



Coronary Artery Calcium Score and Coronary Heart Disease Events in a Large Cohort of Asymptomatic Men and Women

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Coronary artery calcium (CAC), a measure of subclinical coronary heart disease (CHD), may be useful in identifying asymptomatic persons at risk of CHD events. The current study included 10,746 adults who were 22–96 years of age, were free of known CHD, and had their CAC quantified by electron-beam tomography at baseline as part of a preventive medical examination at the Cooper Clinic (Dallas, Texas) during 1995–2000. During a mean follow-up of 3.5 years, 81 hard events (CHD death, nonfatal myocardial infarction) and 287 total events (hard events plus coronary revascularization) occurred. Age-adjusted rates (per 1,000 person-years) of hard events were computed according to four CAC categories: no detectable CAC and incremental sex-specific thirds of detectable CAC; these rates were, respectively, 0.4, 1.5, 4.8, and 8.7 (trend $p < 0.0001$) for men and 0.7, 2.3, 3.1, and 6.3 (trend $p = 0.02$) for women. CAC levels also were positively associated with rates of total CHD events for women and men (trend $p < 0.0001$ each). The association between CAC and CHD events remained significant after adjustment for CHD risk factors. CAC was associated with CHD events in persons with no baseline CHD risk factors and in younger (aged <40 years) and older (aged >65 years) study participants. These findings show that CAC is associated with an increased risk of CHD events in asymptomatic women and men.

arteries; calcium; cohort studies; coronary disease; primary prevention

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; EBT, electron-beam tomography.

Atherosclerotic coronary heart disease (CHD) continues to exact a large economic and public health toll as the leading cause of death in men and women (1). CHD has a lengthy incubation period, during which biologic risk factors interact with genetic and environmental influences to initiate and promote the development of atherosclerotic plaque (2, 3). Once established, CHD can exist in a subclinical state characterized by an absence of clinical signs and symptoms. Sudden death or myocardial infarction is often the initial manifestation of CHD (4). A substantial number of first myocardial infarctions occur among individuals with normal or only slightly elevated CHD risk factors (5, 6). Therefore, additional methods are needed to identify asymptomatic individuals with subclinical disease who would benefit from intensive primary prevention therapy (7, 8).

Coronary artery calcium (CAC) is present in only atherosclerotic arteries (9–12) and is a measure of subclinical CHD (8, 9). Electron-beam tomography (EBT) is sensitive enough to detect and quantify small amounts of CAC (9). EBT-derived CAC scores are directly associated with the number and severity of diseased vessels defined by quantitative coronary angiography (13–17). Although the amount of CAC is related to the burden of atherosclerotic plaque, the association between CAC and incident CHD among asymptomatic individuals is less well understood. A positive association between CAC and CHD-related events has been reported (18–26).

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However, studies of CAC as a predictor of CHD events have been conducted mostly among men, older individuals, or high-risk populations. Experts have concluded that a limited understanding exists regarding the utility of CAC to identify asymptomatic individuals who have an elevated CHD risk and that data are needed from large prospective studies of asymptomatic men and women across a broad age range to more fully assess the clinical usefulness of CAC evaluations (27). To address this paucity of data, we examined the association between CAC and incident CHD in a large cohort of asymptomatic adults free of known CHD at baseline. We also determined whether the association between CAC and incident CHD was independent of prevalent CHD risk factors.

MATERIALS AND METHODS

Between June 1995 and May 2000, 16,097 men and women aged 22–96 years underwent EBT scanning at the Cooper Clinic in Dallas, Texas, as part of a preventive health examination (≈ 45 percent) or because of physician or self-referral (≈ 55 percent). The cohort and clinic examination have been described in detail elsewhere (28). Demographic information and history of smoking, diabetes, hypertension, and hypercholesterolemia were obtained by using a standardized medical questionnaire. We examined the relation between self-reported and measured risk factors in 3,619 participants for whom such data were available (data not shown). On average, levels of CHD risk factors (e.g., blood pressure values, lipid values, glucose values) were significantly higher ($p < 0.0001$) and met clinical thresholds for individuals who reported having the related condition than for those who reported absence of the condition. The distribution of prevalent hypercholesterolemia, hypertension, and diabetes in our population was similar to that observed in other large, population-based studies of CHD (29) and in studies on CAC and CHD (21, 25, 30). We have previously shown a sensitivity of 98 percent and a specificity of 99 percent for self-reported hypertension (31). There is no reason to believe that other CHD risk factors would not be reported with a similar level of precision in this well-educated study population. These self-reported data are valid indicators of the overall coronary risk factor status in our study population. Participants provided written informed consent, and the Cooper Institute Institutional Review Board approved the study protocol annually.

CAC measurement

An EBT scanner (GE Imatron, San Francisco, California) was used to obtain 3-mm-thick slices with 2-mm table (3×2) increments during a breath-holding protocol (28). CAC scores were calculated according to the Agatston method (32).

Endpoint ascertainment

The primary endpoint was hard CHD events (nonfatal myocardial infarction or death from coronary causes). A secondary endpoint was all CHD events defined as hard events plus coronary revascularization (coronary artery bypass graft, percutaneous coronary intervention). Deaths were

identified by using the National Death Index. CHD mortality was defined according to *International Classification of Disease*, Ninth Revision, codes 410.0–414.0. Nonfatal myocardial infarction and revascularization history were obtained from a mail-back questionnaire in which respondents were asked whether they had had a myocardial infarction or revascularization procedure since their EBT scan and the date on which the event occurred. Of the 16,097 individuals who were sent a questionnaire, 11,201 returned them, 450 were excluded because of a history of prior CHD events or stroke, and five were excluded because of missing data, resulting in a final analytic cohort of 10,746 individuals who were free of known CHD.

Statistical analyses

Because the distribution of CAC was skewed, log (Ln)-transformed scores were used for analysis, and median values with interquartile ranges were used for reporting. Student's *t* tests and the Wilcoxon test were used to compare continuous variables. Categorical variables were compared by using chi-square tests. Person-time for each participant was calculated from the date of the EBT scanning to either the date of death, the date of a reported event, or December 30, 2001. Incidence rates were computed as the number of cases divided by person-time follow-up in the following CAC categories: no detectable CAC and sex-specific CAC thirds (men: 1–38, 39–249, ≥ 250 ; women: 1–16, 17–112, ≥ 113). Hazard ratios and 95 percent confidence intervals were computed with Cox regression (33) to quantify the strength of association between CAC and incident CHD. The proportional hazards assumption was confirmed with log-cumulative survival plots. Multivariable regression models included CAC, age (years), current smoker (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), and hypertension (yes/no). Tests of linear trends in CHD event rates across categories of CAC were conducted by ordinal scoring. Stratified analyses were conducted for sex-specific associations between CAC and CHD events according to age (<40, 40–60, >60 years) and number of baseline CHD risk factors (0, 1, or ≥ 2). A priori hypotheses related to sex differences in the association between CAC and CHD events were not tested. Two-tailed *p* values of <0.05 were considered statistically significant.

RESULTS

The overall response rate to the follow-up questionnaire was 70 percent. Baseline variables were not substantially different between nonrespondents and the group of respondents and decedents, respectively: percentage of men (65 percent vs. 64 percent), age (52 years vs. 54 years), median CAC (0 vs. 1), current smoker (26 percent vs. 28 percent), high cholesterol (19 percent vs. 19 percent), high blood pressure (13 percent vs. 12 percent), and diabetes (4 percent vs. 3 percent). We therefore believe that the responders and decedents were representative of the total population who underwent EBT scanning.

The majority of study participants were men (64 percent) and were White (>97 percent); mean age was 53.8 (standard deviation, 9.9) years. Men and women who had had an event

TABLE 1. Baseline characteristics of study participants by sex and coronary heart disease event status, Aerobics Center Longitudinal Study (Dallas, Texas), 1995–2000

	Men		Women	
	Event free (<i>n</i> = 6,597)	CHD† event (<i>n</i> = 238)	Event free (<i>n</i> = 3,862)	CHD event (<i>n</i> = 49)
Age (years)‡	53.3 (10.0)	60.1 (9.7)*	54.1 (9.7)	64.1 (9.1)*
Coronary artery calcium score‡	222.4 (668.4)	1,017.7 (1,133.8)	51.3 (229.1)	619.3 (1,085.2)
Median (IQR)†	7 (138)	634.5 (1,259)*	0 (2)	111 (833)*
High cholesterol (%)	27.6	39.9*	30.5	59.2*
High blood pressure (%)	17.8	27.7*	15.9	46.9*
Diabetes (%)	2.9	10.1*	2.9	24.5*
Current smoker (%)	10.3	13.0	6.7	8.2
CHD death or nonfatal MI† (%)		26.1		38.8

* $p \leq 0.01$ with same-sex, event-free individuals.

† CHD, coronary heart disease; IQR, interquartile range; MI, myocardial infarction.

‡ Data are expressed as mean (standard deviation).

were older and had higher ($p < 0.05$) CAC scores and conventional risk factor values than same-sex, event-free individuals (table 1). The proportion of coronary events classified as CHD death or nonfatal myocardial infarction was higher ($p = 0.08$) among women (39 percent) than among men (26 percent). The prevalence of zero CAC was, respectively, 2.1 percent and 40.7 percent among men with and without coronary events ($p < 0.01$) and 20.4 percent

and 71.7 percent among women with and without such events ($p < 0.01$). With the exception of smoking, all CHD risk factors were directly associated ($p < 0.0001$) with CAC scores for men and women (table 2).

During a mean follow-up of 3.5 (standard deviation, 1.4) years and 37,326 person-years of exposure, 287 CHD events occurred (19 CHD deaths, 62 nonfatal myocardial infarctions, 206 revascularizations). We were able to adjudicate

TABLE 2. Association between conventional coronary heart disease risk factors and coronary artery calcium score for men and women, Aerobics Center Longitudinal Study (Dallas, Texas), 1995–2000

Men (<i>n</i> = 6,835)	Coronary artery calcium score				<i>p</i> linear trend
	0	1–38	39–249	≥250	
No.	2,692	1,381	1,382	1,380	
Calcium score					
Median (IQR)*	0 (0)	9.0 (18)	104.0 (95)	678.5 (916)	
Age (years)†	48.3 (8.5)	52.5 (8.4)	56.3 (8.4)	62.1 (9.0)	<0.0001
High cholesterol (%)	23.3	29.0	31.9	32.4	<0.0001
High blood pressure (%)	12.4	18.2	20.6	26.7	<0.0001
Diabetes (%)	1.6	2.9	3.8	6.1	<0.0001
Current smoker (%)	10.9	10.1	10.6	9.5	0.17
Women (<i>n</i> = 3,911)	Coronary artery calcium score				
	0	1–16	17–112	≥113	
No.	2,780	379	376	376	
Calcium score					
Median (IQR)	0 (0)	9 (18)	45 (42)	306 (435)	
Age (years)†	51.7 (8.6)	57.2 (9.3)	60.2 (8.8)	64.4 (8.8)	<0.0001
High cholesterol (%)	26.5	42.2	38.3	44.4	<0.0001
High blood pressure (%)	11.6	25.9	28.2	29.8	<0.0001
Diabetes (%)	2.4	5.3	4.3	5.3	<0.0001
Current smoker (%)	6.1	6.9	5.6	12.2	0.0006

* IQR, interquartile range.

† Data are expressed as mean (standard deviation).

99 of the CHD events using medical record review by investigators blinded to the EBT results. A total of 95 percent of events were verified as reported. Of the events reported incorrectly, three were cardiac catheterizations without revascularization and two were peripheral revascularization procedures. Of the adjudicated events, all of the CHD deaths or myocardial infarctions were confirmed.

We examined the association between CAC and coronary events across the continuous distribution of log-transformed calcium scores. Separate age-adjusted models were constructed for men and women with and without zero calcium scores included in the distribution. CAC was directly associated ($p < 0.001$) with CHD events in each model for men and women. In the model that included zero scores, the hazard ratios associated with a one-unit change in log CAC for all events and hard events were, respectively, 1.89 (95 percent confidence interval: 1.74, 2.1) and 1.59 (95 percent confidence interval: 1.39, 1.83) for men and 1.51 (95 percent confidence interval: 1.33, 1.72) and 1.32 (95 percent confidence interval: 1.08, 1.59) for women. Similar results were seen for men and women when those with no detectable CAC were excluded from the CAC distribution (data not shown).

CHD event rates according to CAC levels are shown in figure 1. A calcium score of zero is the first category shown on both graphs. The sex-specific CAC tertiles that comprise the second through fourth categories shown on the graphs were considerably different between men (1–38, 39–249, ≥ 250) and women (1–16, 17–112, ≥ 113). Nevertheless, we noted a steep, direct gradient in the age-adjusted rates of hard CHD events across CAC levels for men (trend $p < 0.0001$) and women (trend $p = 0.02$). The association between CAC and rates of all CHD events also was significant for men and women (trend $p < 0.0001$ each).

The hazard ratio for CHD events according to CAC levels are shown for men and women in table 3. More women (70 percent) than men (40 percent) had CAC scores of zero ($p < 0.0001$). A total of 238 CHD events (62 hard events) occurred in men over 23,290 person-years of exposure and 49 events (19 hard events) occurred in women over 14,036 person-years of exposure. The age-adjusted hazard ratio for CHD events rose significantly (trend $p < 0.0001$) with incremental levels of CAC in men and women. Adjustment for conventional CHD risk factors had little effect on the pattern or strength of association between CAC and incident CHD events in either sex.

We also examined the association between CAC and CHD events stratified by categories of age and number of prevalent CHD risk factors at baseline. The number of events was insufficient to allow cross-tabulation of the modifying variables with sex-specific CAC categories. Therefore, we examined the age- and sex-adjusted association between CAC and CHD events according to CAC cutpoints that have been reported as clinically relevant: 0, >0 , ≥ 100 , and ≥ 400 (27, 28, 34). These cutpoints were applied to the entire cohort distribution of CAC for this analysis. The prevalence of 0, 1, and ≥ 2 risk factors, respectively, was 54.4 percent, 32.9 percent, and 12.7 percent in men and 55.7 percent, 32.9 percent, and 11.4 percent in women.

The association between CAC and coronary events according to the number of baseline CHD risk factors is shown

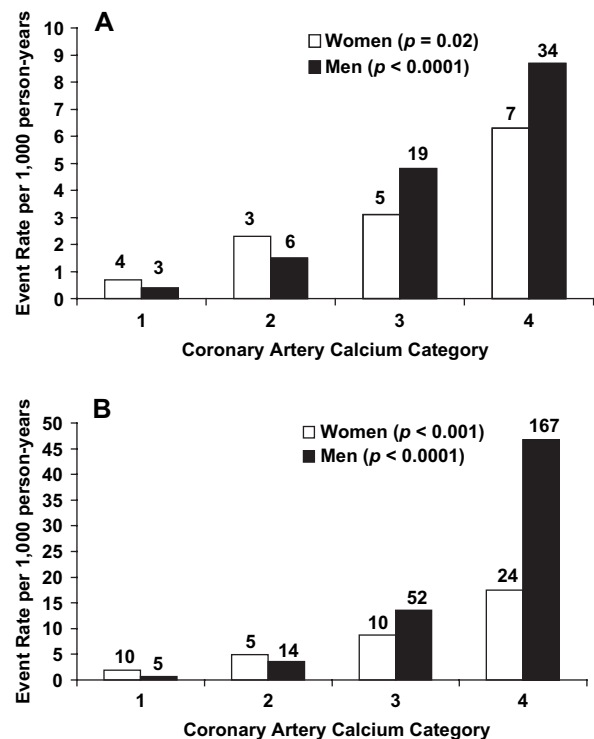


FIGURE 1. Age-adjusted rates of hard coronary heart disease events (coronary heart disease death, nonfatal myocardial infarction) (A) and all coronary heart disease events (hard events plus coronary revascularization) (B) according to sex-specific categories of coronary artery calcium, the Aerobics Center Longitudinal Study (Dallas, Texas), 1995–2000. The calcium scores associated with each category shown on the x-axis were 0, 1–38, 39–249, and ≥ 250 for men; and 0, 1–16, 17–112, and ≥ 113 for women. The number of events is shown above each bar. The p values are for tests of linear trend.

in table 4. The referent group is individuals with no risk factors and a calcium score of zero ($n = 3,263$). Significant increases in the age- and sex-adjusted risk of CHD events were observed among individuals whose CAC score was >0 , ≥ 100 , and ≥ 400 in all risk factor categories. Except among those with multiple coexisting risk factors, the risk of incident coronary events was not significantly elevated among individuals whose CAC was zero.

The association between CAC and CHD stratified on age is shown in table 5. Sex-adjusted event rates increased with age among individuals whose CAC score was zero, but CHD rates were considerably higher among individuals with any calcium (CAC >0) and with CAC scores of ≥ 100 and ≥ 400 within each stratum of age. Even individuals aged <40 years whose CAC scores were >0 and ≥ 100 had a higher rate of CHD events compared with their counterparts whose CAC score was zero.

DISCUSSION

The results reported here show a strong, graded association between CAC scores and incident CHD events among

TABLE 3. Risk of coronary heart disease events according to categories of no detectable calcium and sex-specific thirds of coronary artery calcium, Aerobics Center Longitudinal Study (Dallas, Texas), 1995–2000

Coronary artery calcium score	No.	Person-years	Hard events*					All events†				
			No.	HR‡,§	95% CI‡	HR¶	95% CI	No.	HR§	95% CI	HR¶	95% CI
Men												
0	2,692	8,922	3	1.0		1.0		5	1.0		1.0	
1–38	1,381	4,968	6	3.5	0.9, 14.3	3.3	0.8, 13.4	14	5.1	1.9, 14.3	5.0	1.8, 13.8
39–249	1,382	4,856	19	11.1	3.2, 38.2	10.2	3.0, 35.4	52	19.5	7.7, 49.3	18.5	7.3, 46.6
≥250	1,380	4,544	34	20.0	5.8, 69.6	17.7	5.1, 61.8	167	67.0	26.9, 166.7	61.7	24.7, 153.7
<i>p</i> linear trend				<0.0001		<0.0001		<0.0001			<0.0001	
Women												
0	2,780	9,910	4	1.0		1.0		10	1.0		1.0	
1–16	379	1,414	3	3.3	0.7, 15.3	2.2	0.5, 10.1	5	2.6	0.9, 7.8	1.8	0.6, 5.5
17–112	376	1,384	5	4.6	1.2, 18.4	3.9	1.0, 15.2	10	4.7	1.9, 11.8	3.7	1.5, 9.2
≥113	376	1,328	7	9.3	1.2, 18.9	7.2	0.8, 12.5	24	9.3	4.1, 21.6	6.2	2.7, 14.4
<i>p</i> linear trend				<0.0001		<0.0001		<0.0001			<0.0001	

* Coronary heart disease death, nonfatal myocardial infarction.

† Hard events plus coronary revascularization.

‡ HR, hazard ratio; CI, confidence interval.

§ Adjusted for age.

¶ Adjusted for age, smoking, high cholesterol, high blood pressure, and diabetes.

asymptomatic individuals free of known CHD at the time of EBT scanning. The findings were consistent for men and women and held after adjustment for age and conventional CHD risk factors. CAC was associated with CHD events in individuals with and without baseline CHD risk factors and in young and older study participants. Strengths of this study are the use of CAC scores based on standardized EBT methodology, a large sample of participants free of known CHD at baseline and with extensive follow-up, a relatively large number of hard CHD events ($n = 81$), and

a large enough sample of women to permit meaningful analyses.

EBT-derived CAC scores provide a sensitive, noninvasive method for quantifying the presence and amount of subclinical CHD, and it has been suggested as a means of identifying asymptomatic but high-risk individuals who could benefit from aggressive primary prevention. Because of differences in the distribution of CAC by age and sex (9, 28, 35), sex- and age-specific data are required to adequately examine the clinical usefulness of EBT scanning in

TABLE 4. Age- and sex-adjusted risk of coronary heart disease events by level of coronary artery calcium and number of coronary heart disease risk factors, Aerobics Center Longitudinal Study (Dallas, Texas), 1995–2000

No. of risk factors	Coronary artery calcium level							
	0		>0		≥100		≥400	
	HR*	95% CI*	HR	95% CI	HR	95% CI	HR	95% CI
	<i>Hard events†</i>							
0	1.0		10.2	2.3, 45.9	30.4	6.2, 150.1	61.2	9.9, 376.4
1	0.92	0.08, 10.2	17.9	4.1, 79.4	31.2	6.4, 152.8	41.4	7.0, 243.7
≥2	13.6	2.5, 74.9	14.3	2.9, 68.5	11.8	2.2, 64.1	15.9	2.2, 114.7
	<i>All events‡</i>							
0	1.0		11.9	5.1, 28.1	33.0	13.3, 81.7	72.1	26.9, 193.6
1	0.96	0.24, 3.9	16.5	7.1, 38.9	37.6	15.3, 92.1	76.0	28.8, 200.4
≥2	6.7	2.2, 20.9	31.7	13.3, 75.4	61.9	25.2, 152.5	138.7	51.6, 372.7

* HR, hazard ratio; CI, confidence interval.

† Coronary heart disease death, nonfatal myocardial infarction.

‡ Hard events plus coronary revascularization.

TABLE 5. Sex-adjusted event rates* according to level of coronary artery calcium and age, Aerobics Center Longitudinal Study (Dallas, Texas), 1995–2000

Age (years)	Coronary artery calcium level			
	0	>0	≥100	≥400
	<i>Hard events†</i>			
<40	0.6	4.8	—‡	—‡
40–65	0.03	0.2	6.7	10.6
>65	0.9	6.7	7.1	8.2
	<i>All events§</i>			
<40	0.9	11.3	42.1	—‡
40–65	0.9	10.7	26.8	49.6
>65	1.4	19.4	28.7	40.2

* Per 1,000 person-years.

† Coronary heart disease death, nonfatal myocardial infarction.

‡ Event rates could not be computed because there were no events within the strata.

§ Hard events plus coronary revascularization.

identifying individuals with a high risk of future CHD events. Experts have concluded that there was insufficient evidence of a prospective association between CAC and coronary events to fully understand the prognostic application of EBT scanning, particularly for women, asymptomatic persons, and younger individuals (7, 27). Our findings of a direct association between CAC and incident CHD extends previous observations made in intermediate- and high-risk populations comprised mostly of older men (19, 22–24, 26) to low-risk, CHD-free men and women across a broad age range.

Our study design and primary findings are similar to those of two other prospective investigations that reported sex-specific data (21, 25) and one that reported sex-adjusted data (30) on CAC and CHD events in asymptomatic individuals. Length of follow-up (~3.5 years), CHD endpoints, EBT methods of quantifying CAC, proportion of men (~70 percent) and women (~30 percent), average age at baseline (~53 years), and distribution of self-reported CHD risk factors reported in these studies were comparable to those in our study. Because the sample-specific categories of CAC and the associated number of events differed among studies, a precise comparison of the strength of association between CAC and CHD events between studies is not possible. In our study, as well as in the studies of Arad et al. (21) and Kondos et al. (25), a significantly higher risk of incident coronary events with higher CAC scores was observed for men and women, even after adjustment for age and other CHD risk factors. Because more hard events (coronary death and nonfatal myocardial infarction) occurred in our study (62 men, 19 women) compared with those reported by Wong et al. ($n = 6$), Arad et al. ($n = 18$), and Kondos et al. (52 men, six women) (21, 25, 30), our data provide a more stable estimate of the association between CAC and hard CHD events, particularly for women.

In this regard, our findings are similar to those in a recent study by Greenland et al. (26), who reported a direct asso-

ciation between EBT-derived CAC and hard CHD events ($n = 84$) in 1,461 asymptomatic individuals (90 percent men) with an intermediate CHD risk status at baseline who were followed for a median of 7 years. However, interpretation of these data is limited because the investigators did not address the influence of age and sex on associations between CAC and coronary events. Our observations of increased CHD risk across the distribution of CAC is consistent with reported data showing increases in CHD events in asymptomatic individuals with relatively small amounts of CAC (CAC score: 0–4) (20) as well as in asymptomatic individuals with extreme CAC elevations (>1,000) (24). Taken together, previously reported data (21, 25, 30) and the data reported here indicate that CAC is a significant predictor of fatal and nonfatal CHD events among men and women who were asymptomatic and at generally low risk at the time of EBT scanning. Whether therapeutic intervention guided by CAC scores will influence clinical event rates remains an important focus of research.

The majority of studies on CAC and incident CHD have reported age-adjusted rather than age-specific data to account for the variation in CAC distributions and CHD event rates due to age (18–25). Furthermore, the age ranges in these studies have not included a large proportion of young individuals, among whom the prognostic value of EBT-derived CAC is debated (27). Our study included a broad age range—about 20 percent of participants were less than 40 years of age and approximately the same proportion were older than 65 years of age—which allowed us to examine the association between CAC and CHD events in younger and older individuals. The presence of CAC was associated with higher event rates within each age stratum, and a graded increase in event rates was observed between CAC scores of ≥100 and ≥400 for participants aged 40–65 years and >65 years. Even among younger asymptomatic individuals, CHD rates were higher for those whose CAC scores were >0 or ≥100 compared with zero (table 5). The absence of hard events among young individuals with a CAC score of ≥100 and of any events among young individuals with a CAC score of ≥400 reflects the relative infrequency of CAC scores of >100 ($n = 10$) or >400 ($n = 2$) in younger individuals. Our data suggest that EBT scanning may identify relevant CAC levels for predicting CHD risk in younger populations; however, because the number of events was small in this subgroup, the data must be interpreted cautiously. Additional data are needed from younger populations with diverse demographic and clinical characteristics to understand the usefulness of CAC for coronary risk assessment in younger individuals.

Other studies (21, 25, 30, 36) on the association between EBT-derived CAC and incident CHD events have been criticized for use of mass media and self-referral methods of participant recruitment, inclusion of coronary revascularization as a study endpoint, short follow-up periods, and use of self-reported CHD risk factors (26, 27, 37–39). Therefore, it has been suggested that definitive conclusions as to the prognostic value of EBT-derived CAC cannot be drawn from extant data (27). Media advertisements were not a primary method of recruitment in our study. We accept that physician-referred participants would likely receive preventive

therapy based on their EBT results. However, this would bias associations between CAC and incident events toward the null and may explain the lower risk of events among individuals with multiple risk factors and CAC scores of ≥ 400 shown in table 4. Self-referred participants may reflect a more health-conscious subgroup, but this too would weaken rather than strengthen the prospective association between CAC and CHD events seen in this study.

The association between CAC and coronary death or nonfatal myocardial infarction is important and indicates that coronary calcium identifies those at risk of significant clinical manifestations of CHD. A strength of our study is the large number of hard endpoints that were not driven by diagnostic cardiac catheterization. The association between CAC and coronary revascularization is rightly criticized because the presence of CAC may increase referral for diagnostic catheterizations and revascularization procedures. However, the association between CAC and coronary revascularization strengthens rather than weakens the clinical relevance of EBT-derived CAC scores. Use of this noninvasive method for identifying asymptomatic individuals with advanced subclinical coronary atherosclerosis may enhance selection of additional testing and initiation of aggressive primary prevention therapy to arrest and stabilize disease progression, thereby obviating the need for invasive intervention through percutaneous coronary intervention or coronary artery bypass graft.

Although the use of self-reported risk factors is not ideal in research settings, they have been shown to provide a valid assessment of study participants' overall risk profiles (40), particularly in well-educated populations (41). With the exception of a slightly lower prevalence of smoking, the distribution of self-reported risk factors in our population was similar to that reported in other epidemiologic studies of cardiovascular disease (29) and in previous studies of CAC and CHD events (21, 25, 30). Therefore, we believe that the self-reported data provide a reasonable indication of the overall coronary risk profile of our sample population. Statistical adjustment for these risk factors did not materially alter the strength or pattern of association between CAC and CHD events in our population. It is possible that adjustment for CHD risk factors did not greatly attenuate the CAC association with CHD because of residual confounding by self-reported risk factor data that were only moderately valid. However, we have previously reported a reasonably high level of sensitivity and specificity for self-reported chronic disease status in the overall population from which the current cohort was drawn (31), which reduces the likelihood of residual confounding as the principal explanation.

Another possibility is that, while conventional risk factors clearly initiate and promote atherosclerotic plaque development (3, 42), the presence of subclinical disease (e.g., detectable CAC) may account for a greater variation in event occurrence than the disease antecedents (e.g., CHD risk factors). Our observations that higher levels of detectable CAC were associated with increased risk of CHD-related events within strata of 0, 1, and ≥ 2 self-reported prevalent CHD risk factors is suggestive of additional benefit from CAC for risk assessment beyond conventional methods

(table 4). However, we agree with others (26, 39) that it is necessary to use measured risk factor data when comparing the prognostic value of CAC scores with established clinical methods of individual risk assessment, such as the Framingham risk score (26). Because doing so was not the intention of our study, the use of self-reported risk factor data does not substantially weaken the internal validity of our results. The consistency in the pattern of association between CAC and CHD events seen in our study and others (20, 21, 25, 30, 36) cannot be dismissed on the basis of the aforementioned arguments.

Length of follow-up affects duration of exposure to disease antecedents and to precipitators of clinically manifest disease. Because the time course from subclinical disease to clinical events is highly variable (2, 3), it is important to have information on the association between CAC and incident CHD from studies with both short and long follow-up periods. The length of follow-up in our study is comparable to that of most studies of CAC and CHD events. We agree that studies with precise measures of CHD risk factors, longer follow-up periods, more diverse populations, and additional methods of quantifying subclinical coronary disease are required to fully examine the prognostic utility of EBT-derived CAC for use in global risk assessment. The Multi-Ethnic Study of Atherosclerosis (MESA) study (43) will address many of these issues but will not be completed until about 2008. Until then, continued analysis and reporting of data from large prospective epidemiologic studies such as ours and others (20, 21, 25, 26, 30, 36) will enhance current understanding of CAC as a predictor of CHD events and will provide the necessary background to interpret the findings of studies such as MESA.

Limitations to this study should be considered. Because of the widespread geographic distribution of patients evaluated at the Cooper Clinic, we were unable to verify all reported CHD events. However, of the 99 CHD events adjudicated, 95 percent were confirmed as reported, including 100 percent of the CHD deaths and myocardial infarctions. It is unlikely that adjudication of the remaining events would have materially changed our results. The study population is primarily non-Hispanic Whites of middle-to-upper socioeconomic status, and our observations require confirmation in more diverse populations. Quantification of CAC scores was not blinded to participant clinical information. However, computer-based CAC calculation was confirmed by a radiologist, which reduces our concern over scoring bias.

In conclusion, a direct association between CAC and incident CHD events was observed in an asymptomatic population of men and women with a broad age range. CAC was a significant predictor of both hard and all CHD events, and adjustment for conventional CHD risk factors did not change the strength or pattern of the observed association. The presence of CAC was associated with increased CHD event rates among study participants who were less than 40 years of age and older than age 65 years, and in participants with no baseline CHD risk factors. EBT-derived CAC may be a robust, noninvasive method of identifying asymptomatic individuals with an elevated risk of coronary events for whom intensive primary prevention therapy may be indicated.

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REFERENCES

- American Heart Association. Heart disease and stroke statistics—2004 update. Dallas, TX: American Heart Association, 2003.
- Strong JP, McGill HC Jr. The natural history of coronary atherosclerosis. *Am J Pathol* 1962;40:37–49.
- Fuster V, Lewis A. Conner Memorial Lecture. Mechanisms leading to myocardial infarction: insights from studies of vascular biology. *Circulation* 1994;90:2126–46.
- Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. *J Am Coll Cardiol* 1985;5:141B–9B.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA* 1998;279:1615–22.
- Sacks FM, Tonkin AM, Craven T, et al. Coronary heart disease in patients with low LDL-cholesterol: benefit of pravastatin in diabetics and enhanced role for HDL-cholesterol and triglycerides as risk factors. *Circulation* 2002;105:1424–8.
- Smith SC Jr, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. American Heart Association. *Circulation* 2000;101:111–16.
- Benjamin EJ, Smith SC Jr, Cooper RS, et al. Task force #1—magnitude of the prevention problem: opportunities and challenges. 33rd Bethesda Conference. *J Am Coll Cardiol* 2002;40:588–603.
- Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. *Circulation* 1996;94:1175–92.
- Rumberger JA, Simons DB, Fitzpatrick LA, et al. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 1995;92:2157–62.
- Blankenhorn DH. Coronary arterial calcification: a review. *Am J Med Sci* 1961;242:41–9.
- Eggen DA, Strong JP, McGill HC Jr. Coronary calcification. Relationship to clinically significant coronary lesions and race, sex, and topographic distribution. *Circulation* 1965;32:948–55.
- Rumberger JA, Sheedy PF, Breen JF, et al. Electron beam computed tomographic coronary calcium score cutpoints and severity of associated angiographic lumen stenosis. *J Am Coll Cardiol* 1997;29:1542–8.
- Guerci AD, Spadaro LA, Popma JJ, et al. Relation of coronary calcium score by electron beam computed tomography to arteriographic findings in asymptomatic and symptomatic adults. *Am J Cardiol* 1997;79:128–33.
- Fallavollita JA, Brody AS, Bunnell IL, et al. Fast computed tomography detection of coronary calcification in the diagnosis of coronary artery disease; comparison with angiography in patients <50 years old. *Circulation* 1994;89:285–90.
- Baumgart D, Schmermund A, Goerge G, et al. Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. *J Am Coll Cardiol* 1997;30:57–64.
- Tanenbaum SR, Kondos GT, Veselik KE, et al. Detection of calcific deposits in coronary arteries by ultrafast computed tomography and correlation with angiography. *Am J Cardiol* 1989;63:870–2.
- Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. *J Am Coll Cardiol* 1996;27:285–90.
- Secci A, Wong N, Tang W, et al. Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. *Circulation* 1997;96:1122–9.
- Doherty TM, Wong ND, Shavelle RM, et al. Coronary heart disease deaths and infarctions in people with little or no coronary calcium. *Lancet* 1999;353:41–2.
- Arad Y, Spadaro LA, Goodman K, et al. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;36:1253–60.
- Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850–5.
- Park R, Detrano R, Xiang M, et al. Combined use of computed tomography coronary calcium scores and C-reactive protein levels in predicting cardiovascular events in nondiabetic individuals. *Circulation* 2002;106:2073–7.
- Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002;39:225–30.
- Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. *Circulation* 2003;107:2571–6.
- Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;291:210–15.
- O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol* 2000;36:326–40.
- Cheng YJ, Church TS, Kimball TE, et al. Comparison of coronary artery calcium detected by electron beam tomography in patients with to those without symptomatic coronary heart disease. *Am J Cardiol* 2003;92:498–503.
- Arnett DK, McGovern PG, Jacobs DR Jr, et al. Fifteen-year trends in cardiovascular risk factors (1980–1982 through 1995–1997): the Minnesota Heart Survey. *Am J Epidemiol* 2002;156:929–35.
- Wong ND, Hsu JC, Detrano RC, et al. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000;86:495–8.

31. Blair SN, Goodyear NN, Gibbons LW, et al. Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA* 1984;252:487-90.
32. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-32.
33. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc (B)* 1972;34:187-220.
34. Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects. *Circulation* 1996;93:1951-3.
35. Hoff JA, Chomka EV, Krainik AJ, et al. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol* 2001;87:1335-9.
36. Detrano RC, Wong ND, Doherty TM, et al. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. *Circulation* 1999;99:2633-8.
37. Redberg RF. Coronary artery calcium and cardiac events. *Circulation* 2003;108:E167-E168.
38. Pitt B, Rubenfire M. Risk stratification for the detection of preclinical coronary artery disease. *Circulation* 1999;99:2610-12.
39. O'Malley PG, Taylor AJ. Prognostic value of coronary artery calcification. (Letter). *Circulation* 2003;108:E169.
40. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 1986;123:894-900.
41. Klag MJ, He J, Mead LA, et al. Validity of physicians' self-reports of cardiovascular disease risk factors. *Ann Epidemiol* 1993;3:442-7.
42. Hopkins PN, Williams RR. Identification and relative weight of cardiovascular risk factors. *Cardiol Clin* 1986;4:3-31.
43. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871-81.