaques.[28]

Limitations

We are aware that the hospital referral–based nature of the cohort is a potential study limitation. However, given the expected low percentage of patients in the general population with progressive carotid disease, a population-based approach did not seem feasible. The indications for performing carotid ultrasound at the Departments of Internal Medicine were consensually defined, rather homogeneous, and reproducible. Nevertheless, the generalizability of our findings to younger individuals and ethnic/racial minorities is uncertain. In addition, we examined progression in patients with a high prevalence of baseline MI and stroke. Whether these findings are applicable to unselected community-based individuals also remains to be determined.

The lack of data on plaque burden, intima-media thickness, plaque characteristics like echolucency, and vascular remodeling during the study period must be recognized as another limitation of the study. Based on the present findings, studies investigating the underlying pathophysiology of stenosis progression and its relation to atherothrombotic events in multiple vascular territories are deemed necessary.

Conclusions

Patients with progression of carotid stenosis are at high risk for medium-term adverse events of atherosclerosis affecting the coronary, peripheral, and cerebrovascular circulations, irrespective of the individual's cardiovascular risk profile and prevalent atherosclerotic comorbidities. Duplex scanning of the carotid arteries at 6- to 9-month intervals helps to identify patients who would benefit from intensive medical therapy.

Disclosures

None.

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