Common Carotid Intima-Media Thickness and Framingham Risk Score Predict Incident Carotid Atherosclerotic Plaque Formation

Longitudinal Results From the Study of Health in Pomerania

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Background and Purpose—Cross-sectional studies describe a positive association between common carotid artery intima-media thickness (CCA-IMT) and carotid plaques (CP). However, longitudinal data on the predictive value of CCA-IMT for occurrence of CP are limited. Therefore, the role of increasing CCA-IMT in the atherosclerotic process is still discussed controversially.

Methods—We investigated the predictive value of CCA-IMT and the Framingham risk score (FRS) for incident CP formation in a population-based longitudinal study of 1922 subjects aged 45 to 81 years who underwent ultrasonography of both carotid arteries and received vascular risk factor assessment at baseline and after 5 years. CP was defined as any protruding focal thickening of the intima-media complex. Incident CP formation during follow-up was defined as the appearance of at least 1 CP in a previously plaque-free arterial segment (right and left common, internal, and external carotid arteries and carotid bifurcation).

Results—Among the 636 subjects without CP at baseline, 418 (66%) had at least 1 incident CP during follow-up. In a multivariable negative binominal regression model adjusted for age, gender, and the FRS, the number of arterial segments affected by incident CP was 1.53-fold higher (CI, 1.12–2.07; \( P < 0.01 \)) for subjects in the highest quartile of the overall CCA-IMT distribution compared to those in the lowest quartile.

Conclusions—Both CCA-IMT and FRS independently predict incident CP formation. The risk of CP formation may actually be underestimated in subjects with low FRS and high IMT. (Stroke. 2010;41:2375-2377.)

Key Words: atherosclerosis ■ carotid plaque ■ epidemiology ■ intima media thickness

Cross-sectional studies reported a positive association between common carotid artery intima-media thickness (CCA-IMT) and carotid plaques (CP).\(^1\) However, cross-sectional studies do not account for temporality, whereas longitudinal studies can predict the individual development of a certain variable over time. Because prospective data on the predictive value of CCA-IMT for the occurrence of CP are limited,\(^2\)–\(^4\) the role of increasing CCA-IMT in the atherosclerotic process is still discussed controversially. We used data of the Study of Health in Pomerania to further investigate this topic on a longitudinal basis.

Materials and Methods

Study of Health in Pomerania is a population-based longitudinal survey in northeastern Germany approved by our university’s Review Board. From the total population of 212,157 living in the study area, a representative sample totaling 7008 persons aged 20 to 79 years was selected from population registers. A 2-stage cluster sampling method yielded 12 5-year age strata for both genders, with each including 292 individuals. The response rate was 68.8%, resulting in 4310 participants who gave written informed consent.

Complete ultrasonography examinations (5-MHz linear-array transducer, axial resolution \(<0.5 \text{ mm}; \text{ Gateway VST, GE Diasonics}\) at baseline and after 5 years were available in 1922 subjects (962 women; mean age, 60; SD, 9.1 years). Both carotid arteries were divided into 4 segments: CCA, carotid bulb (ie, the segment between first CCA enlargement and flow divider), and internal and external carotid arteries. CP were qualitatively defined as any focal thickening of the intima-media complex protruding into the vessel lumen or as a focal increase of echogenicity with a homogeneously hyperechoic echotexture within an otherwise hypoechoic intima-media complex. Intraobserver kappa statistics based on repeat evaluation of 96 arterial segments was 0.83. Incident CP formation was defined as the appearance of at least 1 CP at follow-up in a previously plaque-free arterial segment. The number of segments with incident CP formation (with a minimum number of 0, and a maximum number of 8 segments) served as the outcome variable in further analyses. Ten IMT measurements were taken in 1-mm steps at the far wall of the most distal straight portion of each CCA. Mean
CCA-IMT was calculated as the arithmetic mean of all measurements from both sides. Details have been described elsewhere. The combined 10-year risk of stroke, TIA, acute events of coronary heart disease including death, and peripheral artery disease was determined with the Framingham risk score (FRS) for cardiovascular diseases, including the predictor variables age, diabetes, smoking, treated or untreated systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol at baseline.

Statistical Methods
We calculated quartiles of mean IMT at baseline and grouped the subjects by the 10-year FRS for cardiovascular diseases into FRS/10% to 20% and >20%. Risk ratios defined as the exponent of the regression coefficient beta for incident CP for each IMT quartile were determined in multivariable negative binominal regression models adjusted for age, gender, and FRS using SAS 9.1 (SAS).

Results
CP prevalence at baseline was 67%. Among the 636 subjects without CP at baseline (mean age, 55; SD, 7.0 years; 372 women), incident CP occurred in 418 (66%) subjects within 5 years of follow-up. The mean number of arterial segments affected by incident CP was 2.5 (SD, 1.6). Quartile limits of IMT were 0.66 mm (quartile 25), 0.75 mm (quartile 50), and 0.86 mm (quartile 75). The FRS was <10% in 289 (45%), 10% to 20% in 209 (33%), and >20% in 138 (22%) subjects.

In an age- and gender-adjusted multivariable negative binominal regression model, the number of arterial segments affected by incident CP was 1.53-fold higher for subjects in the highest quartile (β=0.42; risk ratio, 1.53; CI, 1.12–2.07; P<0.01) and 1.40-fold higher for subjects in the third quartile (β=0.34; risk ratio, 1.40; CI, 1.11–1.76; P<0.01) of the overall CCA-IMT distribution compared to those in the lowest quartile (Figure). Furthermore, the number of affected segments for subjects with a 10-year FRS >20% was 1.34-fold higher compared to those with a FRS <10% (β=0.30; risk ratio, 1.34; CI, 1.01–1.78; P<0.05).

Discussion
Our study demonstrates a temporal relationship between CCA-IMT at baseline and incident CP formation within a 5-year follow-up period. Although conceivable, a temporal relationship does not necessarily imply that increased CCA-IMT occurs in an earlier phase of the atherosclerotic process. Alternatively, both entities may be driven by the same risk factors. Because IMT has an independent effect on CP formation irrespective of age and those cardiovascular risk factors assessed by the FRS, the risk of CP formation actually may be underestimated in subjects with low FRS and high IMT, which should be considered for future risk evaluation, especially in younger subjects.

Our study design adds new insights compared to the Aging Vascular Study, the Tromsø Study, and the San Daniele Project. First, investigating the number of arterial segments affected by CP instead of the appearance of any atherosclerotic lesion in their carotid arteries at baseline provides assessment of de novo manifestation of atherosclerotic disease. Third, calculation of risk ratios instead of odds ratios may avoid overestimation of the association in longitudinal analyses, which may enhance the validity of our finding that increasing CCA-IMT can predict incident CP formation.

Our qualitative CP definition may account for the high rate of incident CP attributable to the inclusion of small plaques, which would have been excluded if recent quantitative threshold-based definitions had been applied.

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Disclosure
None.
References


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