Coronary Calcification Improves Cardiovascular Risk Prediction in the Elderly

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Background—Coronary calcification detected by electron beam tomography may improve cardiovascular risk prediction. The technique is particularly promising in the elderly because the predictive power of cardiovascular risk factors weakens with age. We investigated the prognostic value of coronary calcification for cardiovascular events and mortality in a general, asymptomatic population of elderly subjects.

Methods and Results—From 1997 to 2000, electron beam tomography scanning to assess coronary calcification was performed in subjects of the population-based Rotterdam Study. Risk factors were measured by standardized procedures. Coronary calcium scores were available for 1795 asymptomatic participants (mean age, 71 years; range, 62 to 85 years). During a mean follow-up of 3.3 years, 88 cardiovascular events, including 50 coronary events, occurred. The risk of coronary heart disease increased with increasing calcium score. The multivariate-adjusted relative risk of coronary events was 3.1 (95% CI, 1.2 to 7.9) for calcium scores of 101 to 400, 4.6 (95% CI, 1.8 to 11.8) for calcium scores of 401 to 1000, and 8.3 (95% CI, 3.3 to 21.1) for calcium scores >1000 compared with calcium scores of 0 to 100. The predictive value in subjects <70 years of age was similar. Risk prediction based on the cardiovascular risk factors improved when coronary calcification was added.

Conclusions—Coronary calcification is a strong and independent predictor of coronary heart disease, also in the elderly. Coronary calcification improves prediction of coronary events based on cardiovascular risk factors. Risk stratification by assessment of coronary calcification may have an important role in the primary prevention of coronary heart disease events in the elderly. (Circulation. 2005;112:572-577.)

Key Words: atherosclerosis ■ epidemiology ■ imaging ■ myocardial infarction ■ population

Coronary calcification, assessed by electron beam tomography (EBT), may be useful for identifying subjects at high risk of coronary heart disease (CHD). Several studies have shown that the amount of coronary calcification is associated with the risk of CHD.1–7 Published studies were conducted in younger populations with wide age ranges; therefore, information in specific groups like the elderly is lacking. The predictive power of cardiovascular risk factors decreases with age, partly because of selective survival and the influence of comorbidity on risk factor levels.8–10 Because calcification of the coronary arteries can be seen as a cumulative measure of lifetime exposure to cardiovascular risk factors, coronary calcification may be especially important for assessing cardiovascular risk in the elderly.

Information on the predictive value of coronary calcification beyond the assessment of risk factors is scarce. Most published studies have used unmeasured, self-reported risk factors,1–3,5 which may underestimate the true prevalence of risk factors. In the only study with measured risk factors, conducted in an intermediate- to high-risk population, a high calcium score was recently shown to modify coronary risk prediction based on risk factors.7

The Rotterdam Coronary Calcification Study is a prospective population-based study with standardized measurement of cardiovascular risk factors among 2013 elderly, of whom 1795 had no history of CHD. We studied the predictive value of coronary calcification for CHD, cardiovascular disease (CVD), and mortality.

Methods

Study Population

The Rotterdam Coronary Calcification Study was designed to study determinants and consequences of coronary calcification detected by EBT. The study was embedded in the Rotterdam Study, a prospective, population-based study among subjects ≥55 years of age that started in 1990. The rationale and design of the Rotterdam Study

References


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Atherosclerosis Measurements

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 research center. Blood pressure was measured at the right brachial artery with a random-zero sphygmomanometer with the participant in sitting position. The mean of 2 consecutive measurements was used. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, and/or use of blood pressure–lowering medication for the indication hypertension. After an overnight fast, blood samples were obtained at the research center. Serum total cholesterol was determined by an automated enzymatic procedure using the Roche CHOD-PAP reagent, and HDL was measured with the Roche HDL cholesterol assay using PEG-modified enzymes and dextran sulfate. We defined hypercholesterolemia as a total cholesterol level of ≥5.5 mmol/L and/or use of cholesterol-lowering medication. Glucose was determined enzymatically by the Hexokinase method. Diabetes mellitus was considered present with current use of antidiabetic medication and/or fasting glucose levels exceeding 7.0 mmol/L. Family history was defined as a family history of myocardial infarction occurring before 65 years of age in first-degree relatives. The median duration between risk factor assessment and EBT scanning was 49 days. During the visit at the research center, the ankle-brachial blood pressure index, carotid intima-media thickness, carotid plaques, and extent of aortic calcification were assessed. Details of these measurements have been published.13 The Medical Ethics Committee of Erasmus University Rotterdam approved the study, and all participants gave informed consent.

Coronary Calcification

We assessed coronary calcifications in the epicardial coronary arteries detected on EBT scans. Imaging was performed with a C-150 Imatron scanner (GE-Imatron). Before the subjects were scanned, they exercised adequate breathing. 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. Using ECG triggering, we acquired images at 80% of the cardiac cycle during a single breathhold. Quantification of coronary calcifications was performed with AccuImage software (AccuImage Diagnostics Corp), displaying all pixels with a density ≥130 Hounsfield units. A calcification was defined as a minimum of 2 adjacent pixels (area, 0.65 mm²) with a density >130 Hounsfield units. Calcium scores were calculated according to Agatston's method.13 Scans were read by 2 readers (R.V., B.S.), one of whom is an experienced radiologist. Before reading of the scans in our study was started, both readers had a training period in which they read scans and compared calcium scoring results informally. The scan readers were blinded to the clinical data of the participants. To conform to the protocol outlines approved by the Medical Ethics Committee, participants were not informed about the calcium score.

Clinical Outcomes

Information concerning the vital status of the participants was obtained from the municipal health service of Rotterdam. Subjects in the Rotterdam Study were continuously monitored for the occurrence of cardiovascular events through automated linkage with the files from general practitioners in the research area of the Rotterdam Study (85% of the cohort). For the 15% of the cohort whose general practitioners had practices outside the research area, information was obtained through checking the participant’s file and by interviewing the general practitioner regularly. Two participants were lost to follow-up; their last dates of contact were used as censoring dates. When myocardial infarction, CABG, PTCA, stroke, or death was reported in the records of the general practitioner, research assistants collected additional information from these records and obtained information from hospital discharge records or nursing home records, including letters from medical specialists. Two research physicians independently coded the possible cardiovascular events according to the International Classification of Diseases, 10th edition.14 In case the research physicians disagreed on the diagnosis of a coronary event or stroke, a cardiologist or neurologist, respectively, reviewed the coded event and performed the definitive coding. The research physicians, cardiologist, and neurologist were not aware of the calcium score outcome. In the analyses, we used the following outcomes: CHD (incident myocardial infarction, CABG, PTCA, and CHD mortality), hard CHD (incident myocardial infarction and CHD mortality), CVD (incident myocardial infarction, CABG, PTCA, stroke, and cardiovascular mortality), and total mortality.

Statistical Analysis

Because the distribution of calcium scores was skewed, medians and 25th and 75th percentiles were reported. Calcium scores were...
divided into 4 categories: 0 to 100, 101 to 400, 401 to 1000, and >1000, adapted from the categorization as proposed by Rumberger et al.15 Age- and sex-adjusted Cox regression analysis was conducted to compute event-free survival curves for the calcium score categories. Hazard ratios of events in increasing calcium score categories were computed as estimates of relative risk. Subjects with a calcium score of 0 to 100 were the reference group. We also computed relative risks in a multivariate model containing, in addition to age and sex, the following cardiovascular risk factors: body mass index, hypertension, total cholesterol, HDL cholesterol, smoking, diabetes mellitus, and family history of myocardial infarction. The aforementioned Cox models were also applied in analyses restricted to subjects >70 years of age and in analyses in which subjects with a history of stroke were excluded. Furthermore, Cox regression analysis with CHD as outcome was also performed using the original calcium score categorization as proposed by Rumberger et al.15

Two additional analyses were conducted. First, the Framingham risk model as derived by Wilson et al16 was applied to calculate 10-year risk probabilities. Age- and sex-adjusted Cox regression analysis was conducted in categories based on the calcium score and Framingham risk score (<20% 10-year risk or >20% 10-year risk). Here, the second and third calcium score categories were combined to increase statistical power. Second, we computed probabilities of the 4 different outcomes for each subject as predicted by the multivariate Cox regression model excluding the calcium score and by a model that included the calcium score. Probabilities of events were also computed as predicted by age, sex, and the calcium score alone and by age, sex, and the Framingham risk score. We applied the probability values as thresholds to categorize results as positive or negative. True- and false-positive rates were determined for each threshold and used to construct receiver-operating characteristic (ROC) curves. Differences in the predicted values were estimated by comparing the areas under the ROC curve (AUC), taking correlation between areas into account.17

Finally, we compared the strength of the relation with CHD between coronary calcification and extracoronary measures of atherosclerosis using age- and sex-adjusted Cox regression analysis. Categorization of the extracoronary measures of atherosclerosis was based on the percentages of subjects in the calcium score categories. All measures of association are presented with 95% CIs. SPSS 11.0 for Windows (SPSS, Inc) was used for data analysis. In the population, information for 1 cardiovascular risk factor was missing for 3%.

Results

Baseline characteristics of the asymptomatic study population are shown in Table 1. The distribution of the calcium score was highly skewed (median, 98; 25th percentile, 10; 75th percentile, 430). The mean follow-up duration was 3.3 years (SD, 0.8 years; maximum, 4.9 years). Of the 1795 asymptomatic participants, 118 died during the follow-up period. Eighty-eight subjects suffered a cardiovascular event, including 40 nonfatal myocardial infarctions and CHD deaths, 11 revascularizations, 38 strokes, and 40 cardiovascular deaths. Of subjects who died during the follow-up, 34% died of cardiovascular disease, 36% died of cancer, 6% died of neurological diseases other than stroke, 3% died as a result of nonnatural causes, 2% died of respiratory diseases, 1% died as a result of fractures, and 18% died of other causes. The rates of events in the calcium score categories are shown in Figure 2.

Figure 3 shows the association between calcium score categories at the start of follow-up and survival free of new cardiovascular events, adjusted for differences in age and sex. The event-free survival increased with increasing calcium
score, with a cumulative incidence at 4 years of 3% for a calcium score up to 100 and 12% for a calcium score >1000.

Table 2 shows relative risks of events for categories of coronary calcification. There was an increasing risk of events with increasing calcium score (test for trend, \( P < 0.01 \) for all outcomes). Compared with a calcium score of 0 to 100, relative risks of events in subjects with a calcium score >1000 ranged from 2.7 for total mortality and 4.3 for CVD to 8.2 for CHD. Additional adjustment for cardiovascular risk factors resulted in generally unchanged risk estimates for all outcomes (2.7, 3.9, and 8.3, respectively). The strength of the associations between cardiovascular risk factors and events ranged from no association to relative risks of 1.5 to 2.6 for hypertension and diabetes mellitus. Additional exclusion of subjects with a history of stroke resulted in similar relative risks. When the Cox regression analyses were restricted to subjects \( \geq 70 \) years of age, similar relative risks of coronary and cardiovascular events were found. For example, among asymptomatic subjects \( >70 \) years of age, the relative risks of CHD for increasing calcium score categories compared with the reference category were 3.3, 5.5, and 8.2, respectively (Table 3). When the original calcium score categorization by Rumberger et al\(^{15}\) was used, relative risks for CHD increased from 5.0 (95% CI, 0.6 to 41.6) for a calcium score of 11 to 100, to 10.3 (95% CI, 1.3 to 79.9) for a calcium score of 101 to 400, to 19.8 (95% CI, 2.6 to 148.2) for a calcium score >400 compared with a calcium score of 0 to 10. The cutoff points of the latter categories matched quartiles in our population (25%, 25%, 26%, 24%).

Figure 4 presents age- and sex-adjusted relative risks of CHD and CVD by categories based on the calcium score and the Framingham risk function. Compared with the reference category (subjects with a calcium score of 0 to 100 and a Framingham risk score <20% 10-year risk), there was an increasing risk with increase in calcium score and Framingham risk score. Relative risks of CHD ranged from 3.2 for a calcium score of 101 to 1000 and Framingham risk score of <20% 10-year risk to 10.3 for a calcium score >1000 and Framingham risk score of >20% 10-year risk. Corresponding relative risks of CVD were 1.9 and 6.9, respectively.

The AUC, which indicates the power to discriminate subjects who will have a CHD event from those who will not, was 0.746 for the model based on age, sex, and calcium score. The AUC for the Framingham risk score was 0.730. Corresponding AUCs for subjects \( \geq 70 \) years were 0.711 and 0.682, respectively. The multivariate model of age, sex, and cardiovascular risk factors fitted for the current population had an AUC of 0.749. When the amount of coronary calcification was added to the multivariate model, the discriminatory power for CHD improved (AUC, 0.774; difference in AUC, 0.024; \( P \) for change=0.02). When coronary calcification was...
added to the multivariate model predicting hard CHD, CVD, and mortality, increases in AUCs of 0.023 (P for change/H11005 0.03), 0.013 (P/H11005 0.03), and 0.006 (P/H11005 0.10), respectively, were found.

Hazard ratios of CHD for the most severe level of extracoronary atherosclerosis compared with the lowest level were 1.5 (95% CI, 0.8 to 2.9) for ankle-brachial index, 1.6 (95% CI, 0.8 to 3.1) for intima-media thickness, 1.9 (95% CI, 1.0 to 3.5) for carotid plaques, and 2.7 (95% CI, 1.2 to 6.0) for aortic calcification.

**Discussion**

This is the first population-based study on the prognostic value of coronary calcification in the elderly. Studies in younger populations with wider age ranges have shown that the amount of coronary calcification increases the risk of CHD.1–7 Results from our study show that coronary calcification is a strong and independent predictor of CHD in the elderly also. The added information to cardiovascular risk factors and improved cardiovascular risk prediction. The predictive value was similar in subjects >70 years of age.

Strengths of the present study include standardized assessment of risk factor levels, subjects’ unawareness of the calcium scoring result, and a population-based sample. By using a standardized assessment of levels of risk factors, we reduced misclassification of risk factors. Awareness of a high calcium score may motivate a positive change in health behavior.18 Because participants in our study were unaware of the calcium score, change in lifestyle or medication use or further cardiac testing (and possible subsequent revascularization) on the basis of the calcium score was prevented. Therefore, revascularization procedures could be included in our study as coronary outcomes without inducing biased results. Most previous studies were conducted in populations of self-referred subjects.1–3,5 These subjects may be more health conscious or at high risk of cardiovascular disease. One study was performed in subjects with at least 1 cardiovascular risk factor.4,6,7 In our study, 61% of the invited population participated. Characteristics of the responders were highly similar to those of the nonresponders. There were no significant differences with regard to total and HDL cholesterol levels, hypertension, diabetes mellitus, and history of CHD. However, the scanned population was younger (mean age difference, 1.7 years), consisted of relatively more men (46.3% versus 37.8%), was more likely to have a history of smoking (70% versus 63%), had a slightly higher body mass index (27.0 versus 26.7), and was somewhat more likely to have a family history of myocardial infarction (19.6% versus 17.0%). Furthermore, compared with the nonresponders, a slightly lower percentage of study participants had a history of stroke (2.5% versus 3.6%). The only considerable difference was found in the percentage of men and women (8.5% more men among the study population compared with nonresponders). Responders and nonresponders did not show material differences in levels of cardiovascular risk factors. Therefore, we think that other reasons not related to cardiovascular risk may have caused the differential response of men and women. Although we think it is unlikely that selection bias has occurred, we cannot

**TABLE 3. Relative Risks of Events According to Calcium Score Category in Subjects >70 Years of Age**

<table>
<thead>
<tr>
<th>Calcium Score</th>
<th>Total/Events, n</th>
<th>Relative Risk (95% CI)</th>
<th>Age and Sex Adjusted</th>
<th>Multivariate Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–100</td>
<td>398/4</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
<tr>
<td>101–400</td>
<td>245/9</td>
<td>3.3 (1.0–10.7)</td>
<td>3.0 (0.9–9.9)</td>
<td></td>
</tr>
<tr>
<td>401–1000</td>
<td>167/11</td>
<td>5.5 (1.7–17.7)</td>
<td>5.4 (1.7–17.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>127/12</td>
<td>8.2 (2.6–26.1)</td>
<td>7.5 (2.3–24.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hard CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–100</td>
<td>398/4</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
<tr>
<td>101–400</td>
<td>245/7</td>
<td>2.5 (0.7–8.6)</td>
<td>2.4 (0.7–8.2)</td>
<td></td>
</tr>
<tr>
<td>401–1000</td>
<td>167/10</td>
<td>5.0 (1.5–16.2)</td>
<td>5.1 (1.5–17.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>127/11</td>
<td>7.5 (2.3–24.3)</td>
<td>7.6 (2.3–25.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–100</td>
<td>398/15</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
<tr>
<td>101–400</td>
<td>245/16</td>
<td>1.6 (0.8–3.2)</td>
<td>1.4 (0.7–3.0)</td>
<td></td>
</tr>
<tr>
<td>401–1000</td>
<td>167/15</td>
<td>2.0 (1.0–4.1)</td>
<td>1.9 (0.9–3.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>127/16</td>
<td>2.9 (1.4–6.1)</td>
<td>2.5 (1.2–5.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–100</td>
<td>398/19</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
<td></td>
</tr>
<tr>
<td>101–400</td>
<td>245/28</td>
<td>2.0 (1.1–3.5)</td>
<td>2.0 (1.1–3.6)</td>
<td></td>
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<tr>
<td>401–1000</td>
<td>167/22</td>
<td>2.1 (1.1–3.9)</td>
<td>2.0 (1.1–3.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>127/19</td>
<td>2.5 (1.3–4.7)</td>
<td>2.3 (1.2–4.5)</td>
<td></td>
</tr>
</tbody>
</table>

*Additionally adjusted for body mass index, hypertension, total cholesterol, HDL cholesterol, smoking, diabetes mellitus, and family history of myocardial infarction.

**Figure 4.** Relative risks of CHD (a) and CVD (b) by low and high Framingham risk score and calcium score categories. *P<0.05, †P<0.01.
exclude a slight underestimation or overestimation of the studied association.

Information on the ability of coronary calcification to improve risk prediction based on cardiovascular risk factors is scarce. Most published studies have used self-reported information on risk factors. Self-reported data on risk factors may result in underestimation of the true prevalence of risk factors. Only 1 study, conducted in an intermediate- to high-risk population, has actually measured risk factors.

In this study, a high calcium score was recently found to alter risk stratification. No data exist on the additive predictive value of coronary calcification over risk factors in the elderly. Our study shows that coronary calcification improves risk prediction based on cardiovascular risk factors in the elderly. The results suggest that a high calcium score (>1000) implies a high risk of CHD events, regardless of a low or high Framingham risk score. However, larger studies are needed to examine in detail the implications of different combinations of calcium scores and Framingham risk scores.

The predictive power of cardiovascular risk factors decreases with age, partly because of selective survival and the influence of comorbidity on risk factor levels. This may be the reason why risk estimates in our study did not diminish after adjustment for risk factors. Calcification of the coronary arteries can be seen as a cumulative measure of lifetime exposure to cardiovascular risk factors and may therefore improve risk stratification at older age. In the elderly, the choice between preventive drug therapy and lifestyle modification is necessary for the primary prevention of CHD. Therefore, accurate cardiovascular risk stratification is of utmost importance. The results of our study suggest that assessment of coronary calcification can be used as a tool for risk stratification in the elderly. The predictive value of coronary calcification was a factor higher than that of extracoronary measures of atherosclerosis.

In summary, this population-based study shows that coronary calcification is a strong and independent predictor of CHD in the elderly. Risk prediction improved when the calcium score was added to cardiovascular risk factors. Risk stratification by assessment of coronary calcification may have an important role in guiding decisions on drug therapy or lifestyle changes for the primary prevention of CHD events in elderly people.

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