Stroke Is Associated With Coronary Calcification as Detected by Electron-Beam CT
The Rotterdam Coronary Calcification Study

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Background and Purpose—Coronary calcification as detected by electron-beam CT measures the atherosclerotic plaque burden and has been reported to predict coronary events. Because atherosclerosis is a generalized process, coronary calcification may also be associated with manifest atherosclerotic disease at other sites of the vascular tree. We examined whether coronary calcification as detected by electron-beam CT is related to the presence of stroke.

Methods—From 1997 onward, subjects were invited to participate in the prospective Rotterdam Coronary Calcification Study and undergo electron-beam CT to detect coronary calcification. The study was embedded in the population-based Rotterdam Study. Calcifications were quantified in a calcium score according to Agatston's method. Calcium scores were available for 2013 subjects (mean age [SD], 71 [5.7] years). Fifty subjects had experienced stroke before scanning.

Results—Subjects were 2 times more likely to have experienced stroke when their calcium score was between 101 and 500 (odds ratio [OR], 2.1; 95% CI, 0.9 to 4.7) and 3 times more likely when their calcium score was above 500 (OR, 3.3; 95% CI, 1.5 to 7.2), compared with subjects in the lowest calcium score category (0 to 100). Additional adjustment for cardiovascular risk factors did not materially alter the risk estimates.

Conclusions—In this population-based study, a markedly graded association was found between coronary calcification and stroke. The results suggest that coronary calcification as detected by electron-beam CT may be useful to identify subjects at high risk of stroke. (Stroke. 2002;33:462-465.)

Key Words: atherosclerosis ■ calcium ■ epidemiology ■ stroke ■ tomography

Several studies have shown that noninvasive measures of atherosclerosis predict cerebrovascular events. Coronary calcification as detected by electron-beam CT is closely related to the amount of coronary atherosclerotic plaque and has been reported to predict coronary events. There is a close relation between calcification of the coronary arteries and the extracoronary plaque burden. Therefore, coronary calcification may also be associated with manifest atherosclerotic disease at other sites of the vascular tree. No data are available on the association between coronary calcification and cerebrovascular events. We studied the association of coronary calcification as detected by electron-beam CT and the presence of stroke in 2013 elderly men and women who participated in the population-based Rotterdam Coronary Calcification Study.

Subjects and 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 was embedded in the Rotterdam Study. The Rotterdam Study is a population-based study that started in 1990–1993. All inhabitants of a suburb of Rotterdam, aged 55 years and older, were invited to participate (response 78%). The rationale and design of the Rotterdam Study have been described elsewhere. Follow-up visits took place in 1993–1994 and 1997–1999. From 1999 onward, the study population has been extended, with a second cohort comprising participants aged 55 years after the baseline examination from 1990–1993 and subjects aged 55 years and older 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 who completed 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. Subjects in nursing homes did not visit the research center and thus were not invited to join the Rotterdam Coronary Calcification Study. We restricted the present analysis to participants from the first cohort, who were scanned from 1997–2000. Of the 3371 eligible participants recruited from the first
Measurements of Heart Disease

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Measurement of Coronary Calcifications

We assessed coronary calcifications in the epicardial coronary arteries detected on electron-beam CT scans. Imaging was performed with a C-150 Imatron scanner (Imatron). Before the subjects were scanned, they exercised adequate breath-holding. From the level of the root of the aorta through the heart, 38 images 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. Every day that the scanner was used, we calibrated the scanner using a water phantom. Quantification of coronary calcifications was performed with AccuImage software (AccuImage Diagnostics Corporation) displaying all pixels with a density of over 130 Hounsfield units. The trained scan readers were blinded to the clinical data of the participants. A calcification was defined as a minimum of two adjacent pixels (area = 0.65 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. We summed the scores for individual calcifications, which resulted in a calcium score for the entire epicardial coronary system. To conform with the protocol outlines as approved by the Medical Ethics Committee, participants were not informed about their calcium score.

Diagnosis of Stroke

A stroke was categorized as present if stroke had occurred before the baseline examination from 1990–1993 or after baseline but before electron-beam CT scanning (1997–2000). Of subjects who reported a history of stroke at the baseline examination, the general practitioner (GP) was asked for supplementary medical information, including a detailed history, information on neuroimaging, and copies of hospital discharge records. After the baseline examination, GPs in the research area, covering 85% of the cohort, reported the possible stroke events to the research center. For 15% of the cohort, of which the GPs had practices outside the research area, information was obtained annually by checking the participant’s GP file and by interviewing the GP. When an event was reported, additional information including the date of the possible stroke was obtained by interviewing the GP and scrutinizing information from hospital discharge records and/or neuroimaging in the case of admission or referral. Medical information was checked and evaluated by an experienced neurologist from the Erasmus Medical Center Rotterdam. Events were coded according to the International Classification of Diseases, 10th version. The neurologist classified the events as definite, probable, possible, and no stroke. A stroke was classified by the neurologist as definite when the event led to a hospitalization, and the hospital discharge record indicated a diagnosis of a new stroke, based on clinical signs and symptoms and/or on neuroimaging during hospital stay. When, in the case of no hospitalization, signs and symptoms associated with the event obtained from the GP records and interview were highly suggestive of a stroke according to the neurologist, the stroke was classified as probable. Definite and probable events were used in the analyses.

Measurement of Cardiovascular Risk Factors

Information on smoking was obtained during the home interview of the Rotterdam Study. We categorized subjects as current, past, or never smokers. Anthropometric measures were obtained during the visit at the Rotterdam research center. Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in sitting position. The mean value of two consecutive measurements was used in the analyses. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher. After an overnight fasting, blood samples were obtained at the research center. Serum total cholesterol was determined by an enzymatic procedure. High-density lipoprotein (HDL) was measured similarly after precipitation of the non-HDL fraction. Diabetes mellitus was considered present with current use of antidiabetic medication or when fasting glucose levels exceeded 7.0 mmol/L.

Statistical Analysis

The distribution of calcium scores was skewed, and therefore, medians and ranges were reported. Linear regression analysis was applied to compare the age-adjusted continuous baseline characteristics of the Rotterdam Coronary Calcification Study and the nonresponders. To compare sex, smoking status, and the percentage of subjects with hypertension, diabetes mellitus, stroke, and myocardial infarction between the study population and the group of nonresponders, the chi-square test was used. Three absolute calcium score categories were defined, based on cut points that were chosen before examining the association with the presence of stroke: 0 to 100, 101 to 500, and above 500. Age- and sex-adjusted odds ratios (OR) with 95% CI for the presence of stroke were calculated per calcium score category using logistic regression analysis. Calcium score category 0 to 100 was used as reference. Analyses for calcium score categories were repeated with additional adjustment for cardiovascular risk factors (smoking, total cholesterol, HDL cholesterol, hypertension, diabetes mellitus). Age-adjusted ORs (95% CI) were also calculated for men and women separately. SPSS 9.0 for Windows, (SPSS Inc) was used for data analysis.

Results

Table 1 describes the characteristics of the 2013 participants of the Rotterdam Coronary Calcification Study. The mean age (standard deviation [SD]) of the study population was 71

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Population (n = 2013)</th>
<th>Nonresponders (n = 1308)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>70.8 ± 5.5</td>
<td>72.5 ± 6.5*</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>46.3</td>
<td>37.8*</td>
</tr>
<tr>
<td><strong>Smokers (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Current</td>
<td>16.2</td>
<td>16.4</td>
</tr>
<tr>
<td>- Past</td>
<td>54.2</td>
<td>46.5*</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>27.0 ± 3.9</td>
<td>26.7 ± 4.1*</td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/L)</strong></td>
<td>5.8 ± 1.0</td>
<td>5.9 ± 1.0</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/L)</strong></td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>54.4</td>
<td>54.5</td>
</tr>
<tr>
<td><strong>Diabetes mellitus (%)</strong></td>
<td>13.2</td>
<td>13.2</td>
</tr>
<tr>
<td><strong>History of stroke (%)</strong></td>
<td>2.5</td>
<td>3.6*</td>
</tr>
<tr>
<td><strong>History of myocardial infarction (%)</strong></td>
<td>11.8</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Calcium score</strong></td>
<td>135 (13–578)</td>
<td></td>
</tr>
<tr>
<td><strong>Log calcium score</strong></td>
<td>4.4 ± 2.4</td>
<td></td>
</tr>
</tbody>
</table>

Values are unadjusted proportions or means ± standard deviation, except for the calcium score, which is expressed as median (interquartile range) because of its skewed distribution.

*P<0.05 compared with nonresponders, adjusted for differences in age and sex (except for the variable age: sex-adjusted).

Calcium scores were expressed as calcium score, which is expressed as median (interquartile range) because of its skewed distribution.
TABLE 2. Risk of Stroke in Calcium Score Categories

<table>
<thead>
<tr>
<th>Calcium score</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>0–100</td>
<td>1.0</td>
<td>...</td>
</tr>
<tr>
<td>101–500</td>
<td>2.1</td>
<td>0.9–4.7</td>
</tr>
<tr>
<td>&gt;500</td>
<td>3.3</td>
<td>1.5–7.2</td>
</tr>
</tbody>
</table>

Test for trend $P=0.001$ $P=0.007$

OR indicates odds ratio; CI, confidence interval; n, number of subjects.

*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, smoking, total cholesterol, HDL cholesterol, hypertension, and diabetes mellitus.

The number of subjects in model 2 is somewhat lower than for model 1 (n=1795), because of missing values for cardiovascular risk factors.

(5.7) years. Comparison of characteristics of study participants and nonresponders demonstrated no significant differences with regard to total and HDL cholesterol levels, hypertension, diabetes mellitus, and history of myocardial infarction. However, the scanned population was significantly younger (mean age difference, 1.7 years), consisted of relatively more men (46% versus 38%), was more likely to have a history of smoking (70% versus 63%), and had a slightly higher body mass index (27.0 versus 26.7). Furthermore, compared with the nonresponders, a slightly lower percentage of study participants had a history of stroke (2.5% versus 3.6%). The median calcium score was 135 (interquartile range, 13 to 578). The median calcium score was higher for men than for women: 312 (interquartile range 62 to 970) and 55 (interquartile range 5 to 261), respectively. In 34 men (3.6%) and 16 women (1.5%), stroke was recorded before electron-beam CT scanning. The mean interval (SD) between the stroke and scanning was 8.8 (7.8) years.

In logistic regression analysis, a graded association was found between the amount of coronary calcification and the presence of stroke (Table 2). The age-adjusted OR of stroke were 2.1 (95% CI, 0.9 to 4.7) in calcium score category 101 to 500, and 3.3 (95% CI, 1.5 to 7.2) in subjects with a calcium score above 500, when compared with subjects in the reference category (calcium score of 0 to 100). Additional adjustment for cardiovascular risk factors did not substantially alter the results (model 2).

Table 3 shows risk estimates for men and women separately. In men, age-adjusted OR for the presence of stroke increased from 3.5 (95% CI, 0.9 to 12.8) in calcium score category 101 to 500, to 5.2 (95% CI, 1.5 to 17.8) in calcium score category above 500, when compared with subjects in the reference category (calcium score of 0 to 100). The corresponding age-adjusted OR in women were 1.3 (95% CI, 0.4 to 4.6) and 2.4 (95% CI, 0.7 to 7.8), respectively. In men, 62% of the strokes occurred in the calcium score category above 500, whereas in women this percentage was 31.

**Discussion**

The amount of coronary calcification showed a graded association with the presence of stroke in a general population of elderly subjects. Subjects in the highest calcium score category (above 500) were 3 times more likely to have experienced a stroke compared with subjects in the reference calcium score category (up to 100). The OR of stroke was 5.2 for men with a calcium score above 500 in comparison to men with a calcium score up to 100. In women with a calcium score above 500, stroke had occurred 2.4 times more often than in women in the reference calcium score category, although the estimates are less certain for women because of small numbers.

Scans were obtained from 2063 subjects recruited from the first cohort of the Rotterdam Study. Comparison of all characteristics of the participants of the Rotterdam Coronary Calcification Study with the nonresponders showed a relevant difference only in the mean age, the percentage of men, and the percentage of subjects with a history of smoking. Subjects with severe disability, possibly resulting from stroke, may not have been included in this study, because the highest calcium scores are to be expected in the subjects with disabling cardiovascular disease. Thus, we were not able to assess the possibly stronger association between coronary calcification and stroke in subjects with severe cardiovascular disease. Secondly, because of small numbers of cases, the confidence intervals of the sex-specific OR are wide. This should induce caution when drawing conclusions on the strength of the association in men and women. To obtain more reliable risk estimates on the association between coronary calcification and stroke by gender, more cases are needed. Furthermore, the threshold used in this study for detection of coronary calcifications was 2 consecutive pixels. Some studies have used higher thresholds to reduce the contribution of noise. However, in a subgroup of subjects, we found a very high correlation coefficient ($r=0.99$) between calcium scores obtained using a threshold of 2 pixels and a threshold of 4 pixels. Thirdly, because of the fact that the association of coronary calcification with stroke was evaluated in a cross-sectional study design, only survivors of a cerebrovascular event were included. It is uncertain whether the same risk estimates would have been found for fatal events.
of stroke are more likely to have had less severe types of stroke, such as lacunar infarctions, possibly limiting the range of stroke severity. Because there was an interval between the occurrence of stroke and scanning of 8.8 years on average, subjects may have been classified into a different calcium score category than the classification would have been if coronary calcification had been measured at the time of the cerebrovascular event. Furthermore, the cerebrovascular event in the past may have initiated medication use to reduce cardiovascular risk. This could have diminished the difference in coronary calcium load between subjects with and without stroke, resulting in underestimation of the OR. After adjustment for cardiovascular determinants, risk estimates changed only slightly. This lack of change may in part be a result of modification of risk factors in subjects after the cerebrovascular event, leading to misclassification of risk factors.

Noninvasive measures of atherosclerosis have been shown to predict cerebrovascular events. Studies investigating the relation of carotid intima-media thickness with stroke have presented relative risks ranging between 3.4 and 8.5 for highest versus lowest quintile or category of intima-media thickness. Low ankle brachial pressure index also indicates an increased risk of stroke, but relative risks of stroke associated with this measure were lower. Because we investigated the association between coronary calcification and stroke in a cross-sectional design, the risk estimates cannot be compared directly with the results from these prospective studies. However, in our study, coronary calcification was strongly related to the presence of stroke. Therefore, coronary calcium detection by electron-beam CT may not only be useful to identify subjects at high risk of coronary heart disease but additionally those at high risk of stroke.

Conclusion
In conclusion, we observed a markedly graded association between the amount of coronary calcification and stroke in an elderly population. This is the first study on the association between coronary calcification as detected by electron-beam CT and stroke. Although prospective data need to confirm our findings, this population-based cross-sectional study suggests that the amount of coronary calcification identifies subjects at high risk of cerebrovascular events.

Acknowledgments
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