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Coronary Calcium Score Improves Classification of Coronary Heart Disease Risk in the Elderly

The Rotterdam Study

Suzette E. Elias-Smale, MD,*‡ Rozemarijn Vliegenthart Proença, MD, PHD,† Michael T. Koller, MD,§ Maryam Kavousi, MD,* Frank J. A. van Rooij, DSC,* Myriam G. Hunink, MD, PHD,‡ Ewout W. Steyerberg, PHD,‖ Albert Hofman, MD, PHD,* Matthijs Oudkerk, MD, PHD,† Jacqueline C. M. Witteman, PHD*

Rotterdam and Groningen, the Netherlands; and Basel, Switzerland

Objectives The purpose of this study was to examine the effect of coronary artery calcium (CAC) on the classification of 10-year hard coronary heart disease (CHD) risk and to empirically derive cut-off values of the calcium score for a general population of elderly patients.

Background Although CAC scoring has been found to improve CHD risk prediction, there are limited data on its impact in clinical practice.

Methods The study comprised 2,028 asymptomatic participants (age 69.6 ± 6.2 years) from the Rotterdam Study. During a median follow-up of 9.2 years, 135 hard coronary events occurred. Persons were classified into low (<10%), intermediate (10% to 20%), and high (>20%) 10-year coronary risk categories based on a Framingham refitted risk model. In a second step, the model was extended by CAC, and reclassification percentages were calculated. Cutoff values of CAC for persons in the intermediate-risk category were empirically derived based on 10-year hard CHD risk.

Results Reclassification by means of CAC scoring was most substantial in persons initially classified as intermediate risk. In this group, 52% of men and women were reclassified, all into more accurate risk categories. CAC values above 615 or below 50 Agatston units were found appropriate to reclassify persons into high or low risk, respectively.

Conclusions In a general population of elderly patients at intermediate CHD risk, CAC scoring is a powerful method to reclassify persons into more appropriate risk categories. Empirically derived CAC cutoff values at which persons at intermediate risk reclassified to either high or low risk were 615 and 50 Agatston units, respectively. (J Am Coll Cardiol 2010;56:1407–14) © 2010 by the American College of Cardiology Foundation

In primary prevention of coronary heart disease (CHD), clinical management is generally based on a person's 10-year CHD risk as estimated by risk-scoring algorithms like the Framingham risk score (FRS). Individuals are typically classified into categories of low, intermediate, and high 10-year CHD risk and are treated accordingly. However, risk-scoring algorithms appear to have limited accuracy to identify persons at high risk for developing CHD. Risk prediction may be improved by use of noninvasive tests of atherosclerosis such as assessment of coronary artery calcium (CAC) by electron-beam tomography (EBT) scan, which is known to predict cardiovascular disease (1–8).

See page 1415

To establish the clinical value of a new test, an important issue is to assess the reclassification of individuals into different risk categories when the new test is added to classical risk factors (9). Additional testing for atherosclerosis is proposed to be most useful if applied to the intermediate-risk category (10% to 20% CHD risk in

From the *Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands; †Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; ‡Department of Radiology, Erasmus Medical Center, Rotterdam, the Netherlands; §Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland; and the ‖Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands. This study is supported by grants from the NESTOR program for geriatric research, the Netherlands Heart Foundation (2003B179), the Netherlands Organization for Scientific Research (Vici 918.76.619), and the Municipality of Rotterdam. None of the funders had any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The authors have reported that they have no other relationships to disclose. Drs. Elias-Smale and Proença contributed equally to this work.

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Abbreviations and Acronyms

AU = Agatston units
CAC = coronary artery calcium
CHD = coronary heart disease
CRP = C-reactive protein
EBT = electron-beam tomography
FRS = Framingham risk score
HDL = high-density lipoprotein
NRI = net reclassification improvement

10 years), in which treatment decisions are uncertain (10–12). However, reclassification percentages for CAC and empirically derived CAC cutoff values at which persons may be reclassified to a more appropriate risk category, based on 10-year CHD risk data, are lacking.

In a population-based cohort study among persons ≥55 years of age with nearly 10-year follow-up data, we studied the usefulness of CAC to reclassify individuals into more accurate risk categories and derived empirically based cutoff values of CAC.

Methods

Study population. The study was embedded in the Rotterdam Study, a prospective, population-based study among persons age 55 years and older in a municipality of Rotterdam. The rationale and design of the Rotterdam Study have been described elsewhere (13). The baseline examination was completed between 1990 and 1993, followed by a second round between 1993 and 1995. The third examination took place from 1997 to 1999. From 1997 onward, participants through 85 years of age were invited to undergo EBT scanning of the heart to perform CAC scoring. This has been referred to as the Rotterdam Coronary Calcification study (8). The inclusion and exclusion of persons in the study (response rate, 61%) have been described in detail by Vliegenthart et al. (8). During the inclusion phase, the study population was supplemented with inhabitants who reached the age of 55 years after the baseline examination and persons aged 55 years and older who migrated into the research area. Data were available for a total of 2,292 participants. Of these, 252 participants had a history of CHD, defined as a history of clinically manifest myocardial infarction, coronary artery bypass grafting, or coronary angioplasty at the time of EBT scanning. Hence the current analysis was carried out in 2,040 asymptomatic subjects. The Medical Ethics Committee of Erasmus Medical Center approved the study, and all participants gave informed consent.

CAC. We assessed CAC in the epicardial coronary arteries detected on EBT scans. Imaging was performed with a C-150 Imatron scanner (GE-Imatron). Before participants 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 electrocardiogram triggering, during a single breath-hold. Quantification of CAC was performed with AccuImage software (AccuImage Diagnostics Corporation), displaying all pixels with a density above 130 HU. A calcification was defined as a minimum of 2 adjacent pixels with a density over 130 HU. A CAC score was calculated according to Agatston's method (14). The trained scan readers were blinded to the clinical data of the participants. The study protocol participants were not informed about the CAC score.

Cardiovascular risk factors. At the third examination, information on medical history, drug use, and smoking behavior was collected using a computerized questionnaire. 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. After an overnight fast, blood samples were obtained at the research center. Serum total cholesterol was determined by an automated enzymatic procedure using the CHOD-PAP reagent agent (Roche, Basel, Switzerland), and high-density lipoprotein (HDL) was measured with the Roche HDL cholesterol assay using polyethylene glycol–modified enzymes and dextran sulfate. Glucose was determined enzymatically by the Hexokinase method. Diabetes was diagnosed based on a fasting plasma glucose level ≥7.0 mmol/l or use of antidiabetic medication. C-reactive protein (CRP) was measured in serum using a nephelometric method (Immage, Beckman Coulter, Brea, California). Median duration between measurement of cardiovascular risk factors and CAC scanning was 62 days.

Clinical outcomes. Information on fatal and nonfatal cardiovascular end points was obtained from general practitioners and letters and discharge reports from medical specialists. All events were classified by study physicians according to the International Statistical Classification of Diseases and Related Health Problems-10th Revision. The follow-up procedures have previously been described in detail (8). Twelve participants were lost to follow-up, which left 2,028 participants for analyses. As an outcome we used hard CHD (nonfatal myocardial infarction and CHD mortality). If a nonfatal event occurred within 28 days before CHD death, the event was attributed to CHD mortality. Persons were followed-up for a median time of 9.2 years (interquartile range 8.3 to 10.0 years).

Statistical analysis. We used a parametric Weibull proportional hazards regression model that allows computation of individual 10-year predicted risk of CHD from our available 9.2 years of median follow-up duration. Hazard ratio estimations from a Weibull model are very similar to those from a Cox model, both models being proportional hazards regression models (15). We chose a Weibull model over the more frequently used Cox model because the latter cannot estimate the 10-year cumulative incidence by extrapolation of the actual median follow-up time of 9.2 years. In contrast, the Weibull model can make this extrapolation because of its parametric nature. We fitted 2 Weibull

prediction models to the Rotterdam Study data: model 1, referred to as the "Framingham refitted" model, was based on variables included in the Framingham risk function, namely age, systolic blood pressure, antihypertensive medication, total and HDL cholesterol, diabetes, and current smoking (16). Sex was used as a covariate in this model. We chose to fit a model comprising Framingham risk factors on our data (Framingham refitted model) instead of using the Framingham risk function (16) because previous research showed that application of the Framingham risk function to the elderly Rotterdam Study population led to systematic overestimation of CHD risk in men (17). In a second step, we extended the Framingham refitted model with the natural logarithm of CAC ln(CAC+1), model 2. We added 1 to all CAC values in order to deal with persons who had a CAC score of 0. We fitted this extended model to our data and compared the performance of these 2 models using the methods described in the next sections. In an extra analysis, we examined the importance of CRP to enhance predictive performance of the Framingham refitted and the Framingham refitted plus CAC model. Because no evidence of a nonlinear effect was found, we added CRP as a linear term to the models.

To determine the functional form used for each predictor, we examined restricted cubic spline transformations for continuous predictors (18) and used the likelihood ratio test to examine the linearity assumption. If appropriate, we chose the simplest form, usually a linear term. We assessed the appropriateness of the Weibull survival time distribution by plotting observed Kaplan-Meier survival curves based on hard CHD events (n = 135) against estimates from the Weibull model in strata of low, intermediate, and high Framingham risk categories and found good agreement.

We compared global model fit using the likelihood ratio chi-square test. To examine the discriminative ability each model, we calculated the optimism-corrected *c*-statistic using 150 bootstrap repetitions for each model by method of Harrell (18,19). Next, we computed reclassification percentages to study the incremental ability of coronary calcium to classify subjects in risk categories according to commonly used categories of 10-year CHD risk: low (<10%), intermediate (10% to 20%), and high risk (>20%) (20). Estimated 10-year risks were calculated for each cell of the reclassification table to show calibration of reclassified observations with observed risk. To evaluate true improvement in classification by addition of coronary calcium to the Framingham refitted model, we calculated the net reclassification improvement (NRI). The original method for calculation of the NRI by Pencina et al. (21) was proposed for binary data. In that case, the number of cases and noncases is apparent. However, in survival data, the number of cases and noncases at the time point of interest usually is not because not all persons have a complete follow-up. We calculated the NRI with the expected number of cases, as recently proposed by Steyerberg and Pencina (22). For each of the 3 risk categories, we first estimated the cumulative incidence of hard CHD events at 10 years by use of Weibull proportional hazard analysis. We then estimated the absolute number of cases in each category by multiplying the cumulative incidence by the number of persons in that category. The number of noncases per category was the total number of persons minus the number of cases. In accordance with the original NRI calculation method, any "upward" movement in persons with an event implied correct reclassification, and any "downward" movement indicated incorrect reclassification. The interpretation was opposite for people who did not develop events. The net improvement in reclassification was quantified as the proportion of correct minus the proportion of incorrect reclassification.

Because additional calcium scoring is proposed to be most useful if applied to the intermediate-risk category (10–12), we derived coronary calcium cutoff values at which individuals at intermediate risk were reclassified into the high- or low-risk category. For this purpose, we included the Framingham risk categories as categorical and ln(CAC+1) as a linear term in the Weibull model. By means of a sex-CAC interaction, we examined the need for sex-specific CAC cutoff values.

Information on covariables was missing in up to 3.5% of persons, except for antihypertensive medication use, which was missing in 24% of persons. Missing values were imputed using the multivariate imputation by chained equations (MICE) library of R, as described previously (17). All analyses were performed using SPSS version 12.01 for Windows (SPSS, Inc., Chicago, Illinois) and R version 2.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study population, overall and by sex, are shown in Table 1. Mean age of the population at baseline was 69.5 years, and 43% of patients were male. During the median follow-up duration of 9.2 years (25th to 75th percentile: 8.3 to 10.0 years), 503 persons died, whereas 135 had their first hard coronary event (81 nonfatal myocardial infarctions and 54 CHD deaths). The median calcium score was 84 Agatston units (AU) (25th to 75th percentile: 8 to 382 AU).

Regression parameters of the Weibull models are displayed in Table 2. Compared with the Framingham refitted model, addition of coronary calcium significantly improved model fit (likelihood ratio chi-square increase: 36.4; $p < 0.001$). The c-statistic improved significantly from 0.72 to 0.76, indicating better average discriminative ability of the model including coronary calcium.

In an extra analysis, we examined the importance of CRP to enhance predictive performance of the Framingham refitted model and found that addition of CRP did not result in a significant improvement of the *c*-statistic (*c*-statistic FRS + CRP model: 0.72 compared with 0.72 of

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Table 1 Baseline Characteristics of the Study Population

Variable	All (n = 2,028)	Men (n = 864)	Women (n = 1,164)
Age, yrs	69.6 ± 6.2	69.5 ± 6.1	69.7 ± 6.3
Male, %	42.6		
Body mass index, kg/m^2	27.1 ± 4.0	26.5 ± 3.2	27.5 ± 4.5
Systolic blood pressure, mm Hg	143 ± 21	144 ± 21	143 ± 21
Diastolic blood pressure, mm Hg	76 ± 11	78 ± 12	75 ± 11
Antihypertensive medication, %	27.6	23.4	30.4
Total cholesterol, mmol/l	5.9 ± 1.0	5.7 ± 1.0	6.0 ± 0.9
HDL cholesterol, mmol/l	1.4 ± 0.4	1.3 ± 0.3	1.5 ± 0.4
Cholesterol-lowering medication, %	14.0	12.0	15.2
Smokers, %			
Current	16.8	19.1	15.1
Former	52.0	68.9	39.6
Serum glucose, mmol/l	5.9 ± 1.5	6.0 ± 1.6	5.8 ± 1.4
Antidiabetic medication, %	6.5	8.0	5.4
Family history of MI, %	18.4	17.0	19.6
Calcium score, AU	84 (8–382)	191 (35–623)	37 (3–210)
Persons without CAC, %	10.5	3.8	15.5

Categorical variables are presented as percentage. Continuous values are expressed as mean ± SD. Median (25th to 75th percentiles) is presented in case of skewed distribution.
CAC = coronary artery calcium; HDL = high-density lipoprotein; MI = myocardial infarction.

the FRS model alone; p = 0.31). Furthermore, CRP did not significantly improve the *c*-statistic of the FRS + CAC model (*c*-statistic FRS + CAC + CRP model: 0.76 compared with 0.76 of the FRS + CAC model; p = 0.61).

Persons stratified according to categories of estimated 10-year hard CHD risk based on the Framingham refitted model and after adding CAC to that model are presented in Tables 3 and 4. In men, percentages in the low-, intermediate-, and high-risk categories were 54%, 33%, and 13%, respectively; for women these percentages were 83%, 15%, and 2%, respectively. The largest proportions of reclassified persons were seen in the intermediate Framingham risk group (n = 451; 22% of the total population). Among men, 51% were reclassified: 30% moved to the low-risk category, and 21% moved to the high-risk group. In women at intermediate risk, 53% were reclassified, with 29% moving downward and 24% moving upward in risk. Reclassification percentages were generally smaller in persons initially classified as low or high with the Framingham refitted model. In men at low Framingham risk, 15% moved to the intermediate-risk group, but only 2 persons moved to the high-risk group; among women in the low-risk group, 9% moved to the intermediate-risk group, and 2 persons moved to the high-risk group. In men at Framingham high risk, 28% moved to the intermediate-risk group and 5% moved to the low-risk group; in women these percentages were 36% and 3%, respectively. Generally, point estimates of the observed risks agreed with the corresponding categories of predicted risk, indicating good calibration. However, in some groups calibration assessment was hampered by small numbers of reclassified persons. In all persons, addition of CAC to the Framingham refitted model significantly improved risk classification, as indicated by an NRI of 0.14 ($p < 0.01$).

Figure 1 displays the association of individual CAC scores against 10-year predicted risk of CHD in persons at intermediate Framingham risk. Because there was no evidence of a sex-specific prognostic effect of CAC (p = 0.55), an overall curve is presented. Empirically derived cutoff values correspond to the cross-section of the curve with the low- and high-risk demarcation. CAC scores above 615 HU and below 50 AU suggest reclassification to the high- or low-risk stratum, respectively.

Discussion

This population-based study among persons ≥55 years of age, with almost 10 years of follow-up, shows that adding CAC to the Framingham risk model leads to substantial reclassification between CHD risk categories, especially in persons at intermediate Framingham risk. More than 50% of both men and women in the intermediate-risk group were reclassified into the high- or low-risk category. The empirically derived cutoff values at which individuals moved from the intermediate to the high- or the low-risk group were 615 and 50 AU, respectively.

Noninvasive assessment of atherosclerosis is regarded as most useful in persons classified as intermediate Framingham risk, in which treatment decisions are uncertain (10–12). In our study, reclassification by additional CAC testing was particularly high in the intermediate-risk group, in which 52% of persons (men and women combined) were reclassified (30% to the low-risk and 22% to high-risk group). This is in accordance with the findings of a recent population-based cohort study by the MESA (Multi-Ethnic Study of Atherosclerosis) among 5,878 individuals who were free of CVD at baseline (mean age 62 years, 46%

Table 2 Parameter Estimates and Performance Measures of the Framingham Refitted and the Framingham Plus CAC Models

	Framingham		Framingham + CAC	
Parameter	HR	95% CI	HR	95% CI
Age*	2.64	1.97–3.52	2.09	1.54–2.83
Male sex	1.61	1.12–2.32	1.18	0.81–1.72
Systolic blood pressure	1.02	0.94–1.11	1.01	0.93–1.10
Anti-HT medication use	1.23	0.85–1.80	1.06	0.73–1.56
Total cholesterol	1.19	1.00–1.43	1.17	0.97–1.40
HDL cholesterol	0.30	0.17–0.53	0.31	0.18–0.54
Diabetes	1.25	0.75–2.08	1.15	0.69–1.91
Current smoking	1.66	1.09–2.52	1.46	0.95–2.23
ln(CAC+1)			1.33	1.21–1.47
Performance measures				
Likelihood chi-square	83.93		120.32	p < 0.001
c-statistic	0.72		0.76	p < 0.001

*HR per 10 years of increase in age instead of per 1-U increase.
CAC = coronary artery calcium; HDL = high-density lipoprotein; HT = hypertension.

Table 3 Cardiovascular Risk Reclassification Comparing the Framingham Refitted Model With the Model Additionally Including CAC

Framingham Refitted 10-Year Risk Categories	Framingham Refitted + CAC 10-Year Risk Categories			n (%) Reclassified
	<10%	10%–20%	>20%	
<10%				
n = 1,438	1,278 (88%)	156 (11%)	4 (1%)	160 (12%)
Observed risk (95% CI)	0.03 (0.02–0.05)	0.13 (0.08–0.20)	NA	
10%–20%				
n = 451	134 (30%)	216 (48%)	101 (22%)	235 (52%)
Observed risk (95% CI)	0.09 (0.05–0.16)	0.14 (0.10–0.20)	0.29 (0.20–0.41)	
>20%				
n = 144	7 (5%)	42 (29%)	95 (66%)	49 (34%)
Observed risk (95% CI)	0.49 (0.15–0.94)	0.13 (0.05–0.31)	0.31 (0.21–0.44)	

CAC = coronary artery calcium; CI = confidence interval; NA = not applicable.

men) that studied the additional value of CAC beyond traditional risk factors using a 5-year CHD risk prediction model (23). In this study, the reclassification proportion in the intermediate-risk group was 55% (39% to the low-risk and 16% to high-risk group). Reclassification percentages by addition of CAC in the intermediate-risk group are much higher than those reported for adding ankle brachial index to classical risk factors in a recent meta-analysis study (24). In this study, 4% of men and 10% of women at intermediate risk were reclassified after adding ankle brachial index to the risk model. The Women's Health Study previously reported 19% reclassification for CRP in women at intermediate risk (25). The Framingham offspring study reported 23% reclassification by addition of CRP in this group (26). Reclassification percentages were smaller in the initial low- and high-risk groups. In men at low Framingham risk, 15% moved to the intermediate-risk group, but only 2 persons moved to the high-risk group; among women in the low-risk group, 9% moved to the intermediate-risk group and 2 persons moved to the high-risk group. In men at Framingham high risk, 28% moved to the intermediate-risk group and 5% moved to the low-risk group; in women these percentages were 36% and 3%, respectively. Overall, 12% of persons in the low-risk group and 34% of persons in the high-risk group were reclassified. These percentages are comparable to those in the recent MESA, which reported 11% reclassification in the low-risk group and 36% reclassification in the high-risk group (23). At present, it is uncertain whether the decline in absolute risk has treatment implications because there is no evidence that intensive

Table 4 Cardiovascular Risk Reclassification Comparing the Framingham Refitted Model With the Model Additionally Including CAC, by Gender

Framingham Refitted 10-Year Risk Categories	Framingham Refitted + CAC 10-Year Risk Categories			n (%) Reclassified
	<10%	10%–20%	>20%	
Men				
<10%				
n = 467	394 (85%)	71 (15%)	2 (0%)	73 (15%)
Observed risk (95% CI)	0.04 (0.02–0.06)	0.12 (0.06–0.24)	NA	
10%–20%				
n = 281	84 (30%)	137 (49%)	60 (21%)	144 (51%)
Observed risk (95% CI)	0.04 (0.01–0.12)	0.15 (0.09–0.23)	0.32 (0.20–0.48)	
>20%				
n = 116	6 (5%)	32 (28%)	78 (67%)	38 (33%)
Observed risk (95% CI)	0.57 (0.19–0.97)	0.13 (0.05–0.36)	0.33 (0.22–0.47)	
Women				
<10%				
n = 966	879 (91%)	85 (9%)	2 (0%)	87 (9%)
Observed risk (95% CI)	0.03 (0.02–0.05)	0.14 (0.08–0.24)	NA	
10%–20%				
n = 170	50 (29%)	79 (47%)	41 (24%)	91 (53%)
Observed risk (95% CI)	0.17 (0.08–0.32)	0.13 (0.08–0.32)	0.26 (0.14–0.45)	
>20%				
n = 28	1 (3%)	10 (36%)	17 (61%)	11 (39%)
Observed risk (95% CI)	NA	0.12 (0.02–0.61)	0.24 (0.09–0.58)	

Abbreviations as in Table 3.

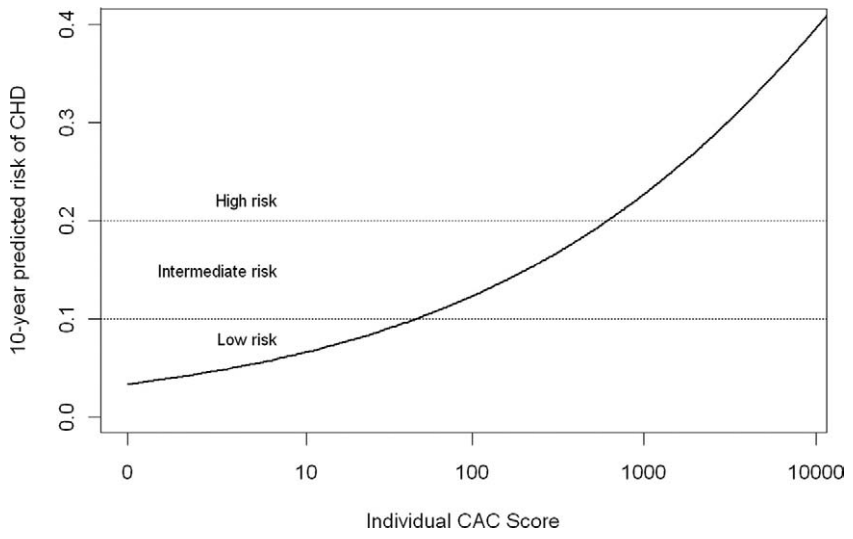

Figure 1 **10-Year Absolute CHD Risk Estimation by CAC Score of the Persons at Intermediate Risk (n = 451)**

Empirically derived cutoff values at which persons reclassified to either high or low risk were 615 and 50 AU, respectively.
CAC = coronary artery calcium; CHD = coronary heart disease.

preventive interventions can be safely mitigated in persons at high Framingham risk (10,11).

Other studies have shown an effect of CAC testing on CHD risk assessment in Framingham risk categories, but did not present reclassification percentages (1,5). Two cross-sectional studies showed that the use of calcium testing enabled identification of a higher risk subset among intermediate-risk individuals (4,6). Finally, a study among patients referred for calcium screening by primary care physicians showed that CAC scoring is an effective risk stratification tool in both young and elderly subjects (7). Limitations of this study are the use of self-reported, categorical risk factors, the possibility of referral bias, and the use of total mortality rather than CHD events as outcome. CAC cutoff values at which individuals reclassify to another risk category are a prerequisite for incorporation of CAC testing in clinical practice. However, currently used cutoff values are not based on empirical data. A recent study by MESA found that using predefined absolute CAC cutoff values of 1, 100, and 400 AU performed better than age-, sex-, and race/ethnicity-specific percentiles in terms of model fit and discrimination. However, this study had a median of 3.75 years of follow-up and therefore no empirically derived absolute cutoff values for classification of 10-year CHD risk (27). To our knowledge, we are the first to have estimated CAC cutoff values based on nearly 10 years of follow-up. Our empirically derived upper cutoff value of 615 AU seems to be higher than the commonly used cutoff values of 400 AU, whereas our lower cutoff value of 50 AU seems to be lower than the commonly use cutoff of 100 AU. However, our cutoff values need to be validated in other large, population-based studies to further establish whether empirically based cutoffs are indeed different from the arbitrary cutoffs of 400 and 100 AU. Furthermore, one should realize that these cutoff values refer only to men and women in the intermediate-risk group that comprised 33% of men and only 15% of women. Using lower boundaries for intermediate-risk category in women would lead to more women eligible to undergo calcium scoring. However, we based our definition of the intermediate-risk group (10% to 20% 10-year CHD risk) on widely used guidelines (20). The contention that CAC testing may be useful for refining risk assessment in women at low to intermediate risk (5% to 20%) has been suggested based on cross-sectional data (28) and an analysis of the MESA based on 24 soft and hard incident CHD events (29).

Study strengths. Strengths of the current study include a large, unselected sample of asymptomatic individuals and an almost 10-year follow-up period. Our cohort provided the opportunity to study the impact of CAC testing on risk classification for hard CHD events and to derive cutoff values at which persons were reclassified to other risk categories. Moreover, participants were unaware of their calcium score; therefore, change in lifestyle or medication use or additional cardiac testing on the basis of the calcium score was unlikely to occur.

Study limitations. Limitations of our study also need to be addressed. First, because previous research within the Rotterdam study showed that application of the Framingham risk function led to systematic overestimation of CHD risk in men (17), we chose to fit a model based on Framingham risk factors to stratify our population in the well-known risk categories. A potential drawback is over-fitting of the model, which could lead to underestimation of the addi-

tional value of CAC measurement. However, the c-statistics of both the Framingham and the Framingham plus CAC model were corrected for over-optimism using the bootstrap method, as described in the Methods section. Second, the model extended with CAC calibrated generally well with observed risks, except in categories with small numbers. We computed 95% confidence intervals to show plausible ranges of observed risk. Third, in order to comply with current guidelines, we extrapolated CHD risk estimates to 10-year risk from an actual follow-up period of 9.2 years using a parametric survival modeling approach. Although the accuracy of the extrapolation cannot be verified, large deviations are very unlikely because the actual follow-up time is so close to 10 years. Fourth, we estimated empirically based cutoff points for CAC suitable for our population. Of course, accruing data is needed to validate this finding before it can be applied in the clinical setting of primary prevention. Furthermore, the ultimate judgment about the selection of persons undergoing CAC scoring and subsequent implications regarding clinical management should also be based on randomized clinical trials and cost-effectiveness analyses. Finally, our study was performed in older persons. The predictive power of traditional cardiovascular risk factors decreases with age, whereas increased CAC can be seen as a cumulative measure of the effect of lifetime exposure to cardiovascular risk factors on the arterial vessel wall and may therefore improve risk stratification, particularly at older age. This implies that our results should not automatically be generalized to a younger population.

Conclusions

In a general population of elderly patients at intermediate CHD risk, CAC scoring is a powerful method to reclassify persons into more appropriate risk categories. On the basis of CAC testing, more than 50% of an asymptomatic older population at intermediate risk was reclassified as having either low or high risk of hard CHD events. Empirically derived CAC cutoff values at which persons at intermediate risk reclassified to high or low risk were 615 and 50 AU, respectively.

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Reprint requests and correspondence: Prof. Jacqueline C. M. Witteman, Department of Epidemiology, Erasmus Medical Center, Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail: j.witteman@erasmusmc.nl.

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