Common Carotid Intima-Media Thickness and Arterial Stiffness
Indicators of Cardiovascular Risk in High-Risk Patients
The SMART Study (Second Manifestations of ARterial disease)

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Background—Common carotid intima-media thickness (IMT) and distensibility are markers of structural and functional vessel wall properties. Both parameters have been found in population-based studies to be associated with cardiovascular risk factors and prevalent cardiovascular disease. We investigated cross-sectionally whether IMT and distensibility are associated with cardiovascular risk in patients who already have vascular disease or atherosclerotic risk factors and evaluated the diagnostic ability of IMT and distensibility to discriminate between low- and high-risk patients.

Methods and Results—IMT and distensibility (change of diameter) of the left and right common carotid arteries were measured in the first 570 patients (537 for distensibility) enrolled in the Second Manifestations of ARterial disease (SMART) study, a cohort study among patients with a manifestation of vascular disease or cardiovascular risk factors. Three risk scores were used to classify each patient’s vascular risk. Areas under the curve (AUCs) of receiver-operating characteristic curves were calculated for IMT and distensibility after the patients were dichotomized on the median of the risk scores as the outcome. Risk scores increased nearly linearly with increasing IMT and decreasing distensibility. The AUCs for IMT predicting high-risk patients were 0.77, 0.73, and 0.77 based on the 3 risk scores. The AUCs for distensibility were 0.65, 0.62, and 0.66.

Conclusions—Common carotid IMT and distensibility are clear markers of cardiovascular risk in patients who already have vascular disease or atherosclerotic risk factors. IMT appears to discriminate between low- and high-risk patients better than distensibility. (Circulation. 1999;100:951-957.)

Key Words: atherosclerosis n risk factors n carotid arteries n imaging

Common carotid intima-media thickness (IMT) and distensibility are markers of structural and functional vessel wall properties. Several cross-sectional community-based studies consistently showed that increased IMT of the carotid artery is associated with prevalent cardiovascular disease and the presence of risk factors.1–5 Moreover, follow-up studies have shown a strong and graded association between increased IMT and increased incidence of myocardial infarction and stroke.7–10 Results of these studies support the view that increased IMT is an indicator of extent of generalized atherosclerosis.11 Distensibility is the ability of the artery to expand as a response to pulse pressure, ie, the change in arterial diameter during the cardiac cycle. Distensibility decreases with age. Cross-sectional studies showed associations between decreased distensibility and cardiovascular risk factors, ie, hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction.12–19

In contrast to these findings in the general population, little is known of an association of IMT and distensibility with cardiovascular risk in patients who are already at high risk of cardiovascular disease. In the present study, we evaluate to what extent previously reported associations of IMT and distensibility with cardiovascular risk also apply to patients who have more severe disease. Another unanswered question is whether measurement of IMT or distensibility can identify patients with a relatively good or poor vascular prognosis when advanced atherosclerotic vessel disease is already present.

We related IMT and distensibility to the level of cardiovascular risk in 577 patients with documented vascular disease or marked cardiovascular risk factors. To assess an individual’s cardiovascular risk, we developed a risk score. In addition, 2 established risk scores from other studies were used to classify the patients. From these scores, the potential

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of IMT and distensibility to discriminate between low- and high-risk patients was investigated.

Methods

Patients
Six hundred patients with peripheral arterial disease, (a)symptomatic internal carotid artery stenosis, abdominal aortic aneurysm, transient ischemic attack (TIA) or minor stroke, diabetic foot, renal artery stenosis, hyperlipidemia, diabetes mellitus, or hypertension were recruited from the outpatient clinic of the Vascular Center and the departments of neurology, internal medicine, and nephrology of the University Medical Center (Utrecht, the Netherlands). They were the first patients referred in the Second Manifestations of Atherosclerosis and Risk太高度比検討 (SMART) study, a single-center, prospective cohort study among patients referred to the University Medical Center at Utrecht for the first time because of atherosclerotic vascular disease or for treatment of marked atherosclerotic risk factors. The objectives of the SMART study were to determine the prevalence of additional vascular disease at other sites of the vascular system and risk factors in patients presenting with a manifestation of vascular disease or risk factor and to study predictors for future cardiovascular events in these high-risk patients. Baseline examinations, including a questionnaire, blood chemistry, and ultrasonography, were performed in all patients to confirm the referral diagnosis, to study atherosclerosis in other parts of the vascular system, and to screen for risk factors. The baseline examinations and definitions of vascular disease and risk factors are described briefly below. The study was approved by the ethics committee of the University Medical Center at Utrecht, and written informed consent was obtained from all participants. Patients ≥80 years of age and those with a terminal malignancy were not enrolled.

IMT of the common carotid artery was available in 570 patients (95%). In 5%, IMT was not measured for logistical reasons. Distensibility of the common carotid artery was available in 537 patients (90%). In 63 patients, no information on distensibility was obtained, mainly because of cardiac arrhythmia, longitudinal movements of the vessel, or logistical reasons.

Indicators of Atherosclerosis
A treadmill test was performed to obtain resting and postexercise ankle brachial pressure indexes (ABPIs). Peripheral arterial disease was defined as resting ABPI of <0.90 or postexercise ABPI decreasing ≥20% in ≥1 leg.20 Color Doppler-assisted Duplex scanning of the carotid arteries was performed to detect hemodynamically significant stenosis of the internal carotid artery (peak systolic velocity >150 cm/s corresponding to a diameter reduction of ≥50%) in ≥1 side.21 Abdominal aortic aneurysm, measured with ultrasound, was defined as a distal anteroposterior diameter ≥3 cm or ≥1.5 times the anteroposterior juxta renal diameter.22 TIA and stroke were defined according to criteria established by a neurologist.21 Renal artery stenosis, measured with angiography, was specified as a diameter reduction of ≥50% of the renal artery in ≥1 side with hypertension or renal failure. Diabetic foot was defined as the presence of tissue necrosis or ulceration at the foot in patients with diabetes.

Common Carotid Artery IMT
The left and right common carotid arteries were examined in the anterolateral, posterolateral, and mediolateral directions with an ATL Ultramark 9 (Advanced Technology Laboratories) equipment with a 10-MHz linear-array transducer. Patients were examined in the supine position, with the head turned 45° from the side being scanned. Reference point for measurement of the IMT was the far wall was frozen. On this image, the sonographer traced the leading edges corresponding to the transition zones between lumen-intima and media-adventitia over a length of 1 cm proximal to the reference point. The total intima-media surface of this selected area was calculated online by built-in software of the ultrasound system. The mean IMT of the 6 measurements in each patient was calculated. In case of missing data at any of the 6 measurements, the mean IMT of the available values was calculated. An intraobserver variability study on IMT measurements among 25 volunteers showed a coefficient of variation of 11.7%. The intraobserver variability was slightly lower than the interobserver variability.24

Common Carotid Artery Distensibility
Distensibility measurements were performed by use of a Wall Track System (Scanner 200, Pie Medical) equipped with a 7.5-MHz linear-array transducer and the vessel wall moving detector system.23 Patients were examined in the supine position, with the head turned 45° from the side being scanned and the sonographer at the right side of the patient. The left and right common carotid arteries were examined in the anterolateral direction with 3 consecutive measurements. The transducer was placed on the carotid bifurcation with the least possible pressure that did not compress the overlying jugular vein and allowed expansion of the carotid artery in all directions. Measurements were performed in the distal common carotid artery 2 cm proximal to the origin of the carotid bulb. Details of the measurements have been given elsewhere.25 Briefly, a longitudinal section of the vessel was obtained in B-mode. With the M-mode, the vessel movement detector system registered for each subsequent cardiac cycle the change in arterial diameter and end-diastolic lumen diameter during a 4-second period. The mean distensibility and lumen diameter of the 3 measurements of the left and right sides in each patient were calculated. In case of missing data at any of the 6 measurements, the mean distensibility and lumen diameter of the available values were calculated. An intraobserver variability study on distensibility and end-diastolic lumen diameter measurements among 10 volunteers showed coefficients of variation of 6.2% and 2.1%, respectively. Between observers, this coefficient was 7.3% and 3.5%. Traditionally, measures of arterial stiffness have been analyzed as change in diameter during the cardiac cycle, distensibility, adjusted for pulse pressure and lumen diameter. Distensibility is the inverse of stiffness: A reduced distensibility reflects an increased stiffness. We used the change in diameter, distensibility, as a measure of arterial stiffness.

Cardiovascular Risk Factors
Height and weight were measured, and body mass index was calculated as weight to height squared. Blood pressure was recorded noninvasively at the right brachial artery with a semiautomated oscillometric device in the supine position every 4 minutes for a total of 25 minutes during the distensibility measurement. Mean blood pressure was calculated as the average of all obtained measurements. Hypertension was defined as systolic blood pressure >160 mm Hg, diastolic blood pressure >95 mm Hg, or the use of antihypertensive drugs.26 Pulse pressure was calculated as systolic blood pressure minus diastolic blood pressure. Pulse rate was obtained during the distensibility measurements with the Wall Track System. A venous blood sample was collected after an overnight fast of ≥8 hours. Plasma total cholesterol, triglycerides, glucose, and creatinine were measured with commercial enzymatic dry chemistry kits (Johnson and Johnson). HDL cholesterol in plasma was determined by means of commercial enzymatic kit (Boehringer-Mannheim) after precipitation of LDL and VLDL with sodium phosphotungstate magnesium chloride. LDL cholesterol was calculated with the Friedewald formula.27 Urinary albumin was determined with immunoturbidimetric assays (Boehringer-Mannheim). Hyperlipidemia was defined as total cholesterol ≥6.5 mmol/L, triglycerides ≥2.3 mmol/L, HDL cholesterol ≤1.0 mmol/L, or the use of lipid-lowering drugs, according to Dutch national guidelines.28 Diabetes mellitus was specified as fasting serum glucose ≥7.0 mmol/L, nonfasting serum glucose ≥11.1 mmol/L, or the use of oral blood sugar-lowering drugs or insulin.29 Renal failure was defined as serum creatinine >120 μmol/L or urinary albumin >20 mg/L.
TABLE 1. SMART Risk Score Based on Preexisting Vascular Disease and Risk Factors

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 30 y</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 40 y</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 50 y</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 y</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 70 y</td>
<td>1</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Body mass index ≥ 30</td>
<td>1</td>
</tr>
<tr>
<td>Smoking, current or past</td>
<td>1</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1</td>
</tr>
<tr>
<td>Medication for indicated hyperlipidemia</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia†</td>
<td>1</td>
</tr>
<tr>
<td>Medication for indicated diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>1</td>
</tr>
<tr>
<td>Medication for indicated hypertension</td>
<td>1</td>
</tr>
<tr>
<td><strong>History of vascular disease</strong></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>TIA or stroke</td>
<td>1</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>1</td>
</tr>
<tr>
<td>Intervention on leg arteries§</td>
<td>1</td>
</tr>
<tr>
<td>Aortic aneurysmectomy</td>
<td>1</td>
</tr>
<tr>
<td><strong>Existing vascular disease</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery stenosis ≥ 50%¶</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm#</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure**</td>
<td>1</td>
</tr>
</tbody>
</table>

*Total cholesterol ≥ 6.5 mmol/L, triglycerides ≥ 2.3 mmol/L, or HDL cholesterol ≤ 1.0 mmol/L.
†Fasting serum glucose ≥ 7.0 mmol/L or nonfasting serum glucose ≥ 11.1 mmol/L.
‡Systolic pressure ≥ 160 mm Hg or diastolic pressure ≥ 95 mm Hg.
§Every vascular intervention on the aorta, iliac, femoral, and crural arteries.
¶Resting ABI ≥ 0.90 or postexercise ABI decreasing ≥ 20% in ≥ 1 leg.
†Peak systolic velocity > 150 cm/s corresponding to diameter reduction ≥ 50% in ≥ 1 side.
#Distal anteroposterior diameter ≥ 3 cm or > 1.5 times the anteroposterior juxta renal diameter.
**Serum creatinine > 120 μmol/L or microalbuminuria > 20 mg/mmol.

Patients filled out a questionnaire on history of cardiovascular disease (based on the Rose questionnaire),30 risk factors, and drug use.

**Risk Scores**

Each patient’s vascular risk was classified according to 3 different risk scores. First, we developed a risk score based on data of preexisting disease and risk factors available in the SMART cohort (SMART risk score). Single points were given for male sex, age, risk factors, and history and presence of cardiovascular disease (Table 1). If ≥ 2 risk indicators were missing, the risk score was classified as missing (n = 2). If ≤ 2 risk indicators were missing, the missing indicator was given 0 points (n = 17).

Second, we used the Framingham risk score predicting 10-year coronary heart disease risk in a population free from cardiovascular disease at baseline.31 Risk indicators included age, HDL cholesterol, total cholesterol, systolic blood pressure, cigarette smoking, diabetes mellitus, and left ventricular hypertrophy on ECG; a point score was assigned to each risk indicator, allowing estimation of an individual’s 5- and 10-year risks of coronary heart disease. Scores were based
on coefficients in logistic regression analysis. Because no ECGs were available in the SMART cohort, none of the patients received points for the risk indicator left ventricular hypertrophy.

Third, we used the risk score predicting an individual’s probability of dying within 11.5 years, which was estimated in a follow-up study (EPOZ) among 6057 subjects from the general population conducted in the Netherlands (EPOZ risk score). In that study, a Cox proportional-hazards model was used to identify the most relevant cardiovascular risk factors for all-cause mortality. Individual risk scores are based on sex-specific contributions of the following characteristics: age, body mass index, systolic blood pressure, pulse rate, cigarette use, antihypertensive drug use, diabetes mellitus, and myocardial infarction.

**Data Analysis**

The SMART, Framingham, and EPOZ risk scores were calculated for those patients in whom IMT or distensibility was measured (n=577). Pearson correlation coefficients between the risk scores were calculated. The associations between common carotid IMT and distensibility and the 3 risk scores were evaluated by use of linear regression analyses (SPSS for Windows 7.0, SPSS). In addition, we determined the associations of pulse pressure and lumen diameter with IMT, distensibility, and SMART risk score.

To evaluate the ability of IMT and distensibility to discriminate between low- and high-risk patients, the area under the curve (AUC) of receiver-operating characteristic (ROC) curves were calculated (STATA 4.0 for Windows, Stata Corporation). As the outcome, patients were dichotomized into low or high risk on the basis of the median of the risk score. IMT and distensibility were taken as the independent variables. If IMT or distensibility does not discriminate between low- and high-risk patients, the AUC will be 0.5; with perfect discrimination, its value will be 1.0.

**Results**

Baseline characteristics of the study population are given in Table 2. Figure 1 shows the distribution of common carotid IMT and distensibility. The median of the SMART risk score was 9 (range, 1 to 17; SD, 3); of the Framingham risk score, 22 (range, 16 to 38; SD, 8); and of the EPOZ risk score, 6.4 (range, 1.8 to 9.2; SD, 1.4). The Pearson correlation coefficient between the SMART and Framingham risk scores was
between the SMART and EPOZ risk scores, 0.82; and between the Framingham and EPOZ risk scores, 0.80 (P<0.01 for all correlations).

Figure 2 presents the associations of common carotid IMT with the 3 risk scores. Risk scores increased nearly linearly with increasing IMT. The SMART risk score increased 1.37 SD (95% CI, 1.15 to 1.60) per 1-mm increase in IMT (Table 3).

Figure 3 shows the relationship of common carotid distensibility and the 3 risk scores. Risk scores decreased with increasing distensibility in a nonlinear way. The SMART risk score decreased 0.23 SD (95% CI, 0.17 to 0.27) per 1-mm increase in distensibility (Table 3).

Lumen diameter and pulse pressure were positively associated with IMT and SMART risk score and were negatively but not significantly related to distensibility.

The AUC for IMT predicting low- and high-risk patients was 0.77 (95% CI, 0.73 to 0.81) for the SMART risk score. The AUC for the Framingham risk score was slightly lower at 0.73, and that for the EPOZ risk score was similar to the SMART risk score, 0.77. The AUC for distensibility was 0.65

### TABLE 3. Associations of Common Carotid IMT and Distensibility and Risk According to 3 Risk Scores

<table>
<thead>
<tr>
<th></th>
<th>SMART (Cardiovascular Risk)</th>
<th>Framingham (Coronary Risk)</th>
<th>EPOZ (Total Mortality Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-Coefficient      95% CI</td>
<td>β-Coefficient      95% CI</td>
<td>β-Coefficient      95% CI</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>1.37             1.15–1.60</td>
<td>1.25             1.02–1.50</td>
<td>1.60             1.37–1.85</td>
</tr>
<tr>
<td>Distensibility, mm</td>
<td>−0.23            −0.27 to −0.17</td>
<td>−0.25            −0.30 to −0.19</td>
<td>−0.29            −0.35 to −0.21</td>
</tr>
</tbody>
</table>

For each unit increase of IMT or distensibility, the β-coefficient reflects the mean increase in SD of the risk scores.
Discussion

Results of this cross-sectional study show that common carotid IMT and distensibility are markers of increased cardiovascular risk in patients who already have manifestations of vascular disease or cardiovascular risk factors. Increased cardiovascular and total mortality risk was nearly linearly associated with increased IMT. Risk increased with reduced distensibility. Results of the AUCs suggest that measurement of IMT discriminates between low- and high-risk patients better than distensibility. Use of both parameters may improve identification of patients at high cardiovascular risk.

We used 3 risk scores to classify patients into cardiovascular risk. First, we developed a risk score cross-sectionally based on information on preexisting cardiovascular disease and risk factors available in the SMART cohort. Single points were given for demographic characteristics, risk factors, and history and presence of cardiovascular disease. We did not give extra points for more severe disease or higher levels of risk factors. The SMART patients have been followed for cardiovascular events since the moment they entered the study, and although the number of events currently is small, a preliminary analysis based on the first events (vascular death, myocardial infarction, or stroke) after a mean follow-up time of 11 months showed a significantly increased risk of cardiovascular events for increasing SMART risk score (relative risk per unit increase in score, 1.33; 95% CI, 1.14 to 1.57). In addition, we performed an indirect validation by comparing the risk scores prospectively developed in the Framingham Heart cohort31 and in a follow-up study conducted in the Netherlands.32 These 2 risk scores were obtained from relatively healthy cohorts and may not be directly applicable to the relatively high-risk SMART cohort. The Framingham risk score was based on subjects free of cardiovascular disease at baseline and used coronary heart disease as the end point. The EPOZ risk score was obtained in a cohort in which subjects at relatively higher risks were enrolled and all-cause mortality was used as the outcome. Framingham and EPOZ risk scores may yield overestimations when applied to the SMART cohort, because the relative contribution of classic risk factors in logistic models is likely to be smaller in a population with cardiovascular disease than in a healthy population. We assume, however, that the associations of IMT and distensibility with risk scores are valid because the possible overestimations do not change the ranking of risk scores. Moreover, the 3 risk scores strongly correlated with each other.

Arterial stiffness has been described by use of several parameters: distensibility coefficient, compliance coefficient,35 stiffness (β),36 pressure-strain elastic modulus,37 Young’s modulus,38 and pulse-wave velocity.39 In most of these parameters, the relationships between distensibility (change in lumen diameter), pulse pressure, and carotid lumen diameter are included. Riley et al40 used component mathematical models in which diameter change was the dependent variable and pulse pressure and lumen diameter were covariates of the predictor variable rather than ratios to describe arterial stiffness. In our data, no statistically significant associations were observed between pulse pressure, lumen diameter, and distensibility; therefore, adjustments for lumen diameter and pulse pressure were redundant. For IMT, usually no adjustments are made for pulse pressure and lumen diameter despite their relationships to IMT. Adjustments for pulse pressure and lumen diameter may be justified if one wants to study associations with distensibility or IMT independent of pulse pressure and lumen diameter. However, our aim was to describe the cardiovascular risk associated with increased IMT and decreased distensibility; therefore, the present results are unadjusted for intermediate factors.

There is increasing evidence that increased IMT and decreased distensibility are associated with the presence of cardiovascular risk factors and cardiovascular disease and that increased IMT is associated with higher risk of future myocardial infarction and stroke.1–10 Furthermore, a positive relationship between IMT and risk scores was also reported for the British Heart Study, Framingham, and EPOZ risk scores.41–43 However, these studies concerned general populations, ie, subjects who were on average at a relatively low risk for cardiovascular disease, whereas the present study was conducted in a population at high risk. Our findings indicate that the associations of IMT and distensibility with cardiovascular risk also apply to high-risk populations. Measures of IMT and distensibility may also prove to be useful as markers of increased cardiovascular risk in a population with extensive cardiovascular disease.

In conclusion, common carotid IMT and distensibility are clear markers of cardiovascular risk in patients who already have cardiovascular disease or risk factors. Increased IMT discriminates between low and high-risk patients better than reduced distensibility.

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Appendix

Participants of the SMART study group are A. Algra, MD, PhD; Y. v.d. Graaf, MD, PhD; and D.E. Grobbee, MD, PhD, Julius Center for Patient Oriented Research; J.D. Banga, MD, PhD, Department of Internal Medicine, B.C. Eikelboom, MD, PhD, Department of Vascular Surgery, L.J. Kappelle, MD, PhD, Department of Neurology, A.J. Rabelink, MD, PhD, Department of Nephrology, W.P.T.M. Mali, MD, PhD, Department of Radiology, and P.P.T. de Jaegere, MD, PhD, Department of Cardiology, University Medical Center, Utrecht, the Netherlands.

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