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Prognostic Markers in CAD

Coronary Calcium Independently Predicts Incident Premature Coronary Heart Disease Over Measured Cardiovascular Risk Factors

Mean Three-Year Outcomes in the Prospective Army Coronary Calcium (PACC) Project

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OBJECTIVES We sought to examine the independent predictive value of coronary artery calcium detection for coronary outcomes in a non-referred cohort of healthy men and women ages 40 to 50 years.

BACKGROUND Existing studies have suggested that coronary calcium might have incremental predictive value for coronary outcomes above standard coronary risk factors. However, additional data from non-referred and younger populations are needed.

METHODS Participants (n = 2,000; mean age 43 years) were evaluated with measured coronary risk variables and coronary calcium detected with electron beam tomography. Incident acute coronary syndromes and sudden cardiac death were ascertained via annual telephonic contacts, with follow-up (mean, 3.0 ± 1.4 years; range, 1 to 6 years) in 99.2% of the cohort.

RESULTS Coronary calcium was found in 22.4% of men and 7.9% of women. A total of 9 acute events occurred in men at a mean age of 46 years, including 7 of 364 men with coronary calcium (1.95%) and 2 of 1,263 men without coronary calcium (0.16%; $p < 0.0001$ by log-rank). No events occurred in women. In these men, coronary calcium was associated with an 11.8-fold increased risk for incident coronary heart disease (CHD) ($p = 0.002$) in a Cox model controlling for the Framingham risk score. Among those with coronary artery calcification, the risk of coronary events increased incrementally across tertiles of coronary calcium severity (hazard ratio 4.3 per tertile). A family history of premature CHD was also predictive of incident events. The marginal cost effectiveness, assuming a 30% improvement in survival associated with primary prevention among at-risk men, was modeled to be $37,633 per quality-adjusted life year saved.

CONCLUSIONS In young, asymptomatic men, the presence of coronary artery calcification provides substantial, cost-effective, independent prognostic value in predicting incident CHD that is incremental to measured coronary risk factors. (J Am Coll Cardiol 2005;46:807–14)
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Recent guidelines have highlighted the potential use of anatomically based coronary heart disease (CHD) risk assessments to refine the risk prediction provided through global risk assessment tools such as the Framingham risk score (FRS) (1–4). One such approach uses computed tomography (CT) to detect coronary artery calcium (CAC), a finding that is clearly related to an increased risk of incident CHD (5,6). However, controversy remains regarding whether, and to what extent, detection of CAC provides incremental risk prediction beyond conventional coronary risk factors. With the exception of the South Bay Heart Watch (7), studies examining the relationship between coronary risk factors, coronary calcium, and outcomes have used self-reported risk factor data (8–11), introducing a potential source of error and bias in the analyses (10,12).

The Prospective Army Coronary Calcium (PACC) project is a prospective cohort study of U.S. Army personnel examining the incremental prognostic value of CAC beyond the FRS for the determination of CHD prognosis. Initiated in 1998, we enrolled healthy asymptomatic men and women between the ages of 40 and 50 years who were presenting for a periodic physical examination. Herein, we report the relationship between CAC and CHD outcomes of myocardial infarction, hospitalized unstable angina, and sudden cardiac death based on mean three-year follow-up of the PACC project cohort.

METHODS

This protocol was approved by the Department of Clinical Investigation of Walter Reed Army Medical Center and

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Abbreviations and Acronyms

BMI = body mass index
CAC = coronary artery calcium
CHD = coronary heart disease
CT = computed tomography
EBCT = electron beam computed tomography
FRS = Framingham risk score
HDL = high-density lipoprotein
LDL = low-density lipoprotein
PACC = Prospective Army Coronary Calcium
QALY = quality-adjusted life years

funded under the Congressionally directed, peer-reviewed medical research program of the Department of Defense. The methods of the PACC project have been previously published (13). Briefly, all active-duty Army personnel, ages 40 to 50 years old and stationed within the National Capital Area of the Walter Reed Health Care System, were recruited at the time of a periodic, Army-mandated physical examination. Individuals with a history of CHD or who indicated a history of angina pectoris by the Rose questionnaire (14) were ineligible. Between October 26, 1998, and February 19, 2003, 2,259 eligible individuals were screened and 2,000 men and women provided written informed consent to undergo electron beam computed tomography (EBCT) and the cardiovascular risk-screening program. One male participant failed to complete the coronary CT scan, leaving 1,999 participants for analysis.

PACC Project procedures. Participants provided details of their medical history, lifestyle behaviors, and psychosocial history. Ethnicity was self-reported. Medical history included a history of hypertension, diabetes mellitus, hypercholesterolemia, and current medications. Smoking was self-reported as current, recent (within six months) or remote (more than six months ago) use of any inhaled tobacco products, except for intermittent cigar consumption. A family history of CHD included a history of sudden death, myocardial infarction, or coronary revascularization in a relative before the age of 55 (males) or 65 (females) years (15). Family history data were collected separately for first- (parents, siblings) or second-degree (grandparents, aunts, uncles, cousins) relatives.

Resting blood pressure was measured using an automated sphygmomanometer, and was recorded as the average of three seated measurements taken 5 min apart. Hypertension was defined as either a systolic blood pressure of >135 mm Hg, a diastolic blood pressure of >85 mm Hg (16), or a history of hypertension (treated or untreated). Height and weight were measured, and body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist girth was measured as the maximum abdominal circumference between the iliac crest and umbilicus. The metabolic syndrome was classified according to the recommendations of the National Cholesterol Education Program (15). Fasting blood was collected for the measurement of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, serum glucose, hemoglobin A1C, lipoprotein(a), homocysteine, fibrinogen, and insulin. Measurement of serum C-reactive protein was added during the course of the study. The predicted 10-year FRS for incident CHD was calculated using measured risk factor variables as specified within regression equations from the Framingham Heart Study (17).

The baseline coronary risk factors and their relationships to CAC in the PACC project have been previously reported (10,18,19). Variables having significant univariate relationships with CAC included gender, Caucasian race, hypertension, a family history of CHD, and metabolic syndrome. Participants with CAC also had significantly higher 10-year FRS for CHD, BMI, waist girth, blood pressure (both systolic and diastolic), total cholesterol, LDL cholesterol, triglycerides, and fasting glucose, and lower HDL cholesterol. All measured emerging cardiovascular risk factors (e.g., lipoprotein(a), homocysteine, fibrinogen, serum insulin, and C-reactive protein) were unrelated to CAC.

EBCT scanning and analysis. For the measurement of CAC, EBCT was performed using an Imatron C-150 LXP scanner (Imatron Corp., South San Francisco, California) calibrated daily with air and water phantoms and twice-monthly with contrast and resolution phantoms. Images were obtained using a 40- to 50-slice (3 mm thickness) protocol with image acquisition triggered to 60% to 80% of the electrocardiographic RR interval while respirations were held. Scans were interpreted in a blinded manner by an experienced radiologist (I. M. F.) using the Agatston scoring method (20). A focus of coronary calcium was defined as the presence of four or more contiguous pixels with >130 Hounsfield units. A total CAC score was determined from the sum of individual scores of the four major epicardial coronary arteries. A scan was considered positive for CAC when the total CAC score was >0 (18,21).

CHD outcomes. The published analysis plan of the PACC project pre-specified an actuarial five-year analysis of the relationship between CAC and CHD events (13). To achieve this, the vital status of the cohort was tracked through annual telephonic contacts during which a structured interview was conducted. Detailed interviews on a reported possible CHD event were conducted by experienced nurse coordinators who obtained details and requested source documents (hospital records) for review. Records of the CHD event were independently reviewed by two researchers and a third independent cardiologist to confirm the nature of the CHD event. These reviews were conducted blinded to all cardiovascular risk factor and CAC data. This analysis reports adjudicated acute CHD events defined as sudden cardiac death (sudden, unexpected death within one hour of the onset of symptoms), myocardial infarction (documented by elevated cardiac biomarkers and a clinical course of care consistent with this diagnosis), and unstable angina pectoris (acute-care hospitalization for new-

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onset or rapidly progressive chest pain or another ischemic equivalent symptom with demonstrated inducible ischemia or obstructive coronary artery disease and a course of care consistent with this diagnosis). Stable chest pain syndromes and asymptomatic revascularization procedures (one asymptomatic patient underwent percutaneous coronary revascularization after a strongly positive screening stress test) were not included.

As of October 26, 2004, 1,983 of the 1,999 participants with coronary CT scans remained in the study, and their vital status was determined using direct telephonic contact (99.2% follow-up). The mean follow-up duration was 3.0 ± 1.4 years. Among the 16 participants not included in this analysis, 5 were known to be alive and well, but withdrew consent for continued participation before their first scheduled follow-up. One died in the Pentagon terrorist attack of September 11, 2001. Ten participants were lost to follow-up, although none were identified in a search of the social security death index or were known to have accessed the military or civilian health care network (ascertained through military administrative health care databases) under a cardiovascular diagnosis or procedure code. These patients were not included in the present analysis.

Statistical analysis. The primary analysis was on the relationship between CHD events and CAC. For univariate analyses, continuous variables were compared using a *t* test for independent groups and categorical variables were compared using the chi-square test. Multivariate analysis was performed using Cox proportional hazards modeling and stepwise methods to examine the independent predictive value of CAC for CHD events. This analysis was conducted for men only because no women experienced a CHD event during follow-up. Two models were established: model I examined how the presence of CAC predicted CHD, and model II further investigated how the incremental severity of CAC predicted CHD. Model II was limited to those participants with any detectable CAC, with CAC coded in tertiles by CAC score. Both forward and backward stepwise methods were used to examine the unique predictive value of CAC. In forward stepwise models, only variables that significantly predicted CHD events ($p < 0.05$) were selected and entered into the equation. In backward stepwise methods, all variables were selected and entered into the equation first, and then removed in each step beginning with the smallest chi-square value until the remaining variables significantly predicted the CHD event. Participants were censored from models after the last follow-up contact. Because of the small number of CHD outcomes, the FRS was the only covariate in a parsimonious model. An exploratory analysis evaluating both the FRS and a family history of premature CHD was also conducted. Family history was categorized as absent (no family history; 68%), and either a first- or second-degree or both first- and second-degree family history (32%), because both have been reported to have predictive value in younger patient populations (22). Models incorporating a more traditional definition (15) of premature family history restricted to first-degree relatives of those with CHD were also evaluated and showed similar but non-significant trends (data not shown). Twenty participants (none with a CHD outcome) with missing data for family history were excluded from the models in which either first- or second-degree or both degrees of family history was used as a predictor. Cox regression results were expressed as hazard ratios and reported with 95% confidence intervals. Hazard ratios for the FRS are presented per 1% increase in 10-year risk. All analyses were performed by an expert statistician (F.C.) using SPSS for Windows (version 12.0, SPSS Inc., Chicago, Illinois). To extend the pre-study sample size calculations as previously published (13), a post-hoc sample size analysis was performed using Sample Power (version 2.0, SPSS Inc.). Data are presented as mean ± standard deviation. A two-tailed p value of $p \leq 0.05$ was considered significant.

Cost effectiveness analysis. We previously published a decision analysis assessing the theoretical cost effectiveness of atherosclerosis imaging in a low-risk population (23). Using the current CHD outcomes analysis, we updated the cost effectiveness analysis using the same decision tree and incorporated the actual relative risk estimates observed, using the 95% confidence limits in the sensitivity analysis. In the model we used Bayesian logic to incorporate EBCT into risk prediction, multiplying the adjusted predicted risk determined by the FRS by the adjusted relative risk increase conferred by the CAC score. In other words, the presence of CAC multiplied the absolute risk by the adjusted relative risk associated with CAC from this analysis. A CAC score of zero was the referent value. We defined "at risk" as having a calculated CHD risk using the FRS of ≥1% per year. This cutoff was chosen because primary prevention has been proven to be cost effective principally when risk exceeds this threshold. The base case assumptions and their derivation sources are included in detail in the prior publication (23). In brief, the annual costs for medications if "at risk" was $400; the utility of being "at risk" was 0.98; the efficacy of primary prevention therapy for "at-risk" individuals was to extend life expectancy by 1.5 years among "at-risk" patients who would live an average of 5 years less than a cohort not "at risk"—in other words, primary prevention would be associated with a 30% relative risk reduction in overall mortality among an at-risk 40-year-old screening population.

RESULTS

The demographic and descriptive characteristics of the 1,983 participants are shown in Table 1, grouped separately by gender. Caucasians were the majority of the cohort. The group was predominately well-educated. For men, the most prevalent cardiac risk factors were hypertension (30.8%) and either a first- or second-degree (31.7%) family history of CHD. The metabolic syndrome was present in 6.6%, and

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Table 1. Characteristics of the Study Participants Included in This Report*

Variable	Men (n = 1,627)	Women (n = 356)
Age (yrs, mean ± SD)	42.9 ± 2.8	42.8 ± 2.7
Caucasian race	71.8%	56.2%
African American race	17.8%	30.6%
College-educated	82.6%	75%
Cardiac risk factors		
Hypertension	30.8%	19.1%
1st-degree family history of CHD	18.5%	20.4%
Either 1st- or 2nd-degree or both degrees of family history for CHD	31.7%	31.5%
Metabolic syndrome	6.6%	3.7%
Current tobacco use	6.9%	11.2%
Diabetes mellitus	0.8%	0%
10-yr Framingham risk index, CHD	4.6 ± 2.6	1.4 ± 1.2
10-yr Framingham risk index, CVD	7.3 ± 3.9	3.2 ± 2.5
Coronary artery calcification score		
Mean	19.5 ± 110.7	3.3 ± 20.0
Median	0	0
CAC score = 0	1,263 (77.6%)	328 (92.1%)
CAC score = 1–9	120 (7.4%)	11 (3.1%)
CAC score = 10–44	120 (7.4%)	8 (2.2%)
CAC score ≥45	124 (7.6%)	9 (2.5%)
Baecke Sports index†	3.0 ± 1.0	2.6 ± 1.2
Body mass index (kg/m^2)	27.8 ± 3.5	25.9 ± 3.7
Waist girth (cm)	95.8 ± 24.9	82.3 ± 10.1
Systolic blood pressure (mm Hg)	124.3 ± 12.0	115.5 ± 13.4
Diastolic blood pressure (mm Hg)	77.6 ± 8.8	72.3 ± 9.1
Total cholesterol (mg/dl)	204.2 ± 36.1	195.8 ± 34.9
LDL cholesterol (mg/dl)	128.5 ± 31.4	112.1 ± 30.0
HDL cholesterol (mg/dl)	50.4 ± 12.62	65.03 ± 16.10
Triglycerides (mg/dl)	129.8 ± 86.5	88.6 ± 51.2
Fasting glucose (mg/dl)	92.7 ± 11.1	87.4 ± 8.9
Hemoglobin A1C (%) (n = 1,581)	5.4 ± 0.6	5.3 ± 0.4
Lipoprotein(a) (mg/dl)	30.1 ± 33.5	38.1 ± 41.3
Homocysteine (μmol/l)	9.6 ± 2.5	8.0 ± 3.6
Fibrinogen (mg/dl)	315.2 ± 58.9	337.8 ± 65.5
Insulin (μU/ml)	8.0 ± 6.0	8.2 ± 4.9
C-reactive protein (mg/l)‡	1.9 ± 2.2	2.4 ± 2.5

*Mean ± standard deviation; †Baecke Sports index score ranges from 1 to 5, 5 being most active; ‡C-reactive protein, n = 832 (men) and 184 (women).

CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cerebrovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

6.9% of participants were active tobacco users. The mean 10-year FRS for CHD was 4.6 ± 2.7%. Coronary artery calcification was detected in 22.4% of male participants, with a mean CAC score of 20 ± 111. Coronary artery calcification was detected in 7.9% of female participants, with a mean CAC score of 3 ± 20. Among the 4.4% (72 of 1,627) of the male study cohort with a 10-year FRS ≥ 10%, 24 had CAC. Thus, a total of 412 patients had either elevated FRS (≥10%) or CAC present.

During the follow-up period (mean, 3.0 ± 1.4 years; range, 1 to 6 years), there were nine acute CHD events (definite myocardial infarction, unstable angina, or CHD death). All of these events occurred in men, with a mean age of 43 years. Among these men, the mean age at the time of the event (46 ± 2 years [at time of event] vs. 46 ± 3 years [at last follow-up]) and FRS (5.7 ± 2.6% vs. 4.6 ± 1.9%; p = 0.19) was similar in those with and without CHD events. Four events occurred in men with a 10-year FRS <6%, and five occurred in men with a FRS between 6% and 10%. No events occurred in the 72 men with an FRS above 10%. Five of the nine events occurred in men with either a first- or second-degree family history of premature CHD (n = 505).

The CHD events occurred in 7 of 364 men with CAC (1.95%) and 2 of 1,263 without CAC (0.16%; p < 0.0001 by log-rank) (Table 2, Fig. 1). Cox regression showed that the presence of any CAC was associated with an 11.8-fold increased risk for acute CHD (p = 0.002) after controlling for the FRS (Table 3). Among those men with CAC present, the risk of CHD related to increasing severity of CAC was found to be incremental across CAC tertiles (hazard ratio, 4.3 per quartile; p = 0.036) after controlling for the FRS (Table 4, Fig. 2). These significant relationships between CAC and CHD outcomes were marginally weaker in exploratory models controlling for both the FRS and a family history of premature CHD (Tables 3 and 4 for model II). A post-hoc sample size analysis indicated that, using the observed prevalence of CAC, hazard rates for CHD outcomes, and time frame of this study, a total sample of 1,200 patients had an 80% power to find a statistically significant result. The actual power of this study was 91%.

Cost effectiveness analysis. Using the adjusted relative risk associated with having CAC in this cohort with its associated 95% confidence interval, the marginal cost effectiveness of incorporating EBCT into a conventional risk prediction assessment was projected to be $37,633/quality-adjusted life year (QALY), ranging from $31,500/QALY using the upper adjusted relative risk limit estimate of 60, to $500,000/QALY using the lower adjusted relative risk limit estimate of 2 (Fig. 3). This was sensitive to the efficacy of primary prevention at

Table 2. The Distribution of CHD Events by Coronary Calcium, Framingham Risk Score Categories, and Family History of CHD

Variable	CHD Events: Yes	CHD Events: No	n
Coronary calcium			
Present	7	357	364
Absent	2	1,261	1,263
Coronary calcium score tertiles			
CAC score = 1–9	0	120	120
CAC score = 10–44	2	118	120
CAC score ≥45	5	119	124
Framingham risk score			
<6%	4	1,233	1,237
6%–10%	5	311	316
>10%	0	72	72
Family history of CHD			
No family history	4	1,093	1,097
With either 1st- or 2nd-degree family history	2	411	413
With both 1st- and 2nd-degree family history	3	94	97

Abbreviations as in Table 1.

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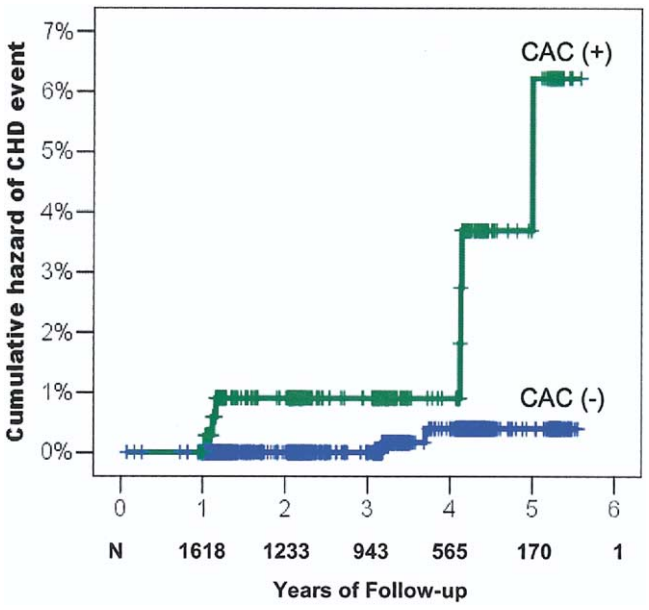


Figure 1. Hazard ratio plot for coronary heart disease (CHD) events including death, unstable angina, and myocardial infarction for male Prospective Army Coronary Calcium project participants with (−) (n = 364) and without (+) (n = 1,263) coronary artery calcium (CAC).

improving overall survival. When the relative improvement in overall survival associated with primary preventive measures (measures unique to at-risk populations: aspirin, statins, lower goals for blood pressure and cholesterol) was assumed to be 25% (Fig. 3), the marginal cost effectiveness was ~$100,000/QALY (ranging from $1,000,000.00/QALY to $79,000.00/QALY using the lower to upper confidence interval on the RR estimates); when the efficacy of primary prevention was assumed to be a 45% relative improvement in survival, the marginal cost effectiveness was ~$13,000.00/QALY (ranging from $22,000/QALY to $11,500/QALY).

DISCUSSION

The results of this pre-specified, mid-term analysis of the PACC project support the presence of a strong, independent relationship between CAC and premature, incident CHD in men. This finding, from a cohort of non-referred study participants with measured cardiovascular risk variables and complete follow-up, persisted after controlling for the FRS, thereby supporting the concept that CAC screening is an incremental tool in the identification of individuals at increased risk for CHD.

Many studies have examined the relationship between CAC, coronary risk factors, and CHD events (7–11,24,25). Although each of these studies has reported an independent relationship between CAC and either mortality or CHD events, there is a substantial degree of variability in the reported strength of this relationship. A recent meta-analysis (6) concluded that three factors, including the manner of risk factor assessment, the adjudication of outcomes, and the inclusion of women in the cohort, accounted for most of these differences. The lowest estimate of the incremental value of coronary CT comes from the only study (an analysis limited to non-diabetic participants of the South Bay Heart Watch [7]) that used measured rather than historical risk factor data. Inaccuracy in the reporting of historical risk factors potentially induces bias in favor of the more accurately measured variable, CAC (8–11,24,25). Thus, use of measured risk factors, as in the PACC project, is the only fully acceptable means of ascertaining the true incremental value of CAC scanning. Outcome assessments blinded to clinical risk factor and CAC scores are crucial to objectively categorize the observed events. Lastly, for a given age, women have lower FRS, lower CAC scores, and a lower event rate (26). Thus, combining genders in any analysis of CAC and outcomes consequently increases the reported relative risk of higher CAC scores (observed more commonly in men), an effect that is magnified in the mixed-gender cohorts that are primarily male. The current analysis of the PACC project adheres to each of these essential study and analysis components.

Direct measurement of coronary risk factors incorporated into a global risk scoring algorithm, such as the FRS, is a necessary starting point in the evaluation of CHD risk. However, the FRS incompletely identifies CHD risk (27) and may lead to systematic overestimation of risk in lower-risk populations. Coupled with an increasing recognition of the low specificity (28) of defined "risk factors" as a direct consequence of lowered thresholds in risk factors (for example, for blood pressure and cholesterol [15]), plaque burden assessments offer a quantitative, anatomic, disease-

Table 3. Cox Models Evaluating the Incremental Predictive Value of Coronary Calcium Presence on the Risk of CHD Events in Men

Variable	Hazard Ratio	p Value	95% Confidence Interval
Model I: controlling for Framingham risk score only (n = 1,627)			
Framingham risk score	1.10	0.37	0.90–1.35
Any CAC	11.82	0.002	2.45–56.93
Model II: controlling for Framingham risk score and family history of CHD (n = 1,607)			
Framingham risk score	1.10	0.40	0.89–1.35
Family history of CHD	2.53	0.043	1.03–6.20
Any CAC	10.75	0.003	2.23–51.84

Framingham risk score per 1% absolute risk change.
Abbreviations as in Table 1.

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Table 4. Cox Models Evaluating the Incremental Value of Coronary Calcium Severity on the Risk of CHD Events in Men With Coronary Calcium Present

Variable	Hazard Ratio	p Value	95% Confidence Interval
Model I: controlling for Framingham risk score only (n = 364)			
Framingham risk score	1.06	0.67	0.81–1.38
Tertile CAC	4.32	0.036	1.10–16.97
Model II: controlling for Framingham risk score and family history of CHD (n = 357)			
Framingham risk score	1.09	0.51	0.84–1.42
Family history of CHD	4.23	0.013	1.36–13.13
Tertile CAC	4.80	0.034	1.13–20.44

Framingham risk score per 1% absolute risk change. Tertile analysis is referent to tertile 1—CAC score 1–9. Abbreviations as in Table 1.

based method of refining the clinical assessment of CHD risk. Consistent with this, the assessment of CAC in primarily intermediate-risk individuals has been advocated in several recent guidelines and position statements (1–3). The PACC project data support this general concept and challenge the notion that plaque burden assessments should not be applied to younger populations at lower absolute CHD risk. Potential advantages of screening individuals 40 to 50 years of age include the generally lower prevalence of CAC limiting the potential for overidentification of individuals identified as at risk because of the dominant relationship between age and CAC. Furthermore, effective therapies arising out of such a screening approach can include lifestyle modifications through a case management approach (29) and low-cost effective pharmacotherapies such as aspirin and generic statins.

Concerns about cost effectiveness are critically important. As our revised cost effectiveness analysis suggests, a screening approach including a global risk assessment tool and coronary calcium imaging for CHD risk detection is relatively cost effective even when considered across long time horizons of modestly effective preventive therapies. Importantly, cost effectiveness is highly dependent on the efficacy of primary CHD prevention. This implies that, after the identification of increased CHD risk, full application of, and adherence to, preventative measures becomes critical. However, because of the low event rate in the overall population, even among those with CAC, unnecessary testing should be avoided. Thus, criteria should be sought for the optimal selection of low-risk individuals with the greatest likelihood of benefit from CAC screening.

Study limitations. The data within this study are generalizable to healthy, physically active individuals from whom the U. S. Army recruits volunteers. Prior studies in this population have confirmed the generalizability of data from U.S. Army cohorts. As expected, based on the younger age of the study population, the CHD event rate was low. Notable, however, is that these individuals all suffered premature CHD events at a mean age of 46 years. Furthermore, it is notable that the actuarial event risk in those men with CAC in this pre-specified analysis was approximately 1% per year overall, with a demonstrable gradient of risk observed across higher CAC scores. Low event rates do

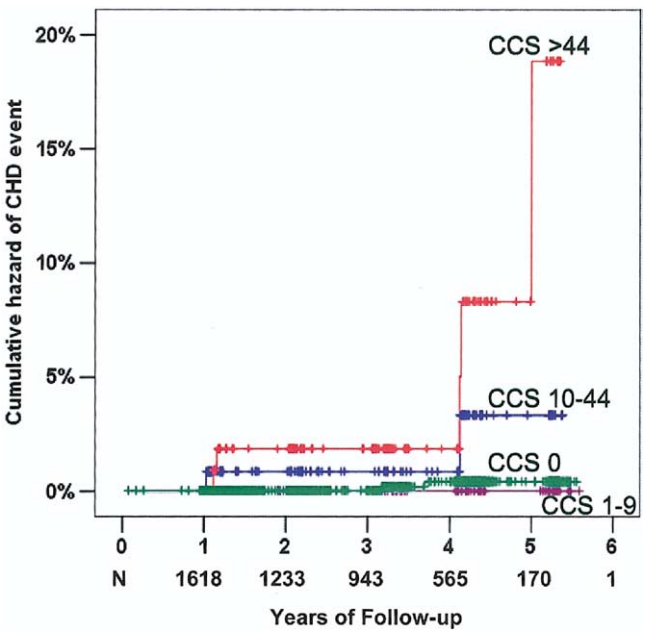


Figure 2. Hazard ratio plot for coronary heart disease (CHD) events including death, unstable angina, and myocardial infarction for male Prospective Army Coronary Calcium project participants with coronary calcium (n = 364) categorized into calcium score tertiles. CCS = coronary calcium score.

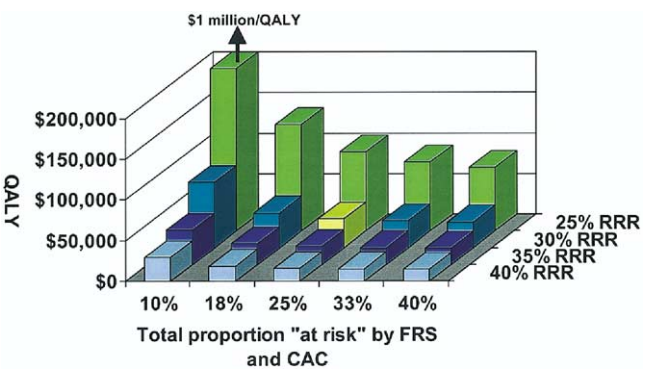


Figure 3. Three-dimensional bar graph showing the interaction of the relative risk reduction (RRR) of coronary interventions and the total proportion of the screened population to be considered as at risk (using both the Framingham risk score [FRS] and coronary calcium testing together) on cost effectiveness (quality-adjusted life years [QALY]). The **yellow bar** indicates the base case for the Prospective Army Coronary Calcium project. CAC = coronary artery calcium.

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diminish the ability to control for additional covariates beyond the FRS, and also diminish the precision of our risk estimates.

The present analysis is underpowered to exclude a relationship between CAC and CHD events in women. Data from Raggi et al. (26) indicate that such a relationship does exist with respect to total mortality, but further study in large female cohorts is needed, specifically with respect to cardiovascular-specific outcomes.

Sensitivity analysis on the effect of the estimated relative risk on cost effectiveness of screening suggests that a strategy of adding CAC to global coronary risk assessments would be cost effective across a broad range of relative risk associated with CAC. The cost effectiveness of screening for CAC is sensitive to the efficacy of primary prevention interventions (e.g., lifestyle and medications) in prolonging quality-adjusted survival. The Multiple Risk Factor Intervention Trial did show an 8% relative risk reduction at 10.5 years in overall mortality during an era of less effective risk factor interventions (30). Thus we feel that it is reasonable to assume that there may be at least a 30% relative risk reduction for primary prevention strategies among higher-risk individuals over a 30- to 40-year lifetime horizon. However, this is unproven.

CONCLUSIONS

Although further studies including women and ethnic minorities are needed to extend these data, the PACC project, including the use of measured coronary risk factors and complete follow-up data, has shown the incremental predictive value of CAC over conventional risk factors for premature CHD outcomes. Beyond this demonstration of incremental prognostic value, important questions such as those of effectiveness and cost effectiveness remain. Although these questions are best answered through dedicated prospective clinical trials, the costs, ethics, and feasibility of such trials are formidable obstacles to their completion.

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