Coronary Artery Calcification, Intima-Media Thickness, and Ankle-Brachial Index Are Complementary Stroke Predictors

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Background and Purpose—Coronary artery calcification (CAC), a marker of coronary atherosclerosis, predicts stroke in addition to established risk factors. Whether CAC’s predictive value can be improved by peripheral atherosclerosis markers, namely carotid intima-media thickness (CIMT) and ankle-brachial index (ABI), was unknown.

Methods—A total of 3289 participants of the population-based Heinz Nixdorf Recall study (45–75 years; 48.8% men) without previous stroke or coronary heart disease were evaluated for incident stroke for 9.0±1.9 years. CAC, CIMT, and ABI were examined as stroke predictors.

Results—Eighty-four strokes occurred during follow-up. In multivariable Cox proportional hazard regressions, CAC (hazard ratio, 1.45 [95% confidence interval, 1.11–1.88] per SD increase in ln(CAC+1); SD, 2.40), CIMT (1.34 [1.08–1.66] per SD increase; SD, 0.127 mm), and ABI (1.55 [1.32–1.82] per SD decrease; SD, 0.148) were associated with stroke in addition to established risk factors. When combined with each other, ln(CAC+1)’s hazard ratio remained similar when CIMT (1.41 [1.09–1.83]) or CIMT and ABI (1.29 [0.99–1.68]) were included. Although CAC alone did not significantly elevate the area under the curve in Harrell’s c-statistics (by 0.009; P=0.379) in addition to established risk factors, the combination of CAC and ABI increased area under the curve (by 0.029; P=0.047), as did ABI (by 0.025; P=0.038) but not CIMT (by 0.002; P=0.795) alone. The combination of CAC and ABI also resulted in significant category-free net reclassification and integrated discrimination improvement.

Conclusions—CAC, CIMT, and ABI provide complementary information about stroke risk. ABI, which is distinctive in a small subpopulation, had the highest and CIMT, which is distributed across a larger range of values, had the lowest predictive value. *(Stroke, 2014;45:2702-2709.)*

Key Words: carotid atherosclerosis ▪ coronary artery disease ▪ peripheral arterial disease

In the population-based and prospective Heinz Nixdorf Recall (HNR) cohort, we have demonstrated previously that coronary artery calcification (CAC) determined by electron-beam computed tomography is a potent predictor of incident stroke in addition to established risk factors that are part of the Framingham risk score. In addition, we have shown that 2 markers of peripheral atherosclerosis, that is, intima-media thickness of the common carotid arteries (carotid intima-media thickness [CIMT]) and ankle-brachial index (ABI) that is a simple ratio of 2 systolic blood pressure values, predicted stroke in addition to established risk factors.

Interestingly, CAC discriminated stroke risk specifically in low- and intermediate-risk subjects in the HNR cohort, whereas CIMT and ABI differentiated stroke risk specifically in high- or intermediate-to-high-risk subjects, respectively. These observations suggested that CAC, CIMT, and ABI contribute to risk prediction in different ways and that they may have an additive prognostic value in different risk categories. In fact, an appropriate set of biomarkers fulfills 2 aims: first, it should detect high-risk subjects, which are falsely classified into low- or intermediate-risk categories. Second, it should identify low-risk subjects misclassified...
into intermediate- or high-risk categories. A strong set of markers provides information about low-, intermediate-, and high-risk categories.

With respect to stroke, the large majority of studies investigating the benefit of subclinical atherosclerosis markers in addition to established risk factors hitherto focused on single atherosclerosis markers. Thus, conclusive studies directly comparing coronary and peripheral atherosclerosis markers were lacking to date, which is noteworthy because stroke embolisms may be of cardiac or peripheral origin. In the Multi-Ethnic Study of Atherosclerosis (MESA), it has been shown recently that CAC is much more strongly associated with coronary heart disease (CHD) than CIMT and ABI in multivariable Cox regression analyses, and it also affords the highest area-under-the-curve (AUC) increment of receiver operating characteristic curves. Based on these results, we examined how CAC, CIMT, and ABI are associated with stroke.

### Methods

#### Study Cohort

The HNR cohort is a random sample of men and women aged 45 to 75 years who were prospectively enrolled via mandatory citizen registries in Essen, Bochum, and Mülheim/Ruhr between December 2000 and August 2003. All subjects gave written informed consent. Exclusion criteria were inability or unwillingness to give informed consent, conditions (medical or other) precluding follow-up for 5 years, severe psychiatric disorders or illegal substance abuse, and pregnancy in women. Computer-assisted interviews and questionnaires were used to document medical histories. The study was approved by the university ethical committee.

Participants were followed up for 9.0±1.9 years. During the follow-up, stroke events (both ischemic and hemorrhagic), defined as focal neurological deficits of presumed cerebrovascular origin that persisted for $\geq24$ hours, were assessed in annual questionnaires and a follow-up visit after 5 years. Stroke events were validated by an independent internal and external end point committee (K. Berger, Münster; M. Dichgans, Munich; and C. Weimar, Essen). Stroke events were

### Table 1. Baseline Characteristics of Heinz Nixdorf Recall Participants Without Previous Stroke, Coronary Heart Disease, or Myocardial Infarcts Receiving Measurement of ABI, CIMT, and CAC, Stratified by Stroke Development During the Observation Period

<table>
<thead>
<tr>
<th>Study Participants</th>
<th>Total (n=3289)</th>
<th>No Stroke (n=3205)</th>
<th>Stroke (n=84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.4±7.7</td>
<td>59.3±7.7</td>
<td>64.2±7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1604 (48.8)</td>
<td>1556 (48.5)</td>
<td>48 (57.1)</td>
<td>0.123</td>
</tr>
<tr>
<td>Education according to ISCED (median [Q1; Q3]), y</td>
<td>13.0 (13.0; 16.5)</td>
<td>13.0 (13.0; 16.5)</td>
<td>13.0 (13.0; 16.4)</td>
<td>0.108</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.8±4.5</td>
<td>27.7±4.5</td>
<td>28.7±4.2</td>
<td>0.055</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>93.9±13.0</td>
<td>93.8±13.0</td>
<td>97.6±11.4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

#### Hypertension (JNC 7)

- Normal or prehypertension: 2058 (62.6) 2027 (63.3) 31 (36.9) ...
- Stage 1: 864 (26.3) 833 (26.0) 31 (36.9) ...
- Stage 2: 365 (11.1) 343 (10.7) 22 (26.2) ...

| Systolic blood pressure, mm Hg | 132.3±20.7 | 131.9±20.5 | 146.6±22.3 | <0.001 |
| Diastolic blood pressure, mm Hg | 81.2±10.8 | 81.1±10.7 | 85.0±12.2 | 0.001 |
| Diabetes mellitus | 228 (7.3) | 217 (7.2) | 11 (13.8) | 0.032 |
| Smoking status | 0.351 |
| Never smoked | 1417 (43.1) | 1384 (43.2) | 33 (39.3) | ...
| Former smoker | 1112 (33.8) | 1086 (33.9) | 26 (31.0) | ...
| Current smoking | 760 (23.1) | 735 (22.9) | 25 (29.8) | ...
| Total cholesterol, mg/dL | 231.1±38.4 | 231.0±38.4 | 234.7±38.6 | 0.389 |
| LDL cholesterol, mg/dL | 147.8±36.1 | 147.8±36.2 | 148.9±33.7 | 0.767 |
| HDL cholesterol, mg/dL | 58.7±17.0 | 58.8±17.0 | 56.3±17.5 | 0.193 |
| Triglycerides (median [Q1; Q3]), mg/dL | 122.0 (80.0; 175.0) | 122.0 (88.0; 174.0) | 135.0 (106.3; 209.8) | 0.012 |
| FRS (median [Q1; Q3]), % | 9.0 (6.0; 15.0) | 9.0 (6.0; 14.0) | 17.0 (8.0; 22.0) | <0.001 |
| Atrial fibrillation | 45 (1.4) | 39 (1.2) | 6 (7.2) | 0.001 |
| CAC score (median [Q1; Q3]) | 12.6 (0.0; 115.2) | 11.9 (0.0; 110.9) | 86.8 (8.5; 464.5) | <0.001 |
| CIMT, mm | 0.67±0.13 | 0.67±0.13 | 0.75±0.15 | <0.001 |
| ABI | 1.14±0.15 | 1.14±0.14 | 1.02±0.23 | <0.001 |
| Antihypertensive drugs | 1045 (31.8) | 1004 (31.3) | 41 (48.8) | 0.001 |
| Lipid-lowering drugs | 309 (9.7) | 303 (9.7) | 6 (7.4) | 0.573 |
| Antidiabetics | 157 (4.9) | 147 (4.7) | 10 (12.3) | 0.006 |
| Platelet inhibitors | 187 (5.8) | 179 (5.7) | 8 (9.9) | 0.142 |

Unless otherwise indicated, data are mean±SD for continuous data and n (%) for categorical data. ABI indicates ankle-brachial index; BMI, body mass index; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; FRS, Framingham risk score; HDL, high-density lipoprotein; ISCED, International Standard Classification of Education; JNC, Joint National Committee; and LDL, low-density lipoprotein.
allocated to the date of stroke diagnosis, nonstroke cases censored at the date of last contact when the person was still alive or date of death.

Of 4814 subjects included, 4356 subjects had a negative history for previous stroke, CHD, and myocardial infarcts. Of these subjects, 3289 had CAC, CIMT, and ABI measurements at baseline. These subjects did not differ from the whole cohort. The major reason for not all subjects receiving CIMT measurements during the baseline examination of the HNR study was the limited availability of examiners or ultrasound equipment in the initial months of this study. All investigators were blinded for clinical information. Participants were not informed about the results of the subclinical atherosclerosis marker studies.

Established Risk Factors

Systemic blood pressure was measured with an automated oscillometric device (Omron 705-CP, Omron, Mannheim, Germany). Hypertension was classified according to Joint National Committee-7 thresholds, for regression analyses present hypertension was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg or taking antihypertensive medication. Participants were considered diabetic in cases of physician-diagnosed diabetes mellitus or when taking antidiabetic medication. Total, low-density lipoprotein, and high-density lipoprotein cholesterol and triglycerides were measured with standardized enzymatic methods. Dyslipidemia was defined as high-density lipoprotein <40 mg/dL or low-density lipoprotein ≥160 mg/dL or prescription of lipid-lowering drugs. The Framingham risk score was determined and body mass index was calculated. Level of education was evaluated according to the International Standard Classification of Education in years.

Coronary Artery Calcification

Nonenhanced electron-beam computed tomographic scans were performed with a C-150 or C-100 scanner (GE Imatron, San Francisco, CA). Contiguous 3-mm-thick slices were obtained at an image acquisition time of 100 ms. CAC was defined as a focus of ≥2 contiguous pixels with a computed tomographic density ≥130 Hounsfield units. The CAC Agatston score was computed.

Intima-Media Thickness

B-mode images were obtained with a Vivid FiVe ultrasound system (GE Ultrasound) using a linear 10-MHz scanner. In longitudinal 2-dimensional images, 10 CIMT measurements were made at the far wall of both common carotid arteries for a 10-mm distance proximal to the bifurcation. Focal plaques were excluded from the analysis. Average values were calculated for the left and right vessel, of which mean values were formed.

Ankle-Brachial Index

Systolic blood pressure measurements were performed using a 8-MHz Doppler transducer on subjects resting on a flat couch for 15 minutes (Logidop, Kranzbühler, Germany). Ankle pressures were measured above the posterior tibial and dorsal foot arteries, brachial pressures above the cubital segment of both brachial arteries. ABI was calculated per leg as ratio of the highest ankle artery pressure recorded either in the posterior tibial or dorsal foot artery and the highest systolic pressure measured in the right and left arm. For further analyses, the lower ABI of both legs was used.

Statistical Analysis

Continuous data are presented as mean±SD (normally distributed) or median (Q1; Q3: non-normally distributed), categorical data as counts (%). Normally distributed data were analyzed by unpaired t tests, non-normally distributed data by Mann–Whitney tests, χ² and Fisher exact tests, as appropriate, were used for comparison of categorical variables. Cox proportional hazards regressions, c-statistics (Harrell’s c), category-free net reclassification improvement (NRI), and integrated discrimination improvement (IDI) for time-to-event data were analyzed. Analyses were performed using SPSS 17 for

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cox Proportional Hazards Regression Analyses for Stroke per 1-SD Increase of ln(CAC+1) and CIMT and per 1-SD Decrease of ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Age, y</td>
<td>2.01 (1.59–2.54), &lt;0.001</td>
</tr>
<tr>
<td>Sex (men vs women)</td>
<td>1.41 (0.92–2.17), 0.118</td>
</tr>
<tr>
<td>Hypertension (yes vs no)</td>
<td>4.17 (2.38–7.26), &lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia (yes vs no)</td>
<td>1.04 (0.67–1.60), 0.860</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs no)</td>
<td>2.20 (1.17–4.16), 0.015</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>1.49 (0.93–2.37), 0.097</td>
</tr>
<tr>
<td>BMI</td>
<td>1.22 (1.01–1.48), 0.041</td>
</tr>
<tr>
<td>Atrial fibrillation (yes vs no)</td>
<td>5.99 (2.61–13.74), &lt;0.001</td>
</tr>
<tr>
<td>Ln(CAC+1)</td>
<td>1.92 (1.54–2.39), &lt;0.001</td>
</tr>
<tr>
<td>CIMT</td>
<td>1.62 (1.38–1.90), &lt;0.001</td>
</tr>
<tr>
<td>ABI</td>
<td>1.96 (1.67–2.27), &lt;0.001</td>
</tr>
</tbody>
</table>

Values represent HR (95% CI), P value. Model 1: age, sex, and ln(CAC+1); model 2: age, sex, and CIMT; model 3: age, sex, and ABI; model 4: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, BMI; atrial fibrillation, and ln(CAC+1); model 5: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, BMI, atrial fibrillation, and CIMT; model 6: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, BMI, atrial fibrillation, and ABI; model 7: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, BMI, atrial fibrillation, ln(CAC+1), and CIMT; model 8: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, BMI, atrial fibrillation, ln(CAC+1), and ABI; model 9: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, BMI, atrial fibrillation, ln(CAC+1), and ABI; model 10: age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, BMI, atrial fibrillation, ln(CAC+1), CIMT, and ABI. SDs: age, 7.72 y; BMI, 4.49 kg/m²; ln(CAC+1), 2.40; CIMT, 0.127 mm; and ABI, 0.148. ABI indicates ankle-brachial index; BMI, body mass index; CIMT, coronary artery calcification; CI, confidence interval; CIMT, carotid intima-media thickness; and HR, hazard ratio.
Results

Baseline Characteristics

Baseline characteristics of HNR participants without previous stroke, CHD, or myocardial infarcts receiving measurement of CAC, CIMT, and ABI are summarized in Table 1. A total of 84 subjects (2.55%; 48 men, 36 women) developed a stroke during the follow-up (75 ischemic, 9 hemorrhagic). Compared with subjects not having a stroke, subjects exhibiting a stroke were older, had a higher waist circumference, more often revealed arterial hypertension, diabetes mellitus and atrial fibrillation, had higher triglycerides, and a higher Framingham risk score. Besides, subjects experiencing a stroke had higher CAC and CIMT values and lower ABI values. They more frequently received antihypertensive and antidiabetic medications.

CAC, CIMT, and ABI as Stroke Predictors

CAC revealed a skew distribution with a high shoulder at the 0 value (1049 participants exhibiting no CAC) and decreasing frequencies toward higher values (median CAC, 12.6 [Q1; Q3=0; 115.2]). In regression analyses, ln(CAC+1) were therefore used, considering that ln(CAC+1) closely resembled normal distribution. To compare the predictive value of CAC, CIMT, and ABI, we first calculated unadjusted Cox proportional hazards regressions using 1-SD increase units for ln(CAC+1) and CIMT and 1-SD decrease units for ABI, considering that high ln(CAC+1) and CIMT values but low ABI values predispose to stroke. Furthermore, we calculated regressions adjusted for age and sex and regressions adjusted for established risk factors (age, sex, hypertension, dyslipidaemia, diabetes mellitus, smoking, body mass index, and atrial fibrillation). Finally, we combined the 3 atherosclerosis markers with each other to investigate whether their combination enhances stroke prediction.

In regression analyses, all 3 subclinical atherosclerosis markers were associated with stroke when individually examined alone or in addition to age, sex, and other established risk factors, as defined above (Table 2). In the model adjusted for established risk factors, a hazard ratio (HR) of 1.59 (1.24–2.04) was reported for each SD ln(CAC+1) increase (SD, 2.40), a HR of 1.41 (1.16–1.71) for each SD CIMT increase (SD, 0.127 mm), and a HR of 1.72 (1.49–2.00) for each SD ABI decrease (SD, 0.148).

When ln(CAC+1) was combined with CIMT in a regression that was also adjusted for established risk factors, ln(CAC+1) and CIMT and were independently associated with stroke with HR similar to the model in which both markers were evaluated alone (model 7 in Table 2: HR for ln(CAC+1)=1.41 [1.09–1.83], HR for CIMT=1.30 [1.05–1.61]). When ln(CAC+1) and ABI were combined (model 8 in Table 2), the HR for ln(CAC+1) decreased to 1.31 (1.01–1.72), whereas the HR for ABI remained similar (1.49 [1.27–1.75]). Conversely, the HR for CIMT (1.29 [1.03–1.60]) and ABI (1.52 [1.30–1.78]) only slightly decreased when both markers were examined together (model 9 in Table 2). In the model that included all 3 atherosclerosis markers in addition to established risk factors (model 10 in Table 2), ABI showed the strongest association with stroke.
(1.47 [1.25–1.72]) followed by CIMT (1.27 [1.02–1.57]), whereas ln(CAC+1) (1.29 [0.99–1.68]) lost significance.

**Stroke Risk in Different CAC, CIMT, and ABI Categories**

Although ABI most strongly affected stroke risk in the above analyses, low ABI values are rare in the general population. In the HNR study, only 4.8% of subjects exhibited ABI values <0.9.3 By contrast, 9.8% (ie, ~10%) of subjects revealed CIMT scores ≥400, which is commonly considered as cut off for the highest CAC category.1,14,15 To further evaluate effects of atherosclerosis markers on stroke risk, we calculated crude stroke incidence rates for categories below and above the 90th CIMT percentile and categories above and below the 10th ABI percentile, equivalent to the CAC ≥400 cut off (Figure 1). These analyses revealed that both CIMT and ABI provided additional information about stroke risk when combined with CAC (Figure 1A and 1B), as did CIMT combined with ABI (Figure 1C). Participant numbers were low in some risk categories, which then resulted in wide confidence intervals.

**Benefits of Combined CAC, CIMT, and ABI Use**

To analyze the benefit of adding subclinical atherosclerosis markers to established vascular risk factors, we computed Harrell’s c-statistics (AUC(t)), IDI, and category-free NRI for time-to-event data, in which the risk factors, age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, body mass index, and atrial fibrillation, were evaluated alone and in combination with atherosclerosis markers. Data are summarized in Table 3 and Table I in the online-only Data Supplement; receiver operating characteristic curves are shown in Figure 2A and 2B.

This analysis revealed that adding CAC or CIMT to the model that included established risk factors did not significantly alter AUC(t) but resulted in significant IDI and NRI (Table 3). Inserting CAC and CIMT into the same model did not further increase discrimination measures. Adding ABI to the risk factor model significantly increased AUC(t), leading also to significant IDI but nonsignificant NRI. Adding CAC and ABI to the risk factor model resulted in significant IDI, NRI, and change in AUC(t). The combination of CIMT and ABI as well as the combination of all 3 atherosclerosis measures did not lead to further risk discrimination improvement.

Inserting CIMT into a model that included established risk factors and CAC led to significant IDI, whereas inserting ABI into the same model resulted in significant IDI and change in AUC(t) (Table 1 in the online-only Data Supplement). Inserting CIMT and ABI into a model that included established risk factors and CAC did not further improve discrimination measures to a relevant extent.

**Discussion**

Using a population-based sample of 3289 subjects aged 45 to 75 years followed up for 9.0±1.9 years, we show that both markers of peripheral atherosclerosis, CIMT and ABI, may successfully be combined with CAC for stroke prediction. When combined with each other, the HR of ln(CAC+1) remained similar when CIMT was also inserted into multivariable regressions but slightly decreased when ABI was included. These data suggest that ABI is a particularly potent stroke predictor. Although CAC and CIMT significantly influenced IDI and NRI, but not AUC in Harrell’s c-statistics, combinations of CAC and ABI, but not CAC and CIMT, increased all 3 discrimination measures, as we for the first time show. The combined use of coronary and peripheral atherosclerosis markers is supported by empirical evidence that CAC, CIMT, and ABI correlate modestly with each other,16,17 suggesting that atherosclerosis may affect the coronary and peripheral arteries to variable degree in different patients. Particularly in early disease stages, atherosclerosis may be...
CAC, CIMT, and ABI as Stroke Predictors

detectable in some, but not in other vascular beds,\textsuperscript{14} for example, in the coronary, but not in leg arteries. Besides, CAC, CIMT, and ABI recognize distinct atherosclerosis features that get evident at different disease stages; CIMT recognizes the most early signs of atherosclerosis reflected by intima-media thickening,\textsuperscript{19,20} CAC indicates more advanced atherosclerosis associated with vessel wall calcification\textsuperscript{21} and ABI identifies lumen-narrowing atherosclerosis compromising blood pressure in the vascular periphery.\textsuperscript{22}

Only few studies evaluated the predictive value of CAC and CIMT in the general population, always with more limited sets of discrimination measures. In MESA\textsuperscript{23} and the Pittsburgh cohort of the Cardiovascular Health Study (CHS),\textsuperscript{24} CIMT, but not CAC, predicted stroke in multivariable regression analyses, in which established risk factors, CAC, and CIMT were evaluated in subjects which had hitherto been asymptomatic for cardiovascular events (including CHD and stroke). Yet, CAC alone did not predict stroke in both studies after adjustment for established risk factors.\textsuperscript{23,24} The authors concluded that CIMT was a better stroke predictor than CAC, whereas CAC was a better predictor of CHD than CIMT.\textsuperscript{23,24} In contrast to MESA and CHS (Pittsburgh), we found that CAC is an independent stroke predictor, even when combined with CIMT in multivariable regression analyses. The number of stroke events in both studies was smaller than in our study (59 in MESA,\textsuperscript{23} 28 in CHS [Pittsburgh]).\textsuperscript{24} The follow-up periods were shorter (5.3 years in MESA,\textsuperscript{23} 5.0 years in CHS [Pittsburgh])\textsuperscript{24} and participants of the CHS (Pittsburgh) were much older than ours (70–99 years),\textsuperscript{24} accumulating high loads of vascular risk factors. Both studies were possibly not sufficiently powered to identify CAC as stroke predictor. Besides, the ethnic composition of MESA and CHS (Pittsburgh), was more heterogeneous than ours.\textsuperscript{23,24} The method of calcium measurement differed between our study and MESA. Thus, a modified Agatston score was evaluated in MESA that compared optical densities with optical densities in calcium phantoms.\textsuperscript{23} Reanalyses after longer follow-up periods may allow more definite conclusions about the role of CAC in MESA and CHS (Pittsburgh). In view of its multiethnic composition, particularly MESA will allow important insights into ethnic factors modifying CAC-related risks.

Although no studies examining the effect of CAC on stroke risk hitherto evaluated ABI, the effect of aortic calcification (assessed by x-ray), CIMT, and ABI has been examined previously in the Rotterdam study.\textsuperscript{25} When all 3 markers were evaluated together in multivariable regression analyses adjusted for established risk factors and history of cardiovascular disease, aortic calcification and CIMT, but not ABI, predicted stroke. That ABI did not predict stroke in addition to vascular calcification and CIMT in the Rotterdam study is surprising. It may be attributed partly to the fact that aortic calcification and ABI evaluate the same vascular territory, which may have decreased the predictive value of ABI. The number of stroke events in the Rotterdam study was slightly higher than in our study (119 strokes). Subjects with previous stroke, but not subjects with previous CHD, were excluded. The follow-up period was shorter (6.1 years) and participants were again older than ours (mean, 67 years).\textsuperscript{25} ABI measurement in the Rotterdam study differed from our study because blood pressure in the lower extremities was evaluated only above the posterior tibial arteries (not above the dorsal foot arteries) and blood pressure in the upper extremities was measured only at the right and not at the left arm. The measurement of blood pressure above additional arteries may have increased the sensitivity of ABI in our study. That low ABI values predict stroke has been shown outside the HNR study in primary care-based patient cohorts\textsuperscript{26,27} and a small cohort of elderly participants from the population-based Framingham study.\textsuperscript{28}

The advantage of CAC and CIMT as risk predictors is that both markers provide valuable risk information across a wide range of measurements. Hence, these markers allow identifying a considerable percentage of subjects at risk. In the HNR cohort, 9.8% and 27.2% of subjects revealed CAC scores ≥400 and ≥100, respectively, which are widely used as cut offs for the highest and second-highest CAC category.\textsuperscript{1,14,15} ABI differs from CAC and CIMT with respect to that low ABI values are rare in the general population, representing a hallmark of advanced atherosclerosis. Thus, only 4.8% of subjects in the

\begin{table}
\centering
\caption{Harrell’s c-Statistics, IDI, and NRI for Stroke Events When CAC, CIMT, and ABI Are Added to a Baseline Model That Includes Established Risk Factors}
\begin{tabular}{lccc}
\hline
Model & Harrell’s \textit{c}-Statistic & Change in \textit{c}-Statistic (95\% CI), \textit{P}-Value* & IDI (95\% CI), \textit{P}-Value* & NRI \% (95\% CI), \textit{P}-Value* \\
\hline
Baseline model\textdagger & 0.751 & NA & NA & NA \\
Baseline model+CAC & 0.760 & 0.009 (–0.011 to 0.029), 0.379 & 0.008 (0.002 to 0.014), 0.009 & 28.74 (6.27 to 51.21), 0.013 \\
Baseline model+CIMT & 0.753 & 0.002 (–0.012 to 0.016), 0.795 & 0.011 (0.001 to 0.020), 0.030 & 28.35 (5.82 to 50.88), 0.014 \\
Baseline model+ABI & 0.776 & 0.025 (0.001 to 0.049), 0.038 & 0.032 (0.008 to 0.057), 0.010 & 9.00 (–13.62 to 31.63), 0.436 \\
Baseline model+(CAC and CIMT) & 0.762 & 0.011 (–0.011 to 0.033), 0.339 & 0.018 (0.004 to 0.032), 0.010 & 20.30 (–2.32 to 42.91), 0.079 \\
Baseline model+(CAC and ABI) & 0.780 & 0.029 (0.001 to 0.057), 0.047 & 0.035 (0.012 to 0.059), 0.003 & 27.27 (4.87 to 49.67), 0.018 \\
Baseline model+(CIMT and ABI) & 0.773 & 0.022 (–0.004 to 0.047), 0.100 & 0.041 (0.016 to 0.066), 0.001 & 22.65 (0.07 to 45.23), 0.050 \\
Baseline model+(CAC, CIMT, and ABI) & 0.778 & 0.027 (–0.002 to 0.054), 0.070 & 0.044 (0.019 to 0.070), <0.001 & 24.72 (2.14 to 47.29), 0.030 \\
\hline
\end{tabular}
\begin{flushleft}
\textit{ABI} indicates ankle-brachial index; CAC, coronary artery calcification; CI, confidence interval; CIMT, carotid intima-media thickness; IDI, integrated discrimination improvement; NA, not applicable; and NRI, net reclassification improvement. \\
*Compared with baseline model.  \\
\textdagger Baseline model includes age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, body mass index, and atrial fibrillation.
\end{flushleft}
\end{table}
HNR cohort exhibited ABI values <0.9. Although reflecting a simple risk predictor that does not require expensive technical equipment, its practical use is limited by the fact that >20 subjects in the general population need to be screened in order that a single subject with reduced ABI is detected. Because of their broader distribution, CAC and CIMT allow risk estimates not only for the highest but also for the intermediate or low values. The group of intermediate-risk subjects is particularly relevant for risk classification, because based on the severity of subclinical atherosclerosis, intermediate-risk subjects may be reclassified either as high or as low risk. Additional population-based studies including larger cohorts and longer follow-up periods are urgently needed to provide a better understanding of how different atherosclerosis markers complement each other, which in turn might allow refinement of clinical recommendations. Based on existing evidence, a class IIb recommendation was made for CAC and ABI measurements in clinically asymptomatic subjects, whereas CIMT only received a class III recommendation.

Although CAC was recently found to be associated more strongly with CHD than ABI in MESA, in which CIMT was not at all associated with CHD, we herein showed that CAC, CIMT, and ABI provide complementary information about stroke risk. The strong association of ABI with stroke is noteworthy. Its practical use is limited by the low percentage of subjects with ABI values <0.9 in the general population. The big strength of this study is a well-characterized cohort of 3289 subjects with exceptionally high follow-up rates of 91% at 5 years, in which CAC, CIMT, and ABI measurements were performed routinely. Because of limited availability of examiners and ultrasound equipment in the first months of this study, only 3460 of 4356 participants of the HNR study without preceding stroke, CHD, and myocardial infarcts received CIMT evaluations. As a matter of fact, subjects receiving CIMT measurements in the HNR study did not differ from the whole cohort. Thus, our data are representative for the general population.

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**Disclosures**

None.

**References**


Coronary Artery Calcification, Intima-Media Thickness, and Ankle-Brachial Index Are Complementary Stroke Predictors


on behalf of the Heinz Nixdorf Recall Study Investigative Group

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## SUPPLEMENTAL MATERIAL

Supplemental Table I. Harrell’s $c$-statistics, IDI and NRI for stroke events when CAC, CIMT and ABI are added to a baseline model that includes established risk factors and CAC

<table>
<thead>
<tr>
<th>Model</th>
<th>Harrell’s $c$-statistic</th>
<th>Change in $c$-statistic (95% CI), $p^\dagger$</th>
<th>IDI (95% CI), $p^\dagger$</th>
<th>NRI % (95% CI), $p^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline model and CAC</td>
<td>0.760</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>(Baseline model and CAC) + CIMT</td>
<td>0.762</td>
<td>0.002 (-0.010 to 0.013), 0.786</td>
<td>0.010 (0.001 to 0.021), 0.048</td>
<td>21.64 (-0.97 to 44.24), 0.061</td>
</tr>
<tr>
<td>(Baseline model and CAC) + ABI</td>
<td>0.780</td>
<td>0.020 (0.001 to 0.0392), 0.048</td>
<td>0.028 (0.005 to 0.050), 0.016</td>
<td>7.44 (-15.17 to 30.06), 0.519</td>
</tr>
<tr>
<td>(Baseline model and CAC) + (CIMT and ABI)</td>
<td>0.778</td>
<td>0.017 (-0.004 to 0.043), 0.117</td>
<td>0.037 (0.014 to 0.060), 0.002</td>
<td>19.67 (-2.87 to 42.20), 0.089</td>
</tr>
</tbody>
</table>

*Baseline model includes age, sex, hypertension, dyslipidemia, diabetes, smoking, BMI, atrial fibrillation.

†compared to baseline model and CAC.

/ indicates not applicable.

ABI indicates ankle-brachial index; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement.