The Association Between Coronary Calcification Assessed by Electron Beam Computed Tomography and Measures of Extracoronary Atherosclerosis

The Rotterdam Coronary Calcification Study

Hok-Hay S. Oei, MD,*† Rozemarijn Vliegenthart, MSc,*† A. Elisabeth Hak, MD,* Antonio Iglesias del Sol, MD, PhtD,* Albert Hofman, MD, PhtD,* Matthijs Oudkerk, MD, PhtD,†‡ Jacqueline C. M. Witteman, PhtD*

Rotterdam and Groningen, the Netherlands

OBJECTIVES
The present study was designed to examine the associations of coronary calcification assessed by electron beam computed tomography (CT) with measures of extracoronary atherosclerosis.

BACKGROUND
Although measures of extracoronary atherosclerosis have been used to predict coronary events, it is not yet known to what extent those measures reflect coronary atherosclerosis.

METHODS
The Rotterdam Coronary Calcification Study is a population-based study in subjects age 55 years and over. Participants of the study underwent an electron beam CT scan. Coronary calcification was quantified according to the Agatston calcium score. Measures of extracoronary atherosclerosis included common carotid intima media thickness (IMT), carotid plaques, ankle-arm index (AAI) and aortic calcification. We used the first 2,013 participants for the present analyses. Age-adjusted geometric mean calcium scores were computed for categories of extracoronary measures using analyses of variance.

RESULTS
Graded associations with coronary calcification were found for the carotid and aortic measures. Associations were strongest for carotid plaques and aortic calcification; coronary calcification increased from the lowest category (no plaques) to the highest category 9-fold in men and 10-fold in women, respectively. A nonlinear association was found for AAI with an increase in coronary calcification only at lower levels of AAI.

CONCLUSIONS
In this population-based study, graded associations were found between coronary calcification and common carotid IMT, carotid plaques and aortic calcification. A nonlinear association was found between coronary calcification and the AAI. (J Am Coll Cardiol 2002;39:1745–51) © 2002 by the American College of Cardiology Foundation

Noninvasive measures of extracoronary atherosclerosis have been used to predict the risk of coronary heart disease (1–5). Although clear associations exist between measures of extracoronary atherosclerosis and coronary events, it is not yet known to what extent those extracoronary measures reflect coronary atherosclerosis. Electron beam computed tomography (CT) is a relatively new technique to measure coronary calcification. Since coronary calcification assessed by electron beam CT is strongly correlated with the amount of coronary atherosclerotic plaque (6,7), the amount of coronary calcification can be used as a measure of coronary atherosclerosis.

Only few studies have examined the association between measures of extracoronary atherosclerosis and coronary calcification (8–11). However, these studies performed measurements only at one extracoronary site (8,9) or included only subjects at high risk for cardiovascular disease (10,11). Therefore, in a large population-based study, we examined the associations between coronary calcification and common carotid artery (CCA) intima media thickness (IMT), carotid plaques, ankle-arm index (AAI) and aortic calcification.

METHODS
Study population. The Rotterdam Coronary Calcification Study was designed to study determinants and consequences of coronary calcification, detected by electron beam CT. The study is embedded in the Rotterdam Study. The Rotterdam Study is a population-based study that started with a baseline visit between 1990 to 1993. All inhabitants of a suburb of Rotterdam, aged 55 years and over, were invited (response 78%). The rationale and design of the Rotterdam Study have been described elsewhere (12). Follow-up visits took place in 1993 to 1994 and 1997 to 1999. From 1999 onward, the study population is extended...
with a second cohort comprising inhabitants who reached the age of 55 years after the baseline examination in 1990 to 1993 and subjects aged 55 years and over who migrated into the research area. Baseline and follow-up visit examinations included noninvasive measurements of atherosclerosis. Measurement protocols for the first and second cohort were identical.

From 1997 onward, participants through 85 years of age completing the third phase of the first cohort or the baseline examination of the second cohort of the Rotterdam Study were invited to participate in the Rotterdam Coronary Calcification Study and undergo an electron beam CT scan. We restricted the present analyses to participants recruited from the first cohort, who were scanned from 1997 to 2000. Of the 3,371 eligibles, scans were obtained for 2,063 subjects (response 61%). Due to several causes, that is, metal clips from cardiac surgery, severe artifacts and registration errors (electrocardiogram [ECG], acquisition), image acquisition data could not be reconstructed or analyzed in 50 subjects (response 61%). Due to several causes, that is, metal clips from cardiac surgery, severe artifacts and registration errors (electrocardiogram [ECG], acquisition), image acquisition data could not be reconstructed or analyzed in 50 subjects. Thus, scores were available for 2,013 participants.

The median duration between the examination of noninvasive measures of extracoronary atherosclerosis and electron beam CT scanning was 50 days. The Medical Ethics Committee of Erasmus Medical Center Rotterdam approved the study, and all participants gave informed consent.

**Coronary calcification.** We assessed coronary calcification in the epicardial coronary arteries detected on electron beam CT scans. Imaging was performed with a C-150 Imatron scanner (Imatron, South San Francisco, California). Before the subjects were scanned, they exercised breath-holding. From the level of the root of the aorta through the heart, 38 slices were obtained with 100-ms scan time and 3-mm slice thickness. We acquired images at 80% of the cardiac cycle, using ECG triggering, during a single breath-hold. The scanner was calibrated on a daily basis using a water phantom. Quantification of coronary calcification was performed with AccuImage software (AccuImage Diagnostics Corporation, South San Francisco, California) displaying all pixels with a density of over 130 Hounsfield units. Trained scan readers were blinded to the clinical data of the participants. A calcification was defined as a minimum of two adjacent pixels (area = 0.52 mm²) with a density over 130 Hounsfield units. We placed a region of interest around each high-density lesion in the epicardial coronary arteries. The peak density in Hounsfield units and the area in mm² of the individual coronary calcifications were calculated. A calcium score was obtained by multiplying each area of interest with a factor indicating peak density within the individual area, as proposed by Agatston et al. (13). We added the scores for individual calcifications, resulting in a calcium score for the entire epicardial coronary system.

**Measures of extracoronary atherosclerosis.** Ultrasonography of both left and right carotid artery was performed according to the protocol of the Rotterdam Study (14). Off-line, the mean and maximum IMT of the CCA were measured (14). For the current analyses, the average of the mean anterior and posterior IMT of both the left and right CCA was used. When one or more of the IMT measurements could not be obtained, the average of the remaining measurements was used. On line, the left and right CCA, bifurcation and internal carotid artery were evaluated for the presence (yes/no) of atherosclerotic lesions (plaques). A plaque was defined as a focal widening (of at least 1.5 times the average IMT) relative to adjacent segments, with protrusion into the lumen. The anterior and posterior wall were evaluated and the number of affected locations counted. If one of the affected locations could not be visualized, the subject was excluded from the analyses. This resulted in a plaque score between 0 and 6.

The AAI is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm. According to the protocol of the Rotterdam Study, the AAI was measured at both legs (15). For the current analyses, we used the lowest measurement. Because of possible measurement artifacts reflecting the presence of rigid or calcified walls, seven participants with an AAI >1.5 were excluded. Subjects with an unmeasurable ankle pressure, which was considered to be due to atherosclerosis, were classified as having an AAI of 0.

Aortic calcification was diagnosed by radiographic detection of calcified deposits in the abdominal aorta (16). Lateral abdominal radiographs were made from a fixed distance with the subject seated. Calcifications in the abdominal aorta were classified as present when linear densities were seen in an area parallel and anterior to the lumbar spine (L1 to L4). Calcification of the anterior and posterior wall was scored separately. The extent of atherosclerosis was classified as absent, dubious, mild, moderate and severe, according to the length of the involved area of the posterior wall (0, ≤1.0 cm, 1.1 to 2.4 cm, 2.5 to 4.9 cm and ≥5 cm, respectively).

**Cardiovascular risk factors.** Information on smoking was obtained during the home interview of the Rotterdam Study and the number of pack-years of smoking was computed. Clinical measures were obtained during a visit at the Rotterdam study center. Height and weight were measured and the body mass index was calculated (weight [kg]/height [m]²). Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in sitting position. The mean of two consecutive measurements was used in the analyses. After an overnight of fasting, blood samples were obtained at the research
center. Serum total cholesterol level was determined by an enzymatic procedure. High-density lipoprotein (HDL) was measured similarly after precipitation of the non-HDL fraction (17). Fasting glucose level was determined enzymatically by the hexokinase method. A history of myocardial infarction was based on self-report checked with records from general practitioner or cardiologist and/or on electrocardiographic evidence. Two research physicians independently coded events, according to the ICD-10 classification (18); final decisions were made by a medical expert in the field who reviewed the coded events.

**Statistical analysis.** The distribution of the calcium score was highly skewed and, therefore, log (total calcium score +1) was used for linear regression analysis. Age-adjusted regression coefficients were computed using extracoronary measures as independent variables and log calcium score as dependent variable. Aortic calcification and carotid plaques were considered as ordinal variables (carotid plaques 0 to 6, aortic calcifications 0 to 4). In subsequent models, we additionally adjusted for cardiovascular risk factors and excluded subjects with a history of myocardial infarction. Age-adjusted standardized regression coefficients were computed to compare the strength of the associations.

We performed analyses of variance to compute age-adjusted geometric means of the calcium score for categories of extracoronary measures. For this endeavor, CCA IMT was categorized into quintiles (cut-off values were 0.78, 0.86, 0.93 and 1.03 for men and 0.73, 0.80, 0.87 and 0.96 for women) and carotid plaques according to the number of carotid plaques present (0, 1, 2, 3 and ≥4). Similarly, AAI was divided into five categories (≥1.20, 1.10 to 1.19, 1.00 to 1.09, 0.90 to 0.99 and <0.90). For all measures, the category reflecting the lowest amount of atherosclerosis was used as the reference category. A Student t test was performed to compare the geometric mean calcium score of each category with the reference category. We used linear regression analysis with continuous variables (IMT, AAI) or ordinal variables (carotid plaques 0 to 6, aortic calcifications 0 to 4) as test for trend. The numbers of subjects with measurements of CCA IMT, carotid plaques, AAI and aortic calcification were 1,857, 1,734, 1,949 and 1,751, respectively. All analyses were performed in men and women separately.

**RESULTS**

Table 1 shows characteristics of the Rotterdam Coronary Calcification Study population. Men had a median calcium score of 312 (interquartile range, 62 to 969) whereas women had a median calcium score of 56 (5 to 261). The CCA IMT, carotid plaques and aortic calcification were positively and AAI was inversely associated with coronary calcification (Table 2). Additional adjustment for cardiovascular risk factors (Table 2) and exclusion of subjects with a history of myocardial infarction (data not shown) slightly attenuated the strength of the associations. Standardized regression coefficients (Table 3) showed that associations with coronary calcification were stronger for carotid plaques and aortic calcification than for CCA IMT and AAI.

Geometric mean calcium scores for categories of the measures of extracoronary atherosclerosis for men and women are shown in Figures 1 and 2, respectively. A graded increase in coronary calcification was seen across quintiles of CCA IMT. Further subdivision of the fifth quintile showed that the highest average calcium score was observed in the upper decile of CCA IMT (373 for men and 100 for women). A strong and graded increase in coronary calcification was seen with an increasing number of carotid plaques present. A further increase in calcium score was found when only five or six carotid plaques were classified in the highest category (854 for men, 212 for women).

The AAI was inversely associated with coronary calcification. While only a slight increase (men) or no increase (women) in coronary calcification was seen in the upper three categories of AAI, increased levels of coronary calcification were found in subjects with an AAI of 0.90 to 0.99 (p < 0.05 for men and p = 0.26 for women, compared to the reference category) and those with an AAI <0.90 (p < 0.001 for men and p < 0.001 for women). Further subdivision of the lowest category of AAI showed that subjects with an AAI <0.70 had the highest calcium score (407 in men, 128 in women).

Aortic calcification was strongly associated with coronary calcification. In men, there was an 11-fold increase in coronary calcification from the lowest category of aortic calcification (calcification absent) to the category of severe calcification. In women, this increase was 20-fold.

### Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n = 933)</th>
<th>Women (n = 1,080)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>71.2 ± 5.6</td>
<td>71.3 ± 5.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.5 ± 3.2</td>
<td>27.4 ± 4.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>144 ± 21</td>
<td>142 ± 21</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77 ± 11</td>
<td>75 ± 11</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.6 ± 0.9</td>
<td>6.0 ± 0.9</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.2 ± 0.3</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>Serum glucose (mmol/l)</td>
<td>6.1 ± 1.7</td>
<td>5.8 ± 1.3</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Past</td>
<td>72</td>
<td>39</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Calcium score*</td>
<td>312 (62-969)</td>
<td>56 (5-261)</td>
</tr>
<tr>
<td>Log calcium score</td>
<td>5.3 ± 2.1</td>
<td>3.7 ± 2.3</td>
</tr>
<tr>
<td>CCA IMT (mm)</td>
<td>0.90 ± 0.17</td>
<td>0.84 ± 0.13</td>
</tr>
<tr>
<td>Carotid plaque (%)†</td>
<td>78</td>
<td>59</td>
</tr>
<tr>
<td>AAI</td>
<td>1.03 ± 0.21</td>
<td>1.04 ± 0.16</td>
</tr>
<tr>
<td>Aortic calcification (%)‡</td>
<td>47</td>
<td>35</td>
</tr>
</tbody>
</table>

Categorical variables are expressed as percentage. Values of continuous variables are expressed as mean ± standard deviation. *Value of the calcium score is expressed as median (interquartile range) because of its skewed distribution; †percentage of subjects with one or more carotid plaques; ‡percentage of subjects with aortic calcification over a length of at least 2.5 cm.

AAI = ankle-arm index; CCA = common carotid artery; HDL = high-density lipoprotein; IMT = intima media thickness.
Table 2. Regression Coefficients for Men and Women Separately, Describing the Increase in Log Calcium Score per Unit Increase of the Extracoronary Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 Beta Coefficients (95% CI)</th>
<th>p Value</th>
<th>Model 2 Beta Coefficients (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA IMT</td>
<td>2.13 (1.31–2.96)</td>
<td>&lt; 0.001</td>
<td>1.83 (0.75–2.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>0.47 (0.39–0.54)</td>
<td>&lt; 0.001</td>
<td>0.45 (0.36–0.54)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AAI</td>
<td>−1.28 (−1.92–−0.65)</td>
<td>&lt; 0.001</td>
<td>−1.02 (−2.08–1.77)</td>
<td>0.007</td>
</tr>
<tr>
<td>Aortic calcification</td>
<td>0.59 (0.49–0.69)</td>
<td>&lt; 0.001</td>
<td>0.59 (0.48–0.70)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA IMT</td>
<td>2.16 (1.08–3.24)</td>
<td>&lt; 0.001</td>
<td>1.77 (0.47–3.06)</td>
<td>0.008</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>0.55 (0.45–0.64)</td>
<td>&lt; 0.001</td>
<td>0.53 (0.42–0.64)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AAI</td>
<td>−1.63 (−2.41–−0.84)</td>
<td>&lt; 0.001</td>
<td>−1.04 (−2.06–2.02)</td>
<td>0.04</td>
</tr>
<tr>
<td>Aortic calcification</td>
<td>0.74 (0.65–0.84)</td>
<td>&lt; 0.001</td>
<td>0.70 (0.59–0.81)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Model 1 is adjusted for age; model 2 is adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, serum glucose and number of pack-years smoked. Regression coefficients describe the increase in log calcium score per unit increase (IMT: per mm, plaques: per plaque, AAI: per unit, aortic calcification: per unit [0 to 4]).

CI = confidence interval; other abbreviations as in Table 1.

**DISCUSSION**

Our population-based study shows clear associations between coronary calcification assessed by electron beam CT and CCA IMT, carotid plaques, AAI and aortic calcification. While graded associations with coronary calcification were found for carotid and aortic measures, a nonlinear association was found for AAI. The associations were strongest for carotid plaques and aortic calcification. Associations were present in both men and women and were only slightly attenuated after correction for cardiovascular risk factors and exclusion of subjects with a history of myocardial infarction.

**Study limitations.** Electron beam CT scans were obtained in 2,063 subjects. Subjects undergoing electron beam CT scanning had approximately the same levels of risk factors and social class as the nonresponders. There were slight differences between responders and nonresponders in age (70.6 vs. 72.4 years), gender (46% vs. 38% male), body mass index (27.0 vs. 26.7 kg/m²) and ever smoking (90% vs. 86% for men, 53% vs. 49% for women). Measurements of extracoronary atherosclerosis and electron beam CT scanning were not performed during the same session. However, since the median duration between the measurements was only 50 days, it is not likely that this has affected our results. All measurements of extracoronary atherosclerosis included missing values. Since these missing values were largely due to logistic reasons, we can assume them to be random. **Previous studies.** Associations between coronary and extracoronary atherosclerosis have been known for decades. Necropsy studies in the 1960s already found a close association between atherosclerosis in the coronary arteries and atherosclerosis in the aorta (19), the iliac artery and the carotid artery (20). Studies in the living had to be awaited until noninvasive measures of atherosclerosis became available. So far, only a limited number of studies examined associations between measures of coronary and extracoronary atherosclerosis. In a population-based study among young subjects (33 to 42 years), an association was found between carotid IMT and coronary calcification (8). Similarly, aortic and coronary calcium scores both assessed by electron beam CT were found to be associated in postmenopausal women (9). In hypercholesterolemic asymptomatic patients, the presence of ultrasonographically detected plaques in the femoral artery and the aorta was found to be associated with coronary calcification assessed by electron beam CT (10). In the latter study, the association between carotid plaques and coronary calcification did not reach statistical significance. In men with at least one cardiovascular risk factor, ultrasound was used to detect plaques in the carotid and femoral artery and the aorta. The number of affected extracoronary sites was found to be associated with coronary calcification assessed by electron beam CT (11). The major limitations of the previous studies are the measurement of atherosclerosis only at one extracoronary site (8,9) and the use of a selected population (10,11). Furthermore, to our knowledge only one study included both men and women (8). **Coronary calcification and measures of carotid atherosclerosis.** It is still a matter of debate whether increased carotid IMT indicates atherosclerosis or merely reflects an adaptive response of the vessel wall to changes in shear and tensile stress (21). The present study showed a graded association between coronary calcification and CCA IMT,
Figure 1. Age-adjusted geometric mean calcium score for categories of carotid intima media thickness (IMT), carotid plaques, ankle-arm index (AAI) and aortic calcification, for men. *Significant higher geometric mean calcium score as compared to the reference category (p < 0.05); †p for trend <0.001.

Figure 2. Age-adjusted geometric mean calcium score for categories of carotid intima media thickness (IMT), carotid plaques, ankle-arm index (AAI) and aortic calcification, for women. *Significant higher geometric mean calcium score as compared to the reference category (p < 0.05); †p for trend <0.001.
which supports the existing evidence that carotid IMT may be regarded as a continuous measure of generalized atherosclerosis. We made a simple quantification of carotid plaques by counting the number of affected locations. The plaque score, however, showed a strong and graded association with coronary calcification.

**Coronary calcification and AAI.** Our results showed the association between AAI and coronary calcification to be nonlinear. Levels of AAI >1.00 were only weakly associated with the calcium score. This may suggest that in the higher range, AAI may not reflect the severity of atherosclerosis and is consistent with the view that an AAI >1.00 rules out significant peripheral arterial narrowing. If so, this implies that the AAI should not be considered as a continuous measure of generalized atherosclerosis. However, the results show that not only subjects with an index <0.90, which is generally used as a cut-off value for the presence of peripheral arterial disease, but also subjects with an index between 0.90 and 0.99 have increased levels of coronary calcification compared to subjects with higher values.

**Coronary and aortic calcification.** In the present study, strong and graded associations were shown between coronary and aortic calcification. The 10-fold increase in calcium score in men and the 20-fold increase in calcium score in women implies that aortic calcification can be seen as a continuous measure of generalized atherosclerosis.

**Measurement techniques.** By using different measurement techniques, we measured different stages of atherosclerosis. Intima media thickening is considered to reflect a less advanced stage of atherosclerosis than the presence of plaques (22). In addition, AAI is considered to be a marker of atherosclerosis that is not only influenced by the presence of plaques but also by hemodynamic factors and vascular stiffness. Furthermore, calcified plaques are generally thought to reflect a more advanced stage of atherosclerosis than noncalcified plaques (23). The use of coronary calcification as a measure of coronary atherosclerosis and the use of aortic calcification as a measure of aortic atherosclerosis may have favored the association between those measures in our study. Due to the measurement of different stages of atherosclerosis, no definite conclusions can be drawn concerning the strength of associations between coronary atherosclerosis and atherosclerosis in the carotid artery, peripheral arteries and aorta.

**Calcium and plaques.** Despite the observation that calcium is frequently present in complicated plaques, histopathologic studies are not conclusive on the role of coronary calcium; calcium is a marker for neither unstable nor stable plaques (24). However, the close association of coronary calcium with the total amount of coronary atherosclerotic plaques (6,7) offers the opportunity to categorize subjects with respect to the extent of atherosclerosis.

**CONCLUSIONS**

Our population-based study shows that graded associations are present between coronary calcification as measured by electron beam CT and CCA IMT, carotid plaques and aortic calcification. A nonlinear association is present between coronary calcification and AAI. This large population-based study supports the concept of generalized atherosclerosis for a variety of vessels of the vascular tree.

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**Reprint requests and correspondence:** Dr. Jacqueline C. M. Witteman, Department of Epidemiology and Biostatistics, Erasmus Medical Center Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands. E-mail: witteman@epib.fgg.eur.nl.

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