Rates and Determinants of Site-Specific Progression of Carotid Artery Intima-Media Thickness
The Carotid Atherosclerosis Progression Study

Andrew D. Mackinnon, MRCP; Paula Jerrard-Dunne, MRCPI; Matthias Sitzer, MD; Alexandra Buehler, MD; Stefan von Kegler, MD; Hugh S. Markus, FRCP

Background and Purpose—Carotid intima-media thickness (IMT) progression rates are increasingly used as an intermediate outcome for vascular risk. The carotid bifurcation (BIF) and internal carotid artery (ICA) are predilection sites for atherosclerosis. IMT measures from these sites may be a better estimate of atherosclerosis than common carotid artery (CCA) IMT. The study aim was to evaluate site-specific IMT progression rates and their relationships to vascular risk factors compared with baseline IMT measurements.

Methods—In a community population (n=3383), ICA-IMT, BIF-IMT, CCA-IMT, and vascular risk factors were evaluated at baseline and at 3-year follow-up.

Results—Mean (SD) IMT progression was significantly greater at the ICA (0.032 [0.109]mm/year) compared with the BIF (0.023 [0.108]mm/year) and the CCA (0.001 [0.040]mm/year) (P<0.001). Only ICA-IMT progression significantly correlated with baseline vascular risk factors (age, male gender, hypertension, diabetes, and smoking). Change in risk factor profile over follow-up, estimated using the Framingham risk score, was a predictor of IMT progression only. For all arterial sites, correlations were stronger, by a factor of 2 to 3, for associations with baseline IMT compared with IMT progression.

Conclusions—Progression rates at the ICA rather than the CCA yield greater absolute changes in IMT and better correlations with vascular risk factors. Vascular risk factors correlate more strongly with baseline IMT than with IMT progression. Prospective data on IMT progression and incident vascular events are required to establish the true value of progression data as a surrogate measure of vascular risk. (Stroke. 2004;35:000-000.)

Key Words: atherosclerosis ■ carotid arteries ■ ultrasonography

Carotid artery intima-media thickness (IMT) can be estimated noninvasively using ultrasound and is now widely used as a marker for early carotid atherosclerosis. Cross-sectional studies have shown that increased baseline carotid IMT correlates strongly with cardiovascular risk factors,1,2 and in a number of prospective cohort studies, increased baseline IMT has been shown to be an independent predictor of future stroke and myocardial infarction risk.3

Based on these outcome data, changes in carotid IMT over time (IMT progression or regression) are increasingly being used as intermediate outcome measures to evaluate the efficacy of therapeutic interventions. An important requirement of any intermediate outcome is that it should translate into clinical risk. To date there are limited data available on the relationships between IMT progression rates and vascular risk factors, and there is a lack of published data showing that the rate of IMT progression translates into an increased risk of vascular events.

Furthermore, there is no consensus on which measures of IMT progression are best suited for use as intermediate outcome measures. A number of methods for measuring IMT have been described which vary in the arterial sites and number of points measured. Analysis can use either the mean or the maximum IMT, and measurements can be performed either manually or using automated edge-tracking software. There are marked differences reported in the progression rates for IMT in different population-based studies, with rates varying between 0.0038 and 0.060 mm per year.4–6 It is likely that these variations mainly reflect methodological differences rather than biological differences between populations.

There are very little data available on site-specific IMT progression rates and their relationships to vascular risk factors. The carotid bifurcation (BIF) and internal carotid artery are predilection sites for atherosclerotic plaque and IMT measures from these sites may be a better estimate of true atherosclerosis than measures from the common carotid...
artery (CCA). This is supported by data showing that baseline internal carotid IMT was a better predictor of incident vascular events than CCA-IMT.\(^7,^8\) Despite this, very little is known about the rates of IMT progression at these different arterial sites.

The primary aim of this study was to evaluate and compare IMT progression rates at different carotid arterial sites. The secondary aim was to determine the relationships between site-specific IMT progression rates and vascular risk factors, compared with baseline IMT measurements.

**Patients and Methods**

**Study Population**

The study sample was drawn from participants in the Carotid Atherosclerosis Progression Study (CAPS), details of which have been published elsewhere.\(^9\) All members of a German primary health care service population (n=32 708) who lived within a radius of 50 kilometers from the study site in Western Germany were invited to participate. Within a predefined time limit, 6975 (age range, 19 to 90 years) agreed to participate. Of these, 5056 (4 of the 5 study sites) were invited to follow-up examination and 3383 (67%) participated. Demographic and risk factor profiles of those invited and not invited for follow-up were very similar; 48 subjects died during the follow-up period.

Risk factors determined included the following: current smoking status (defined as current/ex- or never-smoker), body mass index, low-density lipoprotein cholesterol level, mean systolic and diastolic blood pressure, and history of arterial hypertension (treatment with antihypertensive medication or blood pressure >160 systolic or 95 diastolic in previous measurements), diabetes mellitus, myocardial infarction, or stroke. Risk factor scores were also calculated using the Framingham coronary risk algorithm.\(^10\) These risk scores were then used to measure the change in risk factor load from baseline to follow-up. The follow-up scores were calculated using the age at initial examination so that the follow-up score reflected only the differences in modifiable risk factor profile. The study was approved by the ethical review committee of the University Hospital of Frankfurt am Main.

**Ultrasound Imaging**

For ultrasonic examinations, a 7.5- to 10.0-MHz linear array transducer was used (P700SE; Phillips Medical System). Preprocessing configurations (log gain compensation [60 dB] and image persistence) were held constant during all examinations. The gain was adjusted so that the least dense arterial wall interface was just visible. Using antero-oblique insonation, far-wall carotid IMT was visualized within the CCA (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 bulb (BULB-IMT, 0 to 20 mm distally from the flow divider) on both sides. The images were digitally captured during the systole of a single heartbeat on a personal computer using S-VHS PC-EYE 2-frame grabber (ELTEC Elektronik GmbH) in 16-bit R-G-B packing mode (748×576 pixel) for off-line measurements. Vertical and horizontal calibration measurements were performed every 100th measurement using an ultrasound assurance phantom.

Carotid IMT measurements were performed off-line using an automated imaging processing software (Matlab) as previously reported.\(^11\)

Interobserver reliabilities were assessed in a separate sample of 15 subjects (54 arterial segments) in whom carotid IMT was independently depicted and measured by 4 “blinded” observers. Average intraclass correlation coefficient (Cronbach alpha) was 0.97 (95% CI, 0.96 to 0.98; \(P<0.001\)) and according to the method described by Bland and Altman, the ±2SD of the difference between 2 observers varied between 0.03 and 0.06 mm.\(^12\) Additionally, the intraobserver retest reliability was determined from repeated examinations of 35 subjects (102 arterial segments) by 3 independent observers (time interval between both examinations ranged from 4 to 6 months). The average intraclass correlation coefficient was 0.93 (95% CI, 0.91 to 0.94; \(P<0.001\)) and the ±2SD of the difference between the first and second examination varied between 0.04 and 0.06 mm.\(^12\)

**Statistical Analysis**

Multivariate regression analysis was used to determine associations of risk factors with both baseline IMT and IMT progression. Including the baseline IMT as a covariate when assessing IMT progression has previously been shown to introduce bias because of measurement error.\(^13\) Baseline IMT was therefore not included as a covariate in the regression model initially. However, when an association or correlation was found between a risk factor and IMT progression, baseline IMT was then also entered into the regression model as a covariate to see if the association persisted. All statistical analyses were performed using the SPSS (10.0.7) software package.

**Results**

Baseline demographic data for the study population at baseline and at follow-up are shown in Table 1. The risk factor profiles of subjects followed-up and not followed-up were very similar. The mean (SD) duration of follow-up was 38.53 (4.32) months.

**IMT Progression Rates According to Site**

Table 2 shows baseline and follow-up IMT (mm) and IMT progression rates in mm/year for the common carotid, BIF, and internal carotid arteries. Wilcoxon signed rank testing and paired samples \(t\) test (using log-transformed baseline and follow-up IMT data to normalize the distributions) confirmed that there was significant overall progression of CCA (\(P<0.001\)) bifurcation (\(P<0.001\)) and ICA-IMT (\(P<0.001\)) over time. The mean difference per year for each site varied between 0.02 and 0.06 mm (range 0.01 to 0.07 mm).
−0.382 to +0.722 mm) for CCA-IMT, 0.023 (0.108) mm (range 0.714 to 0.837 mm) for the bifurcation IMT, and 0.032 (0.109) mm (range 0.476 to 1.145 mm) for the ICA-IMT.

Risk Factor Correlations With Baseline IMT
Risk factors correlated more strongly with baseline IMT than with IMT progression, generally by a factor of 2- to 3-fold (Table 3). Baseline IMT at all 3 sites (CCA, bifurcation, and ICA) was positively correlated with age, male gender, smoking at baseline, and hypertension. History of diabetes was associated with bifurcation and ICA baseline IMT but not with baseline CCA-IMT.

Risk Factor Correlations With IMT Progression
Multivariate relationships between vascular risk factors and IMT progression rates are presented in Table 3. Age, male gender, hypertension, diabetes, and current smoking at baseline were all significant predictors of ICA-IMT progression. Age and current smoking were predictors of IMT progression at the BIF. In contrast, baseline vascular risk factors were not associated with CCA-IMT progression (except for a weak negative correlation with hypertension). Additional adjustment for baseline IMT did not significantly alter these associations.

Changes in Risk Factors and IMT Progression
To determine whether changes in risk factor profile during the follow-up period may have influenced the rate of IMT progression, the change in Framingham risk factor score over follow-up was then included in the regression model. An increase in Framingham risk factor score was a significant predictor for ICA-IMT progression ($P = 0.04$ multivariate), but not for CCA-IMT ($P = 0.86$) or bifurcation-IMT ($P = 0.70$) progression.

Discussion
This study demonstrates several important findings that may have implications for future studies using IMT progression as a surrogate outcome measure of vascular risk. Firstly, the rate of IMT progression varies significantly depending on the arterial site used for measurement. IMT progression was greater at the internal carotid compared with either the BIF or the CCAs (Figure 1). In addition, only ICA-IMT progression was correlated with the full range of baseline vascular risk factors. These findings suggest that ICA-IMT progression

| TABLE 2. Baseline and Follow-Up IMT Absolute Values, and IMT Progression Rates for the CCA, BIF, and ICA |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| IMT Measure     | Mean            | Median          | SD              | Min             | Max             | 95% CI          |
| Initial mean CCA-IMT, mm | 0.74            | 0.71            | 0.15            | 0.36            | 2.13            | 0.73–0.74       |
| Follow-up mean CCA-IMT, mm | 0.74            | 0.73            | 0.15            | 0.40            | 3.80            | 0.74–0.75       |
| Initial mean BIF-IMT, mm | 0.92            | 0.84            | 0.33            | 0.34            | 3.60            | 0.91–0.93       |
| Follow-up BIF-IMT, mm | 1.00            | 0.89            | 0.39            | 0.43            | 4.08            | 0.99–1.01       |
| Initial mean ICA-IMT, mm | 0.77            | 0.71            | 0.31            | 0.32            | 3.70            | 0.76–0.79       |
| Follow-up ICA-IMT, mm | 0.87            | 0.75            | 0.43            | 0.37            | 4.41            | 0.86–0.89       |
| Months of follow-up | 38.53           | 37.00           | 4.32            | 17.00           | 61.00           | 38.38–38.67     |

Changes in mean CCA-IMT, mm/y | 0.001           | 0.002           | 0.040           | −0.382          | 0.722           | 0.000005–0.003  |
| Changes in mean BIF-IMT, mm/y | 0.023           | 0.017           | 0.108           | −0.714          | 0.837           | 0.020–0.027     |
| Changes in mean ICA-IMT, mm/y | 0.032           | 0.015           | 0.109           | −0.476          | 1.145           | 0.028–0.036     |

Min indicates minimum; Max, maximum.

| TABLE 3. Correlations (R) and Significance Values (P) Between IMT Values and Risk Factors for Baseline IMT Values and IMT Progression Rates |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Risk Factor     | CCA-IMT         | BIF-IMT         | ICA-IMT         |
|                 | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     | Baseline        | Progression     |
|                 | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   | R   | P   |
| Age             | 0.490 | 0.000* | −0.037 | 0.057 | 0.429 | 0.000* | 0.039 | 0.047* | 0.343 | 0.000* | 0.130 | 0.000* |
| Male            | 0.101 | 0.000* | −0.001 | 0.973 | 0.176 | 0.000* | −0.010 | 0.596 | 0.180 | 0.000* | 0.040 | 0.042* |
| Hypertension    | 0.075 | 0.000* | −0.037 | 0.047* | 0.077 | 0.000* | 0.023 | 0.217 | 0.059 | 0.000* | 0.040 | 0.033* |
| Diabetes        | 0.015 | 0.304 | −0.015 | 0.400 | 0.052 | 0.001* | −0.019 | 0.276 | 0.055 | 0.001* | 0.038 | 0.035* |
| BMI             | 0.071 | 0.000* | −0.027 | 0.163 | −0.007 | 0.657 | −0.024 | 0.222 | 0.033 | 0.057 | −0.028 | 0.146 |
| LDL             | 0.032 | 0.035* | 0.008 | 0.681 | 0.032 | 0.040* | 0.030 | 0.107 | 0.040 | 0.016* | 0.021 | 0.257 |
| HDL             | −0.019 | 0.255 | −0.023 | 0.250 | 0.010 | 0.565 | −0.010 | 0.618 | 0.015 | 0.414 | 0.001 | 0.980 |
| Smoking at baseline | 0.068 | 0.000* | 0.001 | 0.960 | 0.068 | 0.000* | 0.045 | 0.11* | 0.052 | 0.001* | 0.050 | 0.005* |

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.
may be a more robust surrogate measure of vascular risk than the more commonly used CCA-IMT.

IMT progression was greatest at the ICA, followed by bifurcation and then CCA. The progression rate was >30-times greater at the ICA compared with the CCA. Carotid artery IMT is known to be an intermediate phenotype for atherosclerosis. This finding is consistent with what is known about the natural history of the disease, with plaque formation having a predilection for the BIF and ICA.

A number of previous population-based studies have reported on IMT progression rates, but these have largely been limited to measurements from the CCA. The ARIC investigators and the Cardiovascular Health Study looked exclusively at progression of the CCA-IMT. Consistent with the findings of the current study, the Insulin Resistance Atherosclerosis Study (IRAS) reported higher progression rates at the ICA compared with the CCA-IMT. The Kuopio study reported significantly higher progression rates than any of these other studies (in the region of 0.06 mm/year), and this might relate to the site of measurement and the use of maximum rather than mean IMT.

In this study, only ICA-IMT progression was significantly correlated with baseline vascular risk factors. A small number of the larger population based studies have evaluated the relationship between baseline risk factors and carotid artery IMT. Consistent with the findings of our study, the Cardiovascular Health Study (CHS) found no relationship between CCA-IMT progression and baseline vascular risk factors. In the ARIC study, diabetes and current smoking were significant predictors of CCA-IMT progression. One explanation for this discrepancy may be the longer duration of follow-up of the ARIC cohort, which was followed-up >9 years. However, most clinical trials evaluating IMT progression involve much shorter follow-up periods, and our data suggest that measuring progression rates at the ICA rather than the CCA may yield greater absolute changes in IMT and better correlations with vascular risk factors.

Another important finding of this study is that for all arterial sites, risk factor correlations were stronger, generally by a factor of 2 to 3, for associations with baseline IMT as compared with IMT progression. One possible explanation for the weaker associations may relate to the reduced precision of the IMT progression measurements, which show substantially higher within-subject variance than baseline IMT measures. It has also been suggested that a single baseline measurement of IMT is likely to reflect past long-term exposure to risk vascular factors whereas IMT progression may be influenced more by short-term changes in risk factor burden. To test this hypothesis, Framingham risk factor scores were calculated at baseline and then at follow-up. The baseline score was associated with both bifurcation and ICA progression, but changes of risk profile only correlated with ICA-IMT changes. This finding underlies that short-term risk profile changes are more reliably reflected in the ICA-IMT. The stronger associations with baseline values have important implications for the use of IMT to identify associations between novel genetic and other risk factors and atherosclerosis. The use of progression data will be less powerful and require much larger sample sizes.

A further difficulty with using IMT progression measures is that in contrast to the wealth of outcome data available for baseline IMT measures, there is very little data to correlate IMT progression with incident vascular events. In one small study of subjects who had undergone coronary artery bypass grafting, Hodis et al found that IMT progression was predictive of clinical events, but data from the large population-based cohorts are lacking. There are also some methodological issues that need to be considered when analyzing progression data. In particular, it has been demonstrated that measurement error in the baseline IMT may introduce a considerable bias. Thus, although IMT progression is attractive because it offers the possibility of a prospective, longitudinal, short-term measure of vascular risk, the current evidence for IMT progression as a surrogate outcome is not as robust as that available for baseline, cross-sectionally measured IMT values.

In summary, the data suggest that measuring progression rates at the ICA rather than the CCA may yield greater absolute changes in IMT and better correlations with vascular risk factors. Baseline vascular risk factors correlate more strongly with baseline IMT than with IMT progression. Prospective data on IMT progression and incident vascular events are required to establish the true value of progression data as a surrogate measure of vascular risk.

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References
1. Heiss G, Sharrett AR, Barnes R, Chambless LE, Szklo M, Alzola C. Carotid atherosclerosis measured by B-mode ultrasound in populations:


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