Carotid Intima-Media Thickening Indicates a Higher Vascular Risk Across a Wide Age Range
Prospective Data From the Carotid Atherosclerosis Progression Study (CAPS)

Matthias W. Lorenz, MD; Stefan von Kegler, MD; Helmuth Steinmetz, MD;
Hugh S. Markus, FRCP; Matthias Sitzer, MD

Background and Purpose—Carotid intima-media thickness (IMT) is an independent predictor of vascular events in age groups >45 years. However, there is little information about the predictive value of IMT in younger individuals.

Methods—In the Carotid Atherosclerosis Progression Study (CAPS; n=5056; age range 19 to 90 years; mean age 50.1 years), common carotid artery (CCA) IMT, bifurcation IMT, internal carotid artery IMT and vascular risk factors were evaluated at baseline. The incidence of stroke, myocardial infarction (MI), and death was determined prospectively. Data for younger (<50 years; n=2436) and older subjects (≥50 years; n=2620) were analyzed separately using Cox proportional hazard regression models.

Results—During a mean follow-up period of 4.2 years, there were 228 cases of MI, 107 strokes, and 50 deaths. IMT at all carotid segments was highly predictive of all end points (eg, hazard rate ratios [HRRs] per 1 SD CCA-IMT increase were 1.43 [95% CI: 1.35 to 1.51] for MI, 1.47 [1.35 to 1.60] for stroke, and 1.45 [1.38 to 1.52] for MI, stroke or death; all P<0.0001). Even after adjustment for age, sex, and vascular risk factors, the predictive value of CCA-IMT and bifurcation IMT remained significant for MI and the combined end point. For the latter, the HRRs were considerably higher in the younger than in the older age group (eg, HRR per 0.1 mm CCA-IMT was 1.34 [1.16 to 1.55] vis-à-vis 1.10 [1.05 to 1.15]; P=0.011 for age-IMT interaction).

Conclusions—Carotid IMT independently predicts future vascular events. Its predictive value is at least as high in younger subjects as in older subjects. (Stroke. 2006;37:87-92.)

Key Words: carotid arteries ■ intima-media thickness ■ myocardial infarction ■ stroke

Subjects and Methods
The study sample was taken from participants in the Carotid Atherosclerosis Progression Study (CAPS), details of which have been published elsewhere.9,10 All members of a German primary healthcare scheme (n=32,708), living within a 50 km radius of 5 study sites in Western Germany, were invited to participate. Within a predefined time limit, 6962 people (21.3%) agreed to take part. They then underwent ultrasound examination at baseline to determine the IMT in several segments of the carotid arteries. Of them, 5056 (from 4 out of the 5 study sites, ranging from 19 to 90 years of age) were subsequently followed to monitor the incidence of cardiovascular events, stroke, and death. The study was approved by the ethical review committee of the University Hospital of Frankfurt am Main.

Clinical End Points
The mean duration of the follow-up period was 4.2 (range 3.0 to 5.9) years. The risk factors determined at baseline included age, sex, body mass index, mean systolic and diastolic blood pressure, treatment with antihypertensive medication (eg, beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers or...
other antihypertensive agents), low-density lipoprotein cholesterol, treatment with lipid-lowering drugs (among others, statins and fibrates), history of diabetes mellitus, and cigarette smoking quantified in pack years. Details of the risk-factor assessment protocol have already been published.10,11

Follow-up events were identified from the primary healthcare scheme records. Every time medical care was sought, the healthcare scheme was notified of the date and corresponding ICD code. The healthcare scheme records. Every time medical care was sought, the healthcare service before end of the study (n = 141, 2.8%) were censored according to the end of follow-up.

**Ultrasound Imaging**

Ultrasound imaging and IMT image analysis methods have been described in detail in earlier publications.10 In brief, ultrasonic examinations were performed with a 7.5 to 10.0-MHz linear array transducer (P7000SE; Phillips Medical System). Using antero-oblique insonation, far-wall carotid IMT was visualized bilaterally at 3 sites: the common carotid artery (CCA-IMT, 20 to 60 mm proximally from the flow divider), the carotid bifurcation (BIF-IMT, 0 to 20 mm proximally from the flow divider), and the internal carotid artery (ICA) bulb (BULB-IMT, 0 to 20 mm distally from the flow divider). The images were digitally captured during the systole of a single heartbeat for offline measurement. For 1 in every 100 subjects, vertical and horizontal calibration measurements were carried out with an ultrasound quality assurance phantom. Carotid IMT measurements were performed offline using automated imaging processing software as previously reported.10

The average intraclass correlation coefficient for interobserver reliability was 0.97 (95% CI, 0.96 to 0.98; P<0.0001) and the ±2 SD of the difference between 2 observers varied between 0.03 and 0.06 mm.10 Furthermore, the intraobserver test-retest reliability testing revealed an intraclass correlation coefficient of 0.93 (95% CI, 0.91 to 0.94; P<0.0001) and the ±2 SD of the difference between the first and second examination varied between 0.04 and 0.06 mm.10

**Statistical Analysis**

There were no differences between left and right IMT. The analysis was therefore based on the mean IMT. Univariate and multivariate Cox regression models were used to examine the relationships between IMT and the end points “MI”, “stroke”, “death by any cause”, and the combined end point of “MI, stroke or death”. For ease of interpretation and comparability with previous studies, we used nontransformed IMT values for all analyses. However, the use of log-transformed IMT values did not alter the results. In addition, IMT was analyzed as a categorical variable using quartiles. The combined end point of “MI, stroke or death”.

TABLE 1. HRRs of MI as a Function of CCA-, Carotid BIF- and ICA BULB-IMT Expressed as Quartiles and as a Continuous Variable

<table>
<thead>
<tr>
<th>Table 1. HRRs of MI as a Function of CCA-, Carotid BIF- and ICA BULB-IMT Expressed as Quartiles and as a Continuous Variable</th>
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<tbody>
<tr>
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<tr>
<td>Mean CCA-IMT</td>
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<tr>
<td>&lt;0.63 mm</td>
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<td>0.63–0.69 mm</td>
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<td>0.70–0.78 mm</td>
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<td>≥0.79 mm</td>
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<tr>
<td>Per 1 SD (0.16 mm) increase</td>
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<td>P value</td>
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<tr>
<td>Mean BIF-IMT</td>
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<tr>
<td>&lt;0.72 mm</td>
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<tr>
<td>0.72–0.81 mm</td>
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<tr>
<td>0.82–0.97 mm</td>
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<tr>
<td>≥0.98 mm</td>
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<tr>
<td>Per 1 SD (0.34 mm) increase</td>
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<tr>
<td>P value</td>
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<tr>
<td>Mean BULB-IMT</td>
</tr>
<tr>
<td>&lt;0.60 mm</td>
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<tr>
<td>0.60–0.69 mm</td>
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<td>0.70–0.81 mm</td>
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<tr>
<td>≥0.81 mm</td>
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<tr>
<td>Per 1 SD (0.31 mm) increase</td>
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<td>P value</td>
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</tbody>
</table>

*BMI, systolic and diastolic blood pressure, antihypertensive medication, LDL cholesterol, lipid-lowering medication, nicotine consumption, history of diabetes; †statistically significant after adjustment for multiple testing.
Results
Baseline demographic data for the study population are shown in Table 4. At baseline, 1.9% and 2.1% had a history of stroke or MI, respectively. During the follow-up period, MI occurred in 228 subjects, stroke in 107, and death by any cause in 50. The combined end point “MI, stroke or death” occurred in 341 subjects. The absolute incidence rate was 10.7 per 1000 person-years for MI and 5.0 per 1000 person-years for stroke.

IMT Predicts Vascular Events
The results of the Cox proportional hazard models are shown in Tables 1 to 3 for the 3 end points. According to univariate analyses, IMT values at all 3 arterial sites were significantly predictive of all 3 end points: MI (Table 1), stroke (Table 2) and the combined end point (Table 3). When adjusted for age and sex, CCA-IMT and BIF-IMT were significantly predictive of MI and of the combined end point. All IMT measures were predictive of the combined end point. After additional adjustment for cardiovascular risk factors, CCA-IMT and BIF-IMT were still significantly predictive of both MI and the combined end point (see Tables 1 and 3). When stratified for sex, the hazard ratios per CCA- and ICA–IMT increase were equal or higher for females (eg, for stroke: 1.13 [0.98 to 1.32] versus 1.09 [0.99 to 1.19] per 0.1 mm CCA-IMT increase). The risk per BIF-IMT increase was higher for men (eg, for MI: 1.07 [1.03 to 1.10] versus 1.05 [0.99 to 1.11] per 0.1 mm increase).

IMT HRRs Depend on Age
We calculated HRRs for CCA-IMT as a predictor of the combined end point “MI, stroke, or death” separately for younger (below the median age of 50 years) and older subjects. The HRR per 0.1 mm CCA-IMT increase after adjustment for the complete set of risk factors was greater for the age group <50 years (1.26 [1.06 to 1.49]) than in the age group ≥50 years (1.08 [1.03 to 1.14]). Furthermore, when the interaction between CCA-IMT and age was included in the Cox regression model, age emerged as an independent influential factor with a HRR of 0.95 (0.91 to 0.99; \( P=0.0108 \)). This means that if IMT increases, younger subjects are presumably exposed to a higher relative vascular risk than older subjects with an identical absolute IMT increase. As can be seen in the Figure absolute risk increase across IMT categories (eg, highest versus lowest category) is higher for older subjects, but relative risk increase is higher for young subjects.

Discussion
This study shows that baseline carotid IMT predicts future vascular events and death in a community population with a wide age range at study entry (19 to 90 years). Furthermore, the HRRs associated with increased IMT were similar for the
different arterial sites at the carotid bifurcation (ie, CCA-, BIF-, or ICA-IMT), and for the different clinical end points studied (ie, MI, stroke, or combined end point). Interestingly, the HRRs were significantly higher in younger (<50 years old) than in older subjects (≥50 years old).

These data confirm the findings of previous large-scale population-based studies. The Rotterdam Study found that for a mean common carotid IMT increase of 0.163 mm (1 SD), the odds ratio for stroke (adjusted for age and sex) was 1.00. The Cardiovascular Health Study showed that a maximal common carotid IMT increase of 0.2 mm (=1 SD) resulted in an age and sex-adjusted HRR of 1.33 (1.21 to 1.48) for MI and 1.37 (1.25 to 1.51) for stroke. The Atherosclerosis Risk in Communities (ARIC) investigators found that a mean IMT increase of 1 SD (0.18 mm) gave an age and sex-adjusted HRR for stroke of 1.60 (1.41 to 1.81) in women and 1.31 (1.15 to 1.49) in men. The corresponding values for the risk of MI were 1.69 (1.50 to 1.90) in women and 1.36 (1.12 to 1.51) in men per SD (0.19 mm) increase in mean carotid IMT. Despite considerable differences in the IMT measurement protocols used in the above-mentioned studies, the corresponding risk ratios are very similar. Furthermore, these studies all showed that carotid IMT at all arterial sites can predict future vascular events to almost the same level. In conclusion, our current data fit well within this context and reiterated the importance of carotid IMT as a surrogate marker of the inherent atherosclerotic risk in an individual.

An important finding of this study was that the risk associated with a specific increase in IMT is age dependent, the risk being higher in younger individuals. Previously, the ARIC investigators revealed that the HRRs for both MI and stroke are not linearly distributed across the entire IMT range but increase significantly faster for carotid IMT values below 1.0 mm than for higher IMT values. This means that the same absolute IMT difference indicates a higher relative vascular risk if the reference IMT is lower. This may explain the increased predictive value of IMT in younger individuals who tend to have a lower absolute IMT value. In addition, the ability of IMT to indicate future vascular risk may be diminished in older subjects because of a higher prevalence of drug treatments that can influence IMT, such as statins, angiotensin-converting enzyme inhibitors, and beta-blockers (see Table 4).

Another observation may also explain our finding of an age-related difference. In a large meta-analysis on vascular mortality and blood pressure, it was found that the relative risk of hypertension-associated mortality was higher in a younger than in an older subgroup. By contrast, absolute mortality rates reveal an almost identical increase per given blood pressure difference for all age groups but at substantially different levels. As can be seen from the figure, we have a similar effect. Thus, the putative dependency of...
The strength of associations with stroke was of a similar magnitude after full adjustment for all vascular risk factors (see Table 2). This is likely to be the main reason for insignificant HRRs for stroke in the whole population. This is meaningful that the number of outcome events was low. This is because a large portion of the study participants were in a younger age group, which was based on the fact that the follow-up period was relatively short and a high proportion of the study participants were in a younger age group, meaning that the number of outcome events was low. This is likely to be the main reason for insignificant HRRs for stroke after full adjustment for all vascular risk factors (see Table 2). The strength of associations with stroke was of a similar magnitude after full adjustment for all vascular risk factors (see Table 2).

This study had some limitations. It was not population-based, as all participants were members of a single healthcare scheme, but it did represent a typical community population. The follow-up period was relatively short and a high proportion of the study participants were in a younger age group, meaning that the number of outcome events was low. This is likely to be the main reason for insignificant HRRs for stroke after full adjustment for all vascular risk factors (see Table 2). The strength of associations with stroke was of a similar magnitude after full adjustment for all vascular risk factors (see Table 2).
magnitude to that seen with MI, but the number of events was less, thereby reducing the statistical power. The strengths of this study were its size, the well standardized risk factor assessment, ultrasound examination, and IMT measurement.\textsuperscript{10,16,17} Furthermore, the well known associations between vascular risk factors and carotid IMT have been repeatedly confirmed in the CAPS population as well.\textsuperscript{10,16,17}

In conclusion, our results provide further evidence that elevated IMT is an independent predictor of vascular events. The association appears to be particularly strong in younger individuals.

Acknowledgments
This study was supported by grants from the Stiftung Deutsche Schlaganfall-Hilfe (German Stroke Foundation). The authors declare that they have no conflict of interest. We are also indebted to Dr Michael Skutta, Dr Jens Moll, Dr Donata Ruhkamp, and Dr Alexandra Buehler for professional data collection.

References
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Stroke. 2006;37:87-92; originally published online December 8, 2005;
doi: 10.1161/01.STR.0000196964.24024.ea
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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