Common Carotid Artery Intima-Media Thickness and the Risk of Stroke Recurrence

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Background and Purpose—Increased common carotid artery intima-media thickness (CCA-IMT) has been associated with an increased risk of myocardial infarction and stroke. We investigated the relationship between CCA-IMT and recurrent stroke in a cohort of ischemic stroke patients.

Methods—High-resolution B-mode ultrasonographic measurements of the CCA-IMT were performed in a consecutive series of 238 patients hospitalized in our institution with first-ever ischemic stroke. Stroke risk factors and secondary prevention therapies were documented. Patients were followed-up prospectively and the outcome event of interest was recurrent stroke.

Results—During a mean follow-up period of 28.9 months (range: 6 to 60 months), 27 recurrent strokes were documented. Patients who experienced recurrent cerebrovascular events had significantly \( P = 0.005 \) higher CCA-IMT values (1.01 mm, 95% CI:0.92 to 1.11 mm) than subjects who were free of stroke recurrence (0.88 mm, 95% CI:0.85 to 0.91 mm). After adjustment for baseline characteristics, risk factors and stroke subtypes and secondary prevention therapies increasing CCA-IMT was found to be an independent predictor of stroke recurrence. For each increment of 0.1 mm in CCA-IMT the probability of experiencing recurrent stroke increased by 18.0% (95% CI:2.0% to 36.0%, \( P = 0.027 \)).

Conclusions—Increased CCA-IMT values are associated with a higher risk of long-term stroke recurrence. (Stroke. 2006; 37:1913-1916.)

Key Words: atherosclerosis ■ carotid arteries ■ recurrence ■ stroke

A growing body of evidence supports that the intima-media thickness of the common carotid artery (CCA-IMT) can be regarded as an early marker of atherosclerosis. Furthermore, increased CCA-IMT has been associated with conventional cardiovascular risk factors, the presence of other localizations of atherosclerosis and an increased risk of myocardial infarction and stroke. However, there are limited data regarding the potential significance of CCA-IMT in predicting recurrent cerebrovascular events. Assuming that in addition to established risk factors, increased CCA-IMT may constitute an important risk marker for recurrent stroke, the present longitudinal study aimed to evaluate the relationship between CCA-IMT and stroke recurrence in a cohort of consecutive first-ever ischemic stroke (IS) patients.

Materials and Methods

Study Population

A series of 324 consecutive, first-ever acute stroke patients, admitted to the acute stroke unit and the general neurology ward of our institution between January 2000 and December 2003 were screened. All patients were included in “The Athens Stroke Registry,” a computerized prospective observational data bank, gathered in 2 university teaching hospitals. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, IS was classified based on etiopathogenetic mechanisms into the following groups: large artery atherosclerotic stroke (LAA), cardioembolic stroke (CE), small artery occlusion or lacunar infarction (LAC), infarction of other determined origin and infarction of undetermined cause (IUC). Height and weight were recorded and body mass index was calculated as weight to height squared. Risk factors were documented as previously described.

Carotid Ultrasonography Studies

The CCA-IMT of all screened patients was assessed using high resolution B-mode ultrasonography (Acuson 128XP, equipped with a 7-MHz linear-array transducer), within the first 5 days of ictus. The CCA-IMT value was defined as the mean of the IMT of the right and left IMT of the CCA, calculated from 10 measurements on each side, taken 10 mm proximal to the carotid bifurcation. The previously anatomically validated lumen/intima leading edge (I-line) to media/ adventitia leading edge (M-line) method was used. All ultrasonographic measurements were performed by the same experienced sonographer (C. P.), who was blinded to any clinical information about the study population.

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Follow-Up
For the needs of the present study only cases fulfilling the following conditions were recruited (n=253): (1) first-ever IS; (2) ultrasonographic measurements of the CCA-IMT (patients who succumbed during the first 1 to 2 days after admission or patients with unavailable CCA-IMT measurements because of technical reasons were excluded); (3) white origin. Secondary stroke prevention therapies (lipid-lowering, antidiabetic and antihypertensive medications, antiplatelet agents, oral anticoagulants) were administered in the entire cohort in keeping to the European Stroke Initiative recommendations.14 All surviving patients were followed-up prospectively at 1 month, 3 months, 6 months and every 6 months thereafter by a study investigator and a trained nurse by as previously reported.15 Follow-up was routinely performed at the outpatient clinics of our institution. When patients failed to attend their regular follow-up assessments at the hospital, they were contacted by telephone calls. Furthermore, we conducted a face-to-face examination in the patients’ place of residence in cases with severe residual handicap and in patients who missed 2 or more scheduled consecutive follow-up evaluations. The outcome events of interest was recurrent stroke, defined as cerebrovascular events of sudden onset, lasting for >24 hours, clearly resulting in an increase of an existing or in a new neurological deficit.15 They were determined after evaluation of all the available information obtained from hospital records, physicians’ notes in private practice, necropsy findings or death certificates, and the patients’ clinical presentation at the regular follow-up assessments. A total of 15 patients who were lost during the follow-up period (8 cases after having moved from their initial place of residence failed to attend the follow-up evaluations and to return the telephone calls, 3 cases of immigrant workers returned to their country of origin in the first months following the index event, 4 cases declined to continue either the clinical or the telephone follow-up evaluations without providing any specific reasons) were excluded from further evaluation.

Statistical Analysis
Statistical comparisons were performed between patients with and without recurrent stroke in terms of demographic features, stroke risk factors, secondary prevention therapies and carotid ultrasonographic measurements using the χ2 test (or the Fisher exact test) and the unpaired t test (or Mann–Whitney U test) as indicated. We also used ANCOVA (analysis of covariance) to compare the mean CCA-IMT between the 2 stroke subgroups, after adjusting for baseline characteristics. To evaluate which factors contribute to long-term recurrence, we performed Cox proportional hazards analyses. In the initial univariate analyses the association of demographic characteristics, stroke risk factors and subtypes, secondary prevention therapies and CCA-IMT with stroke recurrence was investigated. All factors that contributed to the outcome in the initial univariate analyses at P<0.1 were included in the multivariate model as candidate variables and then removed by a backward stepwise selection procedure. In the final multivariate analysis of covariance (ANCOVA), robustness of multivariate models, we repeated all multivariate analyses excluding cases with unavailable CCA-IMT measurements because of technical reasons.

Results
The final studied population fulfilling all the above-mentioned inclusion criteria consisted of 238 first-ever IS patients. The distribution of IS subtypes was as follows: LAA 24.8% (n=59), CE 25.6% (n=61), LAC 29.4% (n=70) and IUC 20.2% (n=48). During the follow-up period (mean: 28.9 months, range: 6 to 60 months), 51 (21.4%) deaths and 27 (11.3%) recurrent cerebrovascular events (21 cases of IS [8 cases of LAA, 5 cases of IUC, 4 cases of CE and 4 cases of lacunar infarction], 2 cases of intracerebral hemorrhage and 4 cases with unspecified type of recurrence because of lack of follow-up brain imaging) were documented. Patients who experienced recurrent stroke were significantly older (P=0.035) and had a significantly higher
frequency of coronary heart disease (CHD; \( P = 0.048 \)) and of transient ischemic attacks (TIAs; \( P = 0.015 \)) before the IS in comparison to subjects with no recurrent stroke during the observation period (Table). Patients in the recurrence group had significantly (\( P = 0.005 \)) higher CCA-IMT values (1.01 mm, 95% CI: 0.92 to 1.11 mm) than subjects who were free of stroke recurrence (0.88 mm, 95% CI: 0.85 to 0.91 mm) even after adjustment for demographic characteristics and stroke risk factors.

The association of baseline characteristics, stroke subtypes, secondary prevention therapies and CCA-IMT with stroke recurrence was evaluated using univariate Cox proportional hazards analyses. The following variables were significantly related to stroke recurrence and were therefore selected for entry into the final multiple-variable model: age (RR per 10-year increase: 1.83, 95% CI: 1.21 to 2.75; \( P = 0.004 \)), CHD (RR: 2.59, 95% CI: 1.13 to 5.94; \( P = 0.024 \)), hypertension (RR: 2.13, 95% CI: 0.91 to 5.12; \( P = 0.098 \)), history of TIAs (RR: 2.82, 95% CI: 1.19 to 6.67; \( P = 0.018 \)), CCA-IMT (RR per 0.1 mm increase: 1.20, 95% CI: 1.08 to 1.34; \( P = 0.001 \)). The multivariate Cox regression analyses (performed both with the backward-selection and forward-selection procedure) revealed only increasing age (RR per 10-year increase: 2.31, 95% CI: 1.23 to 4.34; \( P = 0.009 \)), history of TIAs (RR: 3.15, 95% CI: 1.10 to 9.01; \( P = 0.033 \)) and increasing CCA-IMT as independent outcome predictors. For each increment of 0.1 mm in CCA-IMT the probability of experiencing recurrent stroke increased by 18.0% (95% CI: 2.0% to 36.0%; \( P = 0.027 \)). Kaplan-Meier curves of groups stratified by CCA-IMT tertiles are presented in the Figure. Subjects with CCA-IMT measurements within the lower tertile had the lowest recurrence rate in comparison to the subgroups of patients with CCA-IMT values within the median or higher CCA-IMT tertile (log rank test: 18.83; \( P = 0.0001 \)).

Because CCA-IMT is a marker of atherosclerosis and has not been associated with a cardiac source of embolism, we repeated all cox regression analyses after having excluded the CE subgroup. A more robust relationship between increased CCA-IMT and the risk of recurrent stroke (RR per 0.1 mm increase: 1.27, 95% CI: 1.11 to 1.46; \( P = 0.003 \)) was documented. Moreover, we included the patients who were lost during the follow-up period in the multivariable Cox proportional hazards model and performed the analyses based on the worst-case scenario (assuming that all 15 patients had experienced recurrent stroke). The association between CCA-IMT and stroke recurrence retained its statistical significance (RR per 0.1 mm increase: 1.15, 95% CI: 1.01 to 1.42; \( P = 0.042 \)). Finally, the relationship between CCA-IMT and the different recurrent IS subgroups was investigated separately for each subtype of cerebral infarction. Increased CCA-IMT was an independent predictor of recurrent LAA stroke (RR per 0.1 mm increase: 1.25, 95% CI: 1.03 to 1.53; \( P = 0.020 \)), whereas its association with recurrent LAC (\( P = 0.134 \)), CE (\( P = 0.578 \)) and IUC (\( P = 0.369 \)) failed to reach the level of statistical significance.

**Discussion**

To the best of our knowledge, no previous study has assessed the prognostic impact of CCA-IMT in predicting stroke recurrence after adjusting for established cardiovascular risk factors, stroke subtypes and secondary prevention therapies. Carotid IMT has been associated with incident cardiovascular\(^4\) and cerebrovascular disease\(^5\) in previously healthy people. Moreover, 2 studies have identified CCA-IMT as an independent predictor of recurrent cardiovascular disease in patients who had undergone coronary artery bypass surgery\(^16\) or had prevalent CHD.\(^17\) It should be noted though that the association between CCA-IMT and stroke recurrence was not investigated in any of the former studies. Hence, the present analyses confirm and extend the findings of previous investigations regarding the prognostic significance of CCA-IMT.

Interestingly, we also noted that increased CCA-IMT correlated more strongly with the risk of recurrent LAA stroke than with other IS subtypes. Because CCA-IMT is a marker of the total atherosclerotic burden of the vascular tree,\(^1,3,12\) it is conceivable that increased CCA-IMT values may reflect a higher risk of recurrent IS caused by an underlying atherothrombotic
mechanism. However, the limited number of patients in the subgroups of recurrent IS should be taken into consideration when interpreting our data.

Increased CCA-IMT values have been related to a variety of vascular risk factors such as older age, hypertension, diabetes mellitus, hyperlipidemia and cigarette smoking. Thus, it can be argued that if IMT reflects exposure to cardiovascular risk factors, it can be considered as an intermediate factor in the causal pathway between risk factors and stroke. Interestingly, in our report increasing CCA-IMT values remained an independent predictor of stroke recurrence after adjustment for conventional risk factors. This suggests that besides being an intermediate phenotype between vascular risk factors and cerebrovascular disease, CCA-IMT may be a risk factor itself. In favor of this assumption is the strong evidence supporting a genetic component to IMT variability, with genetic factors contributing to 38% of the interindividual differences in IMT.

Finally, certain limitations of the present report should be addressed. First, a number of risk factors like smoking and hypertension were defined as binary variables although duration and severity are important. Second, the potential observer’s bias during follow-up, affecting the documentation of recurrent cerebrovascular events, represents an additional limiting factor of our study. Of note though, the recurrent strokes were mostly devastating or fatal (8 cases) and in most cases confirmed by means of hospital records, brain imaging and autopsy findings. Third, although the same experienced sonographer performed the IMT studies, it should be acknowledged that they were conducted by a hand-held transducer and not by semi-automated software. Fourth, association does not meet causality and our study having an observational nature cannot prove a causal relationship of CCA-IMT with stroke recurrence.

In the present study we provide evidence that increased CCA-IMT is an adverse prognostic factor for recurrent stroke in addition to established cardiovascular risk factors. New therapeutic approaches to carotid atherosclerosis underline the potential clinical implications of our work. Antihypertensive drugs (especially angiotensin-converting enzyme inhibitors, and β-blockers) and statin treatment have been shown to reduce the development of atherosclerosis measured as CCA-IMT. Thus, CCA-IMT may be a useful noninvasive adjunctive tool in assessing the risk of recurrent stroke and in distinguishing IS patients that may benefit the most from more aggressive secondary prevention treatment strategies.

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Disclosures
None.

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