

Coronary artery calcium score, risk factors, and incident coronary heart disease events

Timothy S. Church^{a,*}, Benjamin D. Levine^{b,c}, Darren K. McGuire^c,
Michael J. LaMonte^a, Shannon J. FitzGerald^a, Yiling J. Cheng^a, Thomas E. Kimball^d,
Steven N. Blair^a, Larry W. Gibbons^d, Milton Z. Nichaman^a

^a The Cooper Institute, Dallas, TX, United States

^b Institute for Exercise and Environmental Medicine and Presbyterian Hospital, Dallas, TX, United States

^c University of Texas Southwestern Medical Center, Dallas, TX, United States

^d Cooper Clinic, Dallas, TX, United States

Received 6 July 2005; received in revised form 22 November 2005; accepted 1 February 2006

Available online 15 March 2006

Abstract

Background: Whether the absence of coronary artery calcium, or conversely the presence of high volumes of coronary artery calcium, may alter assessment of coronary heart disease risk based on traditional risk factors is uncertain. We sought to identify a potential threshold of coronary artery calcium for clinical use and examine the predictive power of coronary artery calcium in individuals categorized using conventional coronary heart disease risk assessment.

Methods: The study included 10,746 men and women (36.3%) with a mean age of 53.8 ± 9.9 years who were either physician- or self-referred for electron beam tomography scanning to a preventive medical clinic. Coronary heart disease risk factors were elicited by use of a questionnaire.

Results: During a mean follow-up of 3.5 years, 81 primary events (coronary heart disease death or nonfatal myocardial infarction) occurred. Among individuals with a coronary artery calcium score of zero, the primary event rate was very low (0.4 events per 1000 person-years of observation). When participants were stratified by self-reported coronary heart disease risk factors (0–2, or 3–4), a coronary artery calcium score ≥ 100 was associated with substantially increased risk of coronary heart disease events within each level of stratification. In a subgroup of participants with available clinical data, similar results were found when participants were categorized by Framingham risk scores.

Conclusions: Coronary artery calcium score can identify individuals at increased risk for coronary heart disease events who otherwise would be considered low-risk based on clinical assessment. A coronary artery calcium score of zero is associated with very low risk for coronary heart disease in the short to intermediate term (≈ 3.5 years) regardless of the number of risk factors present.

© 2006 Elsevier Ireland Ltd. All rights reserved.

Keywords: Calcium; Coronary disease; Prevention

1. Introduction

Electron beam tomography has the sensitivity to detect and quantify small amounts of coronary artery calcium

(CAC) and has been used with increasing frequency to assess the extent of coronary atherosclerosis [1,2]. A positive qualitative and quantitative association between CAC and clinically manifest coronary heart disease (CHD) has been demonstrated in numerous cross-sectional studies and a few prospective studies [3–16]. However, a number of important issues in regard to the clinical utility of CAC measurement remain unresolved. If CAC is a measure of atherosclerotic burden, it remains to be determined if CAC scores will iden-

* Corresponding author at: The Cooper Institute, 12330 Preston Road, Dallas, TX 75230, United States. Tel.: +1 972 341 3252; fax: +1 972 341 3225.

E-mail address: tchurch@cooperinst.org (T.S. Church).

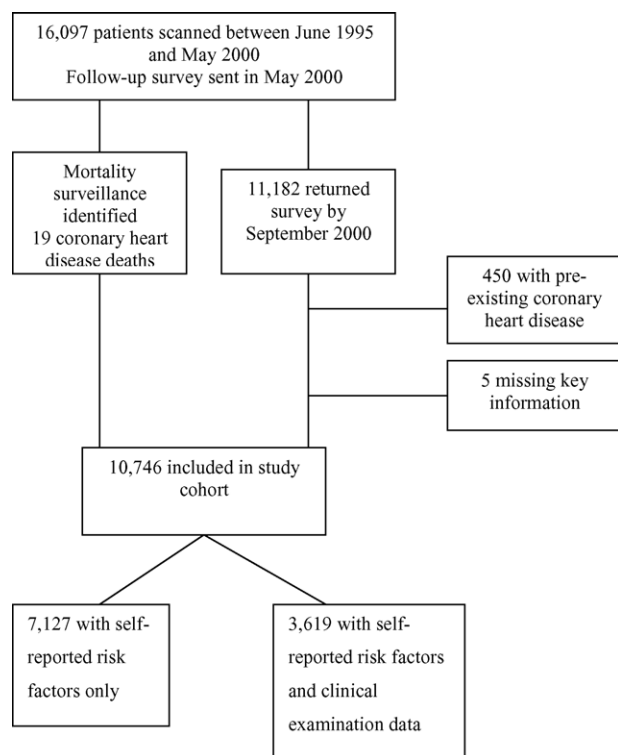


Fig. 1. Study flow chart.

tify high-risk individuals who would otherwise be considered at low or moderate risk based on conventional risk assessments. Whether a CAC score of zero can be used to identify individuals at very low CHD risk also remains unclear. Another critical question to be answered is whether there is a threshold of CAC that can identify individuals who may benefit from aggressive CHD risk-modifying therapies.

Using a large cohort of men and women who underwent electron beam tomography scanning as part of routine preventive care, the purpose of this study was to evaluate the predictive power of quantitative CAC for the development of CHD events in patients without clinical CHD at baseline. Specifically, we (1) assessed the discriminatory power of CAC using Receiver Operator Characteristic curve analyses to determine a potential threshold of CAC for clinical use, and (2) examined the predictive power of CAC in individuals categorized using conventional CHD risk-assessment.

2. Methods

2.1. Study protocol

Between June 1995 and May 2000, study participants underwent electron beam tomography scanning at the Cooper Clinic in Dallas, TX either as part of a periodic preventive medical examination or by self-referral. Systematic follow-up for events was funded by a research grant from the National Heart, Lung, and Blood Institute. As shown in Fig. 1, from

the 16,097 individuals who had an electron beam tomography scan and who were sent follow-up questionnaires in May 2000, 19 died from CHD and 11,182 returned these questionnaires (~70% response rate). Of the individuals who returned questionnaires, 450 were excluded due to a history of CHD at baseline and 5 were excluded because of missing data, resulting in a final study cohort of 10,746 individuals. Age, sex, height, and weight were acquired at the baseline exam on all participants. Self-reported history of diabetes, hypertension, smoking, and hypercholesterolemia were ascertained from baseline questionnaires. There were no meaningful differences between nonrespondents and the combined group of respondents and decedents in age, gender distribution, risk factor prevalence, or median CAC (0 versus 1, respectively). Participants provided written informed consent to participate in the clinical examination and follow-up and to use their examination data for research purposes. The Cooper Institute Institutional Review Board annually reviewed and approved the study protocol.

2.2. Electron beam tomography imaging

Using an electron beam tomographic scanner (Imatron C-150XP or an Imatron C-300), 3-mm thick slices were obtained with 2-mm table (3×2) increments during a breath-holding protocol, and Agatston score was calculated as previously described [9]. Our methods for quantifying CAC score have previously been reported to both be highly reproducible and free of bias from scorers who may be unblinded to the clinical characteristics of the patients [9]. Of note because of the prospective nature of the study, all scans were interpreted blinded to the clinical outcome.

2.3. Clinical examination

A subset of patients ($n=3619$) had the electron beam tomography scan as part of a comprehensive medical and laboratory evaluation. For these individuals, measured blood pressure, lipid profiles, and fasting glucose were available, and in this subgroup, 10-year Framingham risk scores (FRS) were calculated [17]. The details of this preventative medicine examination have been previously described [18].

2.4. Endpoint ascertainment

The primary outcome was incident coronary events defined as CHD death or nonfatal myocardial infarction. The secondary outcome was combined incident events of CHD death, myocardial infarction, or a coronary revascularization, including coronary artery bypass grafting or a percutaneous coronary intervention. CHD deaths (ICD codes 410.0–414.0) were identified using the National Death Index Plus service. Nonfatal CHD events were ascertained from the mail survey. An attempt to confirm each outcome through detailed medical record review was made. However, Cooper Clinic patients come from all 50 states, and therefore due to expense and dis-

Table 1

Mean values of clinical measures within self-reported categories of hypertension, hypercholesterolemia, and diabetes for 3619 participants with both self-reported and clinic measures available

	Self-report hypertension		<i>p</i>
	No (82.1%)	Yes (17.9%)	
Systolic blood pressure (mmHg)	120.4 (14.2)	136.3 (16.4)	<0.0001
Diastolic blood pressure (mmHg)	80.6 (9.4)	88.7 (10.1)	<0.0001
	Self-report hypercholesterolemia		<i>p</i>
	No (69.4%)	Yes (30.6%)	
Total cholesterol (mg/dL)	196.6 (32.3)	221.3 (37.5)	<0.0001
LDL cholesterol (mg/dL)	118.8 (29.9)	138.4 (33.7)	<0.0001
HDL cholesterol (mg/dL)	54.8 (16.7)	51.4 (15.3)	<0.0001
Triglycerides (mg/dL)	115.5 (74.5)	157.7 (100.0)	<0.0001
	Self-report diabetes		<i>p</i>
	No (95.6%)	Yes (4.4%)	
Fasting glucose (mg/dL)	98.6 (9.0)	146.2 (49.8)	<0.0001

tance, complete medical records were only available for 99 of the 268 nonfatal events (37%). Each record was reviewed by at least two physicians experienced in event verification who were blinded to electron beam tomography results.

2.5. Statistical analyses

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were compared using Student's *t*-test, and categorical variables were compared using chi-square or Fisher's exact test where appropriate. Univariable and multivariable Cox proportional hazards models were used to assess the associations between coronary events and the self-reported risk factors.

Receiver Operator Characteristic curves were constructed to determine the discriminatory power of CAC (log [CAC + 1]) for predicting future CHD events (area under the curve; *c*-index) and to identify potential prognostic CAC cut-points [5]. Stratified analyses were performed using a cut-point derived from the Receiver Operator Characteristic analyses within subgroups based on the presence of self-reported CHD risk factors and according to the number of conventional CHD risk factors present at baseline (0–2, or 3–4). Further, for the subset of 3619 individuals in whom clinical data were available for the computation of 10-year

Framingham risk estimates, participants were categorized into low (<10%) and moderate/high-risk (≥10%) groups, and CHD incidence rates were calculated for CAC levels of 0, 1–99, and ≥100 across the Framingham risk categories.

3. Results

3.1. Demographic characteristics

The majority of participants were men (64%) and white (>97%), with a mean age of 53.8 ± 9.9 years. Prevalence of current smoking was 9.1%, previous smoking 27.8%, hypercholesterolemia 30.0%, diabetes 3.2%, and hypertension 17.9%.

The relationship between self-reported risk factor status and measured clinical values was examined in a subset of 3619 participants for whom such data were available (Table 1). In each instance the measured risk factors were significantly higher and met clinically relevant thresholds among individuals who reported having the related condition compared with those who reported not having the condition. Further, only 1.6% of individuals who report no history of hypertension had a systolic blood pressure ≥160 mmHg, 8% of individuals who reported not having a history of high

Table 2

Self-reported risk factors and coronary artery calcium

Self-report risk factors ^a	<i>n</i>	Mean CAC (S.D.)	Adjusted mean CAC ^b (95% CI)	Median CAC (95% CI)	Prevalence of CAC > 0
0	4264	138 (545)	165 (148–182)	0 (0–38)	41
1	2487	149 (470)	151 (129–172)	0 (0–71)	50
2	2387	192 (622)	185 (163–207)	1 (0–97)	51
3–4	1608	323 (780) ^{***}	258 (231–285) ^{***}	26 (0–263)	66 ^{***}

CAC, coronary artery calcium.

^a Risk factors are current smoking, hypercholesterolemia, diabetes, and/or hypertension.

^b Adjusted for age and gender.

^{***} *p* for trend <0.0001.

Table 3

Descriptive characteristics by event status and univariable association between risk factors, coronary artery calcium, and cardiac events

	Event free (<i>n</i> = 10,665)	Nonfatal MI or CHD death (<i>n</i> = 81)	Between group differences, <i>p</i> -value
Age (years)	53.8 (9.9)	61.0 (10.2)	<0.001
Follow-up (years)	3.5 (1.4)	1.7 (1.3)	<0.001
Mean calcium score ^a	177 (588)	664 (835)	<0.001
Median calcium score	0 (0–75)	244 (79–976)	<0.001
Male gender (yes/no) (%)	63.5	76.5	0.01
Hypercholesterolemia (yes/no) (%)	29.9	34.6	0.36
Diabetes (yes/no)	3.1	17.2	<0.001
Hypertension (yes/no) (%)	17.8	30.9	<0.001
Smoking (%)			
Never	62.2	49.4	0.04
Past	27.8	38.3	
Current	9.0	12.3	

MI, myocardial infarction; CHD, coronary heart disease.

^a For models log (coronary calcium + 1) was used.

cholesterol had LDL cholesterol ≥ 160 mg/dL, and none of the individuals who reported not having diabetes had a fasting glucose ≥ 126 mg/dL. The Cooper Clinic patient population has been shown to have a sensitivity and specificity for self-reported hypertension of 98% and 99%, respectively, and 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, affluent study population [19].

3.2. Self-reported risk factors and CAC

Mean CAC, age- and gender-adjusted mean CAC, and median CAC was higher in the groups with the highest number of self-report risk factors present (Table 2). Similarly the prevalence of individuals with detectable CAC (CAC > 0) was higher in the groups that reported the highest number of self-reported risk factors ($p < 0.001$).

3.3. Predictors of CHD events

During a mean follow-up period of 3.5 years (37,326 person-years), 287 CHD events occurred (19 CHD deaths, 62 nonfatal myocardial infarctions, 106 percutaneous revascularizations, and 100 coronary bypass grafts). Among the 99 nonfatal CHD events that underwent adjudication, 95% (94/99) were verified as reported. Of the misreported events, 3 were cardiac catheterizations without revascularization and 2 were peripheral revascularization procedures. Nineteen of these 99 events were nonfatal myocardial infarctions, all of which were confirmed as reported.

Individuals who had a primary CHD event were older, male, had a shorter total follow-up, and had a higher prevalence of diabetes, hypertension, hypercholesterolemia, and past/current smoking as compared to that in participants who remained event free (Table 3). Univariable analyses showed that log CAC score (RR [95% CI]: 1.5 [1.4–1.7]), age (per 10 years) (2.0 [1.6–2.4]), male sex (2.0 [1.2–3.3]), diabetes (6.5 [3.6–11.5]), hypertension (2.0 [1.3–3.2]), and past smoking (1.7 [1.1–2.7]) were each associated with increased risk

of primary events. In a multivariable model that included each of the exposures listed above, only log CAC score (1.5 [1.3–1.7]) and diabetes (4.0 [2.2–7.1]) were significant predictors of primary CHD events. The use of secondary CHD outcomes produced similar results.

3.4. CAC of zero and risk of event

Of the 81 CHD deaths or nonfatal myocardial infarctions, 7 occurred in individuals ($n = 5472$) without detectable CAC (CAC = 0), resulting in event rate of 0.4 events per 1000 person-years. In the 5274 individuals with detectable CAC (CAC > 0) at baseline, there were 74 CHD deaths or nonfatal myocardial infarctions resulting in an event rate of 4.0 events per 1000 person-years. After adjusting for age and gender, the relative risk (95% CI) of a primary CHD event

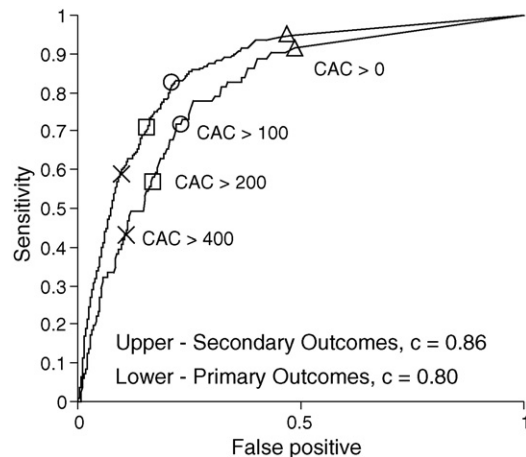


Fig. 2. Receiver Operator Characteristic curve for coronary artery calcium score (log [CAC + 1]) and both the primary outcomes of nonfatal myocardial infarction and coronary heart disease death (lower curve) and secondary outcomes of primary plus revascularizations (upper curve). A perfect test would have an area under the curve (c-index) of Fig. 1. For clarity purposes, individual data points are not presented and only the best-fit line with the approximate positions of coronary artery calcium scores of 0, 100, 200, and 400 are shown.

was 0.13 (0.06–0.3) in individuals without detectable CAC at baseline compared to individuals with CAC. Further adjustment for the presence of self-reported risk factors had little effect (0.15 [0.07–0.34]) on the protective benefit of having no detectable CAC.

3.5. Discriminatory power of CAC for future CHD events

Based on receiver operator curve analysis, CAC score was found to have good discriminatory power for identifying individuals who developed a CHD event (Fig. 2). The c-index for CAC score for primary and secondary events was 0.80 and 0.86, respectively. The points along the curve for CAC >0, 100, 200, and 400 are identified in the figure. A sharp decline in the curve occurs at a CAC score of 100, suggesting that this value may be a possible prognostic threshold.

3.6. CAC across categories of CHD risk factors

Individuals were grouped according to the presence or absence of a history of diabetes, hypertension, hypercholesterolemia, and current smoking. Additional grouping was done based on the total number of prevalent risk factors. With the referent group being individuals not reporting the specific risk factor of interest and having a CAC <100, the age- and gender-adjusted risk of having a primary CHD event was higher when the risk factor was present regardless of CAC <100 or CAC ≥100 (Tables 4 and 5). However, among indi-

viduals who reported having the risk factor, having a CAC ≥100 was associated with more than twice the risk compared to that in those who had a CAC <100. Further, within each risk factor category, those individuals that did not report having the risk factor but had a CAC ≥100 were at substantially greater age- and gender-adjusted risk (RR range 6.8–10.0) of having a primary CHD event compared to those individuals not reporting the risk factor and having a CAC <100. The results were similar when examining the age- and gender-adjusted relative risks of primary events across number of risk factors present (Fig. 3). Within each level of risk factor stratification, a CAC ≥100 was associated with much greater risk of having a primary CHD event. The findings were similar when secondary outcomes were examined.

Rates of CHD according to levels of CAC and FRS were computed for the subgroup of 3619 individuals with measured clinical phenotypes (Fig. 4). A total of 14 primary events and 72 secondary events occurred in these study participants. In both the low-risk group (FRS <10%) and moderate–high-risk group (FRS ≥10%), seven primary events occurred, and the incidence of both primary and secondary events was higher in individuals with CAC ≥100. Among the 1021 individuals with a Framingham risk score ≥10%, 248 had a CAC score of 0 (24%) among whom there were no CHD events. Based on Receiver Operator Characteristics analysis for the FRS alone and for the FRS plus CAC, the c-index for primary CHD events was 0.60 and 0.87, respectively, and for secondary events 0.78 and 0.90, respectively.

Table 4
Risk of nonfatal MI or CHD death by coronary artery calcium categories and self-report risk factors

	CAC < 100			CAC ≥ 100		
	N (events)	Rate ^a	RR _{adj} (95% CI)	N (events)	Rate ^a	RR _{adj} (95% CI)
No HTN	6967 (14)	0.6	1.0 (ref)	1852 (42)	6.7	8.3 (4.3, 16.4)
No DM	8032 (18)	0.6	1.0 (ref)	2369 (49)	6.1	6.8 (3.7, 12.5)
No Chol	5906 (11)	0.5	1.0 (ref)	1620 (42)	7.7	10.0 (4.8, 20.8)
No smoke	7518 (18)	0.7	1.0 (ref)	2253 (53)	6.9	7.3 (4.0, 13.4)
HTN reported	1267 (9)	2.0	3.1 (1.3–7.1)	660 (16)	7.1	8.4 (3.8, 18.3)
DM reported	202 (5)	6.9	10.2 (3.8–27.6)	143 (9)	20.1	21.3 (9.0, 50.3)
Chol reported	2328 (12)	1.4	2.6 (1.1–5.9)	892 (16)	5.2	7.1 (3.2, 15.9)
Smoker	716 (5)	2.0	3.1 (1.2–8.5)	259 (5)	5.6	6.5 (2.3, 17.9)

HTN, hypertension. DM, diabetes, Chol, hypercholesterolemia.

^a Per 1000 person-years. RR_{adj} = relative risk of event adjusted for age, sex, and self-reported history of smoking (except in the smoking subgroup analysis).

Table 5
Risk of nonfatal MI or CHD death by coronary artery calcium category and number of conventional risk factors reported

Risk factors ^a	Nonfatal MI or CHD death			
	CAC < 100		CAC ≥ 100	
	n (events)	Rate ^b	n (events)	Rate ^b
0	3498 (5)	0.4	766 (16)	6.4
1	2419 (7)	1.0	548 (9)	4.8
2	1797 (2)	0.3	590 (5)	7.4
3–4	1000 (9)	2.4	608 (18)	8.4

MI, myocardial infarction; CHD, coronary heart disease; CAC, coronary artery calcium.

^a Risk factors are self-reported history of current smoking, hypercholesterolemia, diabetes, and/or hypertension.

^b Per 1000 person-years.

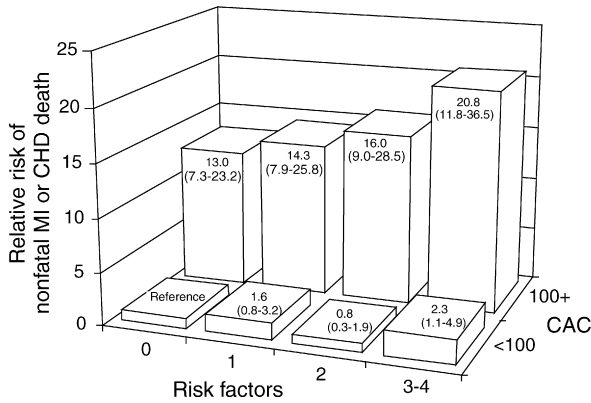


Fig. 3. Age- and gender-adjusted relative risk of nonfatal myocardial infarction and coronary heart disease death in those with coronary artery calcium ≥ 100 compared with those with coronary artery calcium < 100 with stratification by number of the self-reported risk factors of current smoking, hypercholesterolemia, diabetes, and/or hypertension. The relative risks (95% CI) are provided on each bar.

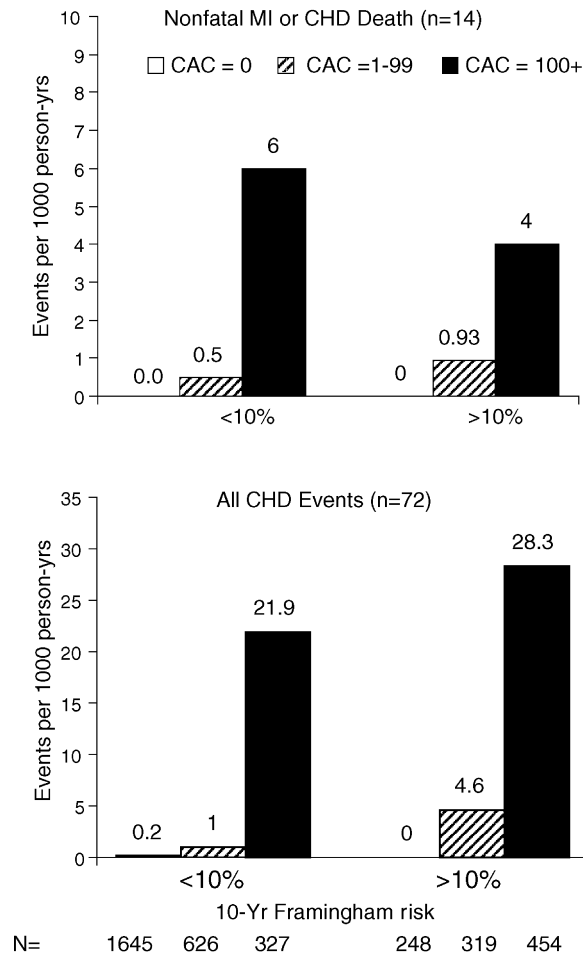


Fig. 4. Rate of coronary heart disease events across levels of coronary artery calcium with stratification by 10-year Framingham risk score for 3619 men and women with clinical examination data available. Top panel presents rates of the primary outcomes of nonfatal myocardial infarction and coronary heart disease death, and bottom panel presents the secondary outcomes of primary plus revascularizations. Height of bars and numbers on top depict events per 1000 person-years.

4. Discussion

The primary findings from this study of 10,746 men and women free of known CHD at baseline are that (1) CAC score can reasonably discriminate between individuals likely to have future coronary heart disease events and those who will not have an event, (2) a CAC score ≥ 100 is associated with substantially higher CHD risk even in patients otherwise considered low-risk based on the traditional CHD risk assessment, and (3) in our population, individuals with no detectable CAC (CAC = 0) have a relatively low short-term risk of having a CHD event.

Although a history of hypertension, diabetes, and current smoking were associated with the presence of CAC and with future coronary events, CAC scores remained significantly associated with the incidence of CHD events even after adjusting for the presence of CHD risk factors. Furthermore, a CAC score ≥ 100 identified increased CHD risk in individuals grouped according to the presence or absence and number of CHD risk factors at baseline. A CAC score ≥ 100 also appeared to add prognostic value beyond the FRS in a subgroup of study participants for whom measured clinical data were available. The number of participants and number of events for this subgroup analysis were relatively small, and these observations should be interpreted cautiously.

It has been suggested that use of electron beam tomography results to guide therapeutic intervention should be confined to individuals with moderate CHD risk based on conventional risk factor assessment, because high-risk patients already require aggressive cardiovascular risk modification and low-risk individuals are perceived to not need further evaluation [15]. The present study provides evidence to the contrary. Our study population included many individuals who reported no history of diabetes, current smoking, hypertension, or cholesterol abnormalities and yet had a CHD event. Approximately 52% of primary CHD events occurred in individuals who reported having 0 or 1 risk factor (other than age and gender) at baseline. Even among these individuals who would generally be considered at low risk for CHD events, a CAC score of ≥ 100 was a strong predictor of the development of clinically manifest CHD.

The rate of primary CHD events in individuals with a CAC score of zero was lower in the current study compared to a recent report by Greenland et al. (0.1% versus 4.0% for hard events, respectively) [15]. There are a number of potential reasons for the differences in event rates between these two studies. Compared with the study reported herein, the population under study by Greenland et al. was older (65.7 years versus 53.8 years), had higher baseline CHD risk factor profiles (93% had a FRS $\geq 10\%$), and was followed for a longer period (6.3 years versus 3.5 years). While a longer follow-up period may seem to be a strength in this study, it may also result in misleading results regarding the association between CAC and incident CHD events. CAC increases exponentially with age, and a longer follow-up period increases the likelihood for large changes in CAC to occur. This could result in

a substantial misclassification on exposure and bias the estimate of association away from the null. In contrast, the shorter follow-up period in the present study may have resulted in less significant progression of CAC, which may allow for a more stable estimate of CHD risk from a single baseline measure of CAC. Nonetheless, the low risk for CHD events in individuals with no detectable CAC in the present study should only be assumed for a limited period of time (<3.5 years).

Although the findings of this study indicate that CAC scanning may be a valuable noninvasive method for identifying subclinical CHD among asymptomatic adults, there are many important issues regarding the clinical applications of CAC scores in the context of primary CHD prevention that have yet to be resolved. For example, at what age should the first CAC scan be obtained and how often should the scan be repeated based on the initial CAC score, age, gender, risk factor profiles, and lifestyle habits? A better understanding is needed on the issues related to the costs and benefits of routine CAC scanning in the general population. The rapid commercialization of CAC scanning prior to the accrual of adequate scientific support justifiably caused concern over the widespread use of EBT technology in clinical settings. However, the findings reported here and elsewhere provide compelling evidence that CAC scanning has the potential to be a valuable clinical tool and justifies further research to refine the use of CAC scores as an adjuvant to existing methods of individual risk assessment for primary CHD prevention.

One of the strengths of this study is the use of “hard” CHD events (CHD death or myocardial infarction) as the primary outcome. Although the assessment of revascularization, alone or combined with hard CHD events, substantially increases the number of events available for analysis, it also has the potential to bias estimates of association between baseline CAC and future CHD events. For example, an elevated CAC score may prompt additional diagnostic tests that may lead to revascularization, thus biasing the data toward a stronger prediction of revascularization events associated with CAC. Conversely, knowledge of electron beam tomography results could have influenced physicians to institute more aggressive risk-modifying therapies among participants with detectable CAC. This would likely bias the predictive power of CAC toward rather than away from the null. Other strengths of this study include the large sample size with high internal validity, the high proportion of participants available for follow-up, and accuracy of event reporting demonstrated by the results of the adjudication process.

There also are limitations in this study. Due to the widespread geographic distribution of patients evaluated at the Cooper Clinic and the inability to collect all clinical source documentation, we were unable to verify all reported CHD events. However, of the 99 CHD events adjudicated, 95% were confirmed as reported. Thus, it is unlikely that adjudication of the remaining events would have materially changed our results. The study population is primarily Cau-

casian and middle-to-upper-socioeconomic status. Although these characteristics strengthen the internal validity of our sample, similar to that in other well known highly selected demographic groups such as Harvard college alumni or U.S. nurses, they also weaken the external validity of our sample requiring that the observations reported here be confirmed in more diverse populations.

It has been suggested that 3×2 scanning overestimates coronary calcium by up to 16%, thus, although our CAC categories may not be directly comparable to those in other electron beam tomography studies, the validity of our results should not be affected. However, the use of a 3×2 scanning protocol is less likely to miss small calcium deposits and thus the opportunity to misclassify individuals as CAC-free is lower. Although we relied on self-reported diagnosis for diabetes, hypercholesterolemia, and hypertension, the accuracy of self-reported diagnoses in this cohort has been previously reported [19]. Further, in a subset of participants, the measured risk factors were significantly higher and met clinically relevant thresholds among individuals who reported having the related condition compared to that in those who reported not having the condition. The finding that self-reported diabetes, hypertension, and smoking were all predictors of CHD events in univariable analysis provides additional evidence that the self-report measures in this population are of reasonable accuracy.

5. Conclusions

CAC is a strong predictor of incident CHD events and can reasonably discriminate between individuals who are likely to have a future CHD event and those who are not. A CAC score can identify individuals at increased risk for CHD events among those who otherwise would be considered to have a low risk of developing clinically manifest CHD on the basis of conventional clinical risk assessment. The present data suggest that in the short to intermediate term (≈ 3.5 years), a CAC score of zero is associated with very low risk of having a CHD event. Additional prospective studies on diverse populations of women and men are needed to expand on the observations reported in this study.

Acknowledgements

Supported in part by NIH grants AG06945 and HL62508. Additional support has been provided by the Communities Foundation of Texas on recommendation of Nancy Ann and Ray L. Hunt. We thank our many participants; the Cooper Clinic physicians, in particular Kenneth H. Cooper, MD, MPH; the technicians for collecting the baseline data; Susan Devers, RN; Melba Morrow, MA, for editorial assistance; Jason Wallace, MPH, Carolyn Wright, MS, and the Center for Data Management for conducting the mail survey and overall management of the database.

References

- [1] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte Jr M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–32.
- [2] Dixon AK, Couleden RA. Coronary artery calcification on computed tomography. *Lancet* 1997;350:1265.
- [3] 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.
- [4] Fallavollita JA, Brody AS, Bunnell IL, Kumar K, Canty Jr JM. 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.
- [5] 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.
- [6] Hoeg JM, Feuerstein IM, Tucker EE. Detection and quantitation of calcific atherosclerosis by ultrafast computed tomography in children and young adults with homozygous familial hypercholesterolemia. *Arterioscler Thromb* 1994;14:1066–74.
- [7] Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 1995;92:2157–62.
- [8] Rumberger JA, Sheedy PF, Breen JF, Schwartz RS. Electron beam computed tomographic coronary calcium score cutpoints and severity of associated angiographic lumen stenosis. *J Am Coll Cardiol* 1997;29:1542–8.
- [9] 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.
- [10] 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.
- [11] Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;36:1253–60.
- [12] Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000;86:495–8.
- [13] 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.
- [14] Detrano RC, Wong ND, Tang W, et al. Prognostic significance of cardiac cinefluoroscopy for coronary calcific deposits in asymptomatic high risk subjects. *J Am Coll Cardiol* 1994;24:354–8.
- [15] Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;291:210–5.
- [16] LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. *Am J Epidemiol* 2005;162:421–9.
- [17] Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486–97.
- [18] Blair SN, Kohl III HW, Paffenbarger Jr RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 1989;262:2395–401.
- [19] Blair SN, Goodyear NN, Gibbons LW, Cooper KH. Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA* 1984;252:487–90.