ORIGINAL INVESTIGATION

Using the Coronary Artery Calcium Score to Predict Coronary Heart Disease Events

A Systematic Review and Meta-analysis

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Background: Primary prevention of coronary heart disease is most appropriate for patients at relatively high risk. Measurement of coronary artery calcium has been proposed as a way to improve risk assessment, but it is unknown whether it adds predictive information to standard risk factor assessment.

Methods: We systematically searched electronic databases for relevant articles published between January 1, 1980, and March 19, 2003, and hand searched bibliographies. We included studies that reported measuring the coronary artery calcium score by electron beam computed tomography in asymptomatic subjects and subsequent follow-up of those patients for coronary events and that presented score-specific relative risks, adjusted for established risk factors. Two abstractors verified inclusion criteria and abstracted data from each study. We estimated adjusted relative risks associated with 3 standard categories of coronary artery calcium scores (1-100, 101-400, and >400), compared with a score of 0, and used a random-effects model for meta-analysis.

Results: Meta-analysis of the 4 studies meeting inclusion criteria yielded a summary adjusted relative risk of 2.1 (95% confidence interval, 1.6-2.9) for a coronary artery calcium score of 1 to 100. Relative risk estimates for higher calcium scores were higher, ranging from 3.0 to 17.0 but varied significantly among studies. Subgroup analyses suggested that differences among studies in outcome adjudication (blinded or not), measurement of other risk factors (direct or by patient history), tomographic slice thickness (3 or 6 mm), and/or proportion of female study subjects may account for this heterogeneity.

Conclusion: The coronary artery calcium score is an independent predictor of coronary heart disease events.

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RECENTLY UPDATED EVIDENCE-based guidelines call on internists to make a careful assessment of their patients' baseline coronary heart disease (CHD) risk and to target primary prevention efforts such as cholesterol-lowering drugs[1] and aspirin[2] to high-risk patients. Predicting who will develop CHD events, however, is difficult. Standard risk factor analysis can help stratify patients into risk groups, but events are still uncommon in patients considered to be at high risk (2% per year) and not rare in patients considered to be at lower risk (0.5%-1.0% per year).[1] More effective assessment of CHD risk may improve the cost-effectiveness and safety of such primary prevention efforts.

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Coronary artery calcium (CAC) may be a marker of an increased risk of CHD events. Coronary artery calcium is only present in atherosclerotic arteries[3] and can be quantified quickly and noninvasively with electron-beam computed tomography (EBCT) at a cost of approximately $400 to $500 per scan. The resulting CAC score represents an assessment of the presence and extent of atherosclerosis and may therefore be useful in predicting future

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CHD events. On the other hand, calcification may be merely a reflection of increased atherosclerosis conferred by standard CHD risk factors such as age, sex, cholesterol, blood pressure, smoking, and diabetes. Calcification may actually reflect stabilization and maturation of atherosclerotic plaques and lead to fewer myocardial infarctions and CHD deaths.[4,5] Assessment of the predictive value of the CAC score after adjustment for standard CHD risk factors is therefore critical.

Several cohort studies have been published in which previously asymptomatic persons were studied with EBCT and fol-

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lowed-up over time for CHD events. These studies, as well as a meta-analysis,[6] have reported that higher CAC scores are associated with higher risks of CHD events. The question of whether the CAC score adds incremental value to standard CHD risk factor assessment, however, remains controversial.

In the present study, we systematically searched published literature, extracted and standardized relative risk estimates adjusted for established CHD risk factors from each eligible study, calculated clinically relevant summary estimates of relative risk for patients with different CAC scores, and investigated why results might differ among studies.

METHODS

LITERATURE REVIEW

We searched MEDLINE and Current Contents databases for articles published between January 1, 1980, and July 25, 2001, and PubMed for articles published between July 1, 2001, and March 19, 2003. Because no specific Medical Subject Headings (MeSH) are consistently used for studies of CAC, we used a broad title word search to maximize sensitivity for identifying all potentially relevant articles and relied on manual review to discard the many irrelevant articles we captured. We used the following search strategies: MEDLINE, *f (xxs cardiovascular diseases or xxs coronary vessels) and (tw coronary calci# or tw electron or tw ultrafast)*; Current Contents, *f tw coronary calci# or tw electron tomography or tw electron ct or tw ultrafast ct or tw ultrafast tomography*; and PubMed, *((“Cardiovascular diseases”[MESH] OR “coronary vessels”[MESH]) AND ((coronary[TI] AND ((calcium[TI] OR calcification[TI]) OR calcifications[TI])) OR ((electron[TI] AND (tomography[TI] OR ct[TI])) OR (ultrafast[TI] AND (tomography[TI] OR ct[TI])))))*. We also reviewed bibliographies of key articles and consulted with experts in the field to identify all important patient cohorts. Abstracts and titles were scanned and articles were eliminated if inclusion criteria were clearly not met. When unclear, articles were reviewed in full. Studies reported in abstract form only were excluded.

STUDY ELIGIBILITY

We included articles that reported identifying a cohort of individuals who were initially without symptoms of active coronary artery disease, and who were studied with noncontrast EBCT to obtain a CAC score and then followed up over time for the development of CHD events. Only articles that presented CAC score–specific relative risks adjusted for established CHD risk factors such as age, hypertension, high cholesterol, diabetes, and smoking were included. Articles that presented duplicate or overlapping data were grouped, and only the article presenting the data in the most definitive and extractable form was included. Two of us (M.J.P. and M.P.) independently abstracted inclusion criteria for all articles presenting CAC score–specific relative risks.

DATA EXTRACTION

Two of us (M.J.P. and J.A.T.) abstracted data from each eligible article using a standard data extraction form, collecting data on study subjects (recruitment source, selection criteria, demographics, and CHD risk factors with method of determination), the EBCT protocol used (scanner make and model, slice thickness, and scoring method), follow-up (tracking method, mean follow-up time, and proportion lost to follow-up), method of outcome adjudication (types and definitions of CHD events recorded, formal outcome adjudication by more than 1 investigator, and blinding of adjudicators to CAC score), and blinding of study subjects and their physicians to the CAC score. Disagreements were resolved by consensus. Adjusted CAC score–specific odds ratios, relative risks, or hazard ratios were abstracted in whatever categories or form was available. Confidence intervals (CIs) from 1 study[7] were supplied at our request in a written communication from the first author (Nathan D. Wong, PhD, July 9, 2002).

DATA STANDARDIZATION

To provide clinically relevant and easily applied results, we standardized results into 4 CAC score categories (0, 1-100, 101-400, and >400). These or similar categories have been used in several previous publications[8,9] and represent a simple categorization of the range of CAC scores encountered in clinical practice. This standardization was accomplished in 1 of 2 ways, depending on how the data were presented.

There were 2 articles that reported adjusted relative risk measurements in CAC score categories that were different than the categories we chose.[7,10] For these articles, we first calculated crude relative risks from presented data and then estimated the effects of multivariate adjustment on the point estimate and standard error by comparing these crude estimates with the adjusted estimates presented in each article. We then estimated crude relative risks in each standard CAC score category (1-100, 101-400, and >400, compared with 0) and applied the multivariate adjustment effect, as estimated above.

The other 2 articles[11,12] presented adjusted relative risk measurements per unit increase in the CAC score (log-transformed,[11] or age- and sex-adjusted percentile—the “CS%” score[12]). To obtain an adjusted relative risk estimate for each of our standard CAC score categories (1-100, 101-400, and >400, compared with 0), we estimated the median absolute CAC score and the median CS% score in each of these categories using published cross-sectional data,[12] and assuming that the subject of our investigation was a 50- to 54-year-old man. The median absolute CAC scores were 0 (for a CAC score of 0), 26 (in the 1-100 category), 183 (in the 101-400 category), and 664 (in the >400 category). The median CS% scores were 0% (for a CAC score of 0), 31% (in the 1-100 category), 75% (in the 101-400 category), and 94% (in the >400 category). These representative scores were used to calculate adjusted relative risk estimates using the equations presented in each article.

The primary assumptions we made to standardize the data were that (1) CAC scores were distributed uniformly within CAC score categories,[7,11] (2) the maximum CAC score was 1000,[7,11] (3) the effect of multivariate adjustment was homogeneous across categories within each study,[7,11] and (4) the subject of interest was a 50- to 54-year-old man.[11,12] Assumptions 2 and 4 were amenable to sensitivity analyses.

DATA SYNTHESIS

Summary adjusted odds ratios for each standard CAC score category were calculated by combining standardized odds ratios from each study using a random effects model.[13] These were reported as relative risks because outcomes were rare. Heterogeneity was assessed statistically, using a conservative P value cutoff of .10.[14] Analyses were repeated using a fixed effects model for comparison. Statistical analyses were performed using Stata 7.0 (Stata Corp, College Station, Tex).

SUBGROUP ANALYSES

To explore potential sources of heterogeneity and assess the effects of potentially important differences in study methodology, we performed several subgroup analyses. We grouped

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Table 1. Articles Presenting Data on Coronary Heart Disease Outcomes and CAC Scores

Source	Inclusion Criteria					
	Is This the Definitive Data Presentation?*	Patients Asymptomatic?†	Patients Followed up Prospectively After EBCT Scan?	Multivariate Adjustment Attempted?	CAC Score–Specific Risk Extractable?‡	Included in Meta-analysis?
Arad et al,[15] 1996	No (Arad et al,[10] 2000)	Yes	Yes	No	Yes	No
Secci et al,[16] 1997	No (Yang et al,[11] 1999)	Yes	Yes	Yes	Yes	No
Detrano et al,[17] 1999	No (Yang et al,[11] 1999)	Yes	Yes	Yes	Yes	No
Doherty et al,[5] 1999	No (Yang et al,[11] 1999)	Yes	Yes	No	Yes	No
Yang et al,[11] 1999	Yes	Yes	Yes	Yes	Yes	Yes
Arad et al,[10] 2000	Yes	Yes	Yes	Yes	Yes	Yes
Raggi et al,[9] 2000	No (Raggi et al,[12] 2001)	Yes	Yes	Crude	Yes	No
Wong et al,[7] 2000	Yes	Yes	Yes	Yes	Yes	Yes
Raggi et al,[12] 2001	Yes	Yes	Yes	Yes	Yes	Yes
Wayhs et al,[18] 2002	No (Raggi et al,[12] 2001)	Yes	Yes	No	No	No
Wong et al,[19] 2002	No (Wong et al,[7] 2000)	Yes	Yes	Yes	Yes	No
Park et al,[20] 2002	No (Yang et al,[11] 1999)	Yes	Yes	Yes	Yes	No
Vliegenthart et al,[21] 2002	Yes	Yes	No§	Yes	Yes	No

Abbrevations: CAC, coronary artery calcium; EBCT, electron beam computed tomography.

*If data from the same subjects were presented in a subsequent article in a more complete form, the article was not considered the definitive data presentation. The article thought to contain the definitive data presentation is listed in parentheses.

†If patients were noted to be symptomatic or also received a coronary angiogram or stress test (and were not specifically noted to be asymptomatic), the patients in the article were determined to be symptomatic and the article was not included in the meta-analysis.

‡If the distributions of events and total persons were reported for specific CAC scores or CAC score–specific risk estimates were reported in any way, the article was determined to have an "extractable" score-specific risk.

§This is a cross-sectional study. Persons in the sample who had had a heart attack in the past (before their EBCT scan) were compared with persons who had not had an attack. There was no follow-up after EBCT scanning presented, so this study was found to be ineligible.

studies according to (1) types of outcomes included, (2) whether formal blinded outcome adjudication was performed, (3) tomographic scan thickness (3 mm vs 6 mm), (4) overall annual CHD rate, and (5) proportion of female subjects. Statistical testing for interaction and linear trends were performed using meta-regression commands available in Stata 7.0.

RESULTS

LITERATURE SEARCH

We identified 2809 articles from MEDLINE, Current Contents, and PubMed that met our preliminary search criteria and eliminated 1196 based on the title, 1500 based on title and abstract, and 101 based on review of the full-text article. In total, 1616 were eliminated because EBCT was not used, 333 because CAC was not measured (EBCT was used for a different purpose), 313 because no follow-up for CHD outcomes was documented, 19 because the patients were not asymptomatic, and 516 because they were duplicates, review articles, editorials, conference proceedings, or other types of articles not containing original data. This left 13 articles[5,7,9-12,15-21] for consideration (**Table 1**).

DATA EXTRACTION AND STANDARDIZATION

Four studies met all inclusion criteria.[7,10-12] There were differences in study subjects, EBCT scan thickness, follow-up completeness, types of CHD events recorded, outcome adjudication methodology, annual event rate, and method of assessing CHD risk factors among the 4 studies (**Table 2**). No study reported blinding of study subjects and/or physicians to the subject's CAC score. Mean follow-up was 3.6 years or less. Most studies assessed risk factors by self-report rather than direct measurement. In total, these studies represent over 13 000 person-years of observation time.

We estimated adjusted relative risks for each CAC score category in each study (**Table 3**). This process led to wide confidence intervals for the article by Arad et al[10] because only 1 subject in the reference (CAC score = 0) category had a coronary event during follow-up.

DATA SYNTHESIS (META-ANALYSIS)

After adjusting for established CHD risk factors, the risk of CHD events increased progressively with greater calcification (**Figure 1**). The relative risk estimates among studies were similar for the CAC score 1 to 100 category (P for heterogeneity = .48) but varied significantly for the 101 to 400 (P = .07) and greater than 400 (P = .02) categories. Fixed-effects modeling yielded slightly different results: adjusted relative risks were 2.1 (95% CI, 1.6-2.9) for the CAC score 1 to 100, 4.2 (95% CI, 2.5-7.2) for the 101 to 400, and 7.2 (95% CI, 3.9-13.0) for the greater than 400 categories compared with the 0 category.

SENSITIVITY ANALYSES

Adjusted relative risks and CIs changed only slightly when we varied our assumptions (**Table 4**). Relative risks were statistically significant under any set of assumptions.

SUBGROUP ANALYSES

We grouped studies according to study characteristics that we thought could affect the relative risks they re-

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Table 2. Characteristics of Studies Selected for Meta-analysis

Source	Subjects	Slice Thickness, mm	Follow-up, Mean Duration; % Completed*	No. of Events/ Types (No.)	Blinded Outcome Adjudication	Annual Event Rate, %†	CHD Risk Factors Assessed, Risk Factor (Method of Assessment‡)
Yang et al,[11] 1999	N = 1196; age (mean ± SD), 66 ± 8 y; 11% female; 12% nonwhite	6	41 mo; 99	46/CHD death (17), nonfatal MI (29)	Yes	1.1	Age (continuous), sex, diabetes mellitus (direct, categorical), hypertension (direct, categorical), smoking (direct, categorical), LDL-C and HDL-C (direct, continuous), family history of CAD (history, categorical),§ LVH (direct, categorical), alcohol use (direct, categorical)
Arad et al,[10] 2000	N = 1172; age (mean ± SD), 53 ± 11 y; 29% female; 5% nonwhite	3	43 mo; 99.6	39‖/CHD death (3), nonfatal MI (15), revascularization (21)	No¶	0.5	Age (categorical),§ sex,§ diabetes mellitus (history, categorical), hypertension (history, categorical), smoking (history, categorical),§ hypercholesterolemia (history, categorical), family history of CHD (history, categorical)§
Wong et al,[7] 2000	N = 926; age (mean ± SD, 54 ± 10 y; 21% female; % nonwhite, NR	3	39.6 mo; 61	28/CHD death (0), nonfatal MI (6), stroke (2), revascularization (20)	Yes	0.2	Age (NR),# sex,# diabetes mellitus (history, categorical),# hypertension (history, categorical),# smoking (history, categorical),# hypercholesterolemia (history, categorical)#
Raggi et al,[12] 2001	N = 676; age (mean ± SD), 52 ± 10 y; 49% female; % nonwhite, NR	3	32 mo; NR	30/CHD death (9), nonfatal MI (21)	No¶	1.7	Age (continuous),§ sex,§ diabetes mellitus (history, categorical),§ hypertension (history, categorical),§ smoking (history, categorical), hypercholesterolemia (history, categorical)§

Abbreviations: CHD, coronary heart disease; EBCT, electron beam computed tomography; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; NR, not reported.

*Percentage of persons originally studied for whom the presence or absence of cardiac events was obtainable.

†Calculated from total number of MI and CHD deaths/total estimated person-years of observation.

‡Assessment of CHD risk factors was considered "direct" when an actual measurement was taken (ie, by sphygmomanometry) and/or by "history" when the patients were asked about their history or medication use to assess presence of a risk factor. Whether the risk factor was included in the multivariate model as a "categorical" variable or a "continuous" variable was also noted.

§The risk factor was considered in the modeling process but not included in the final multivariate model.

‖Multivariate analysis in the article was performed on all events (including revascularizations); our study results simulate this multivariate adjustment for the hard events only (MI and CHD death only).

¶Verified by communication with authors.

#The risk factor was considered in the modeling process, but it is unclear whether it was actually included in the final multivariate model.

ported. Differences in measurement of CHD risk factors (direct or by patient history), outcome adjudication (blinded or not), tomographic slice thickness (3 mm or 6 mm), and proportion of female subjects may have contributed to the observed differences in the 2 highest CAC score categories (**Figure 2**). Inspection and influence diagramming showed that 1 study,[11] which reported the lowest relative risk measurements, was primarily responsible for these differences. This study was also the only one to measure coronary artery disease risk factors directly and use an EBCT slice thickness of 6 mm, was 1 of 2 studies with blinded outcome adjudication, and included the lowest proportion of women (11%). If we excluded this study, relative risks in the remaining 3 studies[7,10,12] were similar and summary estimates were higher: 2.6 (95% CI, 1.7-4.0) for the CAC score 1 to 100, 8.8 (95% CI, 4.1-19.0) for the 101 to 400, and 17 (95% CI, 6.9-40.0) for the greater than 400 categories (all *P* values for heterogeneity >.32). Meta-analysis of the 2 studies in which the outcome adjudication process was blinded[11,12] yielded lower relative risks: 1.7 (95% CI, 1.1-2.7) for the CAC score 1 to 100, 3.0 (95% CI: 1.3-6.9) for the 101 to 400, and 4.3 (95% CI: 1.5-12.0) for the greater than 400 categories (all *P* values for heterogeneity >.17).

COMMENT

In the present study, we show that CAC is associated with an increased risk of CHD events, even when other risk factors for CHD are taken into account. The relative risks associated with increasing CAC score are at least as large as those associated with established CHD risk factors. Persons with even low amounts of CAC (CAC score, 1-100) have about twice the risk of CHD events compared with persons who have no evidence of CAC (relative risk, 2.1), and high CAC scores (>400) are associated with very

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Table 3. Adjusted Odds Ratios Associated With Different CAC Scores as Presented in Each Study and After Standardization

	Results as Predicted in Each Study		Same Results After Standardization	
Source	CAC Score as Formulated in Each Study	Relative Risk* (95% CI)	CAC Score in Standard Categories	Relative Risk† (95% CI)
Yang et al,[11] 1999	Odds ratio, adjusted per unit increase in log(CAC score + 1)	1.44 (1.05-1.97)	0 1-100 101-400 >400	1.0 (Reference) 1.7 (1.1-2.6) 2.3 (1.1-4.7) 2.8 (1.2-6.8)
Arad et al,[10] 2000	>80 (vs <80) >160 (vs <160) >600 (vs <600)	14.3 (4.9-42.3) 19.7 (6.9-56.4) 20.2 (7.3-55.8)	0 1-100 101-400 >400	1.0 (Reference) 1.1 (0.1-13) 11 (1.6-80) 43 (7.0-270)
Wong et al,[7] 2000	0 1-15 16-80 81-270 ≥271	1 (Reference)‡ 0.72 (0.08-6.55) 3.29 (0.85-12.84) 4.54 (1.22-16.84) 8.79 (2.20-35.08)	0 1-100 101-400 >400	1.0 (Reference) 2.3 (0.6-8.9) 5.7 (1.5-22) 8.4 (2.3-31)
Raggi et al,[12] 2001	Odds ratio, adjusted per percentile increase in age- and sex-adjusted CAC percentile score	1.03 (1.02-1.05)	0 1-100 101-400 >400	1.0 (Reference) 2.7 (1.7-4.3) 11.0 (3.7-32.0) 20.0 (5.2-79.0)

Abbreviations: CAC, coronary artery calcium; CI, confidence interval.
*Relative risk was estimated by the odds ratio[10-12] or the relative hazard[7] in the original studies.
†Odds ratios were used for the standardized estimate of relative risk in all studies.
‡Confidence intervals were obtained by written communication with Nathan D. Wong, PhD (July 9, 2002).

high relative risks (4.3-17.0). In comparison, the presence of diabetes or tobacco use or extreme values of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or blood pressure confer a relative risk of approximately 1.5 to 3.4.[22] Our findings are consistent with a previous meta-analysis[6] but are more clinically applicable because they are adjusted for established risk factors.

More precise estimates of the relative risks associated with medium to high CAC scores would be helpful for clinicians and researchers, but large differences among studies make this goal currently unattainable. The source of these differences has been the subject of ongoing public debate[23-30]; the present analysis serves to clarify and extend that discussion in several ways. First, through our data standardization process, we make it possible to directly compare results across studies. Second, we document that the evident differences in study results are not likely to be merely the result of chance. Finally, our analysis of different subgroups of studies (Figure 2) helps identify which study characteristics may have accounted for the observed differences.

For example, 2 study characteristics previously thought to be important do not appear to account for differences among studies. Some have postulated that studies including patients with high average CHD risk might find the CAC score less helpful in predicting risk[28,31]; this trend was not evident. Others contend that studies including myocardial infarctions, CHD death, and revascularizations ("soft" CHD events) might find the CAC score to be more predictive because high CAC scores may in themselves lead to more aggressive revascularization.[16] Again, no such trend was evident.

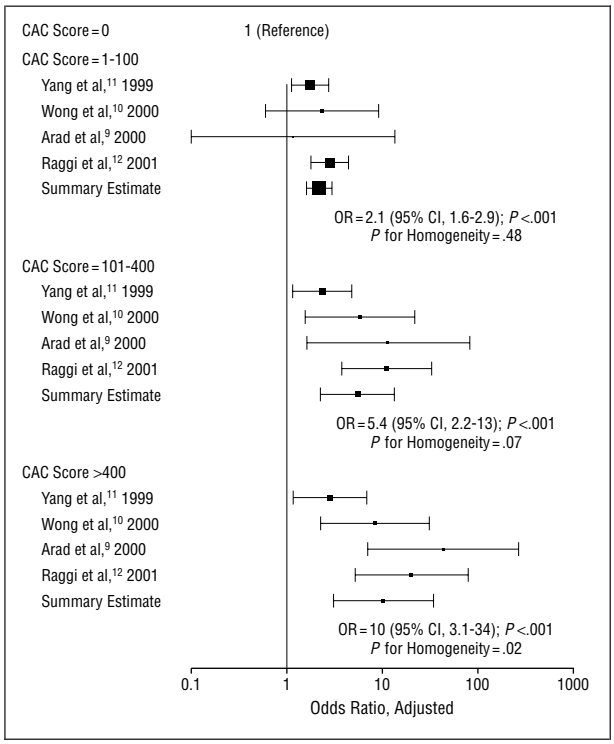

Figure 1. Adjusted odds ratios (ORs) comparing risk of a coronary heart disease event in persons with low (1-100), medium (101-400), and high (>400) coronary artery calcium (CAC) scores to persons without calcification. Error bars indicate 95% confidence interval (CI).

On the other hand, a number of other study characteristics seemed to be important in explaining differences in study results. Studies reporting unblinded out-

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Table 4. Sensitivity Analysis: Summary Adjusted Odds Ratios for Each CAC Score Category Under Different Assumptions

Assumption	Summary Adjusted Odds Ratio (95% CI) in Given CAC Score Category*		
	1-100	101-400	>400
CAC distribution used for calculation of median scores in each category			
40-year-old man	2.2 (1.2-4.0)	6.1 (2.1-17)	11 (3.1-36)
50-year-old man†	2.1 (1.6-2.9)	5.4 (2.2-13)	10 (3.1-34)
60-year-old man	1.8 (1.4-2.3)	4.1 (2.3-7.3)	9.4 (3.1-29)
40-year-old woman	2.2 (1.0-4.7)	6.4 (2.3-18)	11 (3.1-36)
50-year-old woman	2.2 (1.2-4.0)	6.0 (2.1-17)	11 (3.1-36)
60-year-old woman	2.0 (1.5-2.7)	5.3 (2.3-13)	10 (3.1-34)
Maximum CAC score used for extrapolation in highest CAC score category			
600	2.1 (1.6-2.9)	5.5 (2.3-14)	10 (2.9-36)
1000†	2.1 (1.6-2.9)	5.4 (2.2-13)	10 (3.1-34)
2000	2.1 (1.6-2.9)	5.4 (2.2-13)	11 (3.3-33)
4000	2.1 (1.6-2.9)	5.3 (2.2-13)	11 (3.6-32)
Meta-analytic model			
Fixed effects	2.1 (1.6-2.9)	4.2 (2.5-7.2)	7.2 (3.9-13)
Random effects†	2.1 (1.6-2.9)	5.4 (2.2-13)	10 (3.1-34)

Abbreviations: CAC, coronary artery calcium; CI, confidence interval.
*Compared with a CAC score of 0.
†Assumption used in primary analysis.

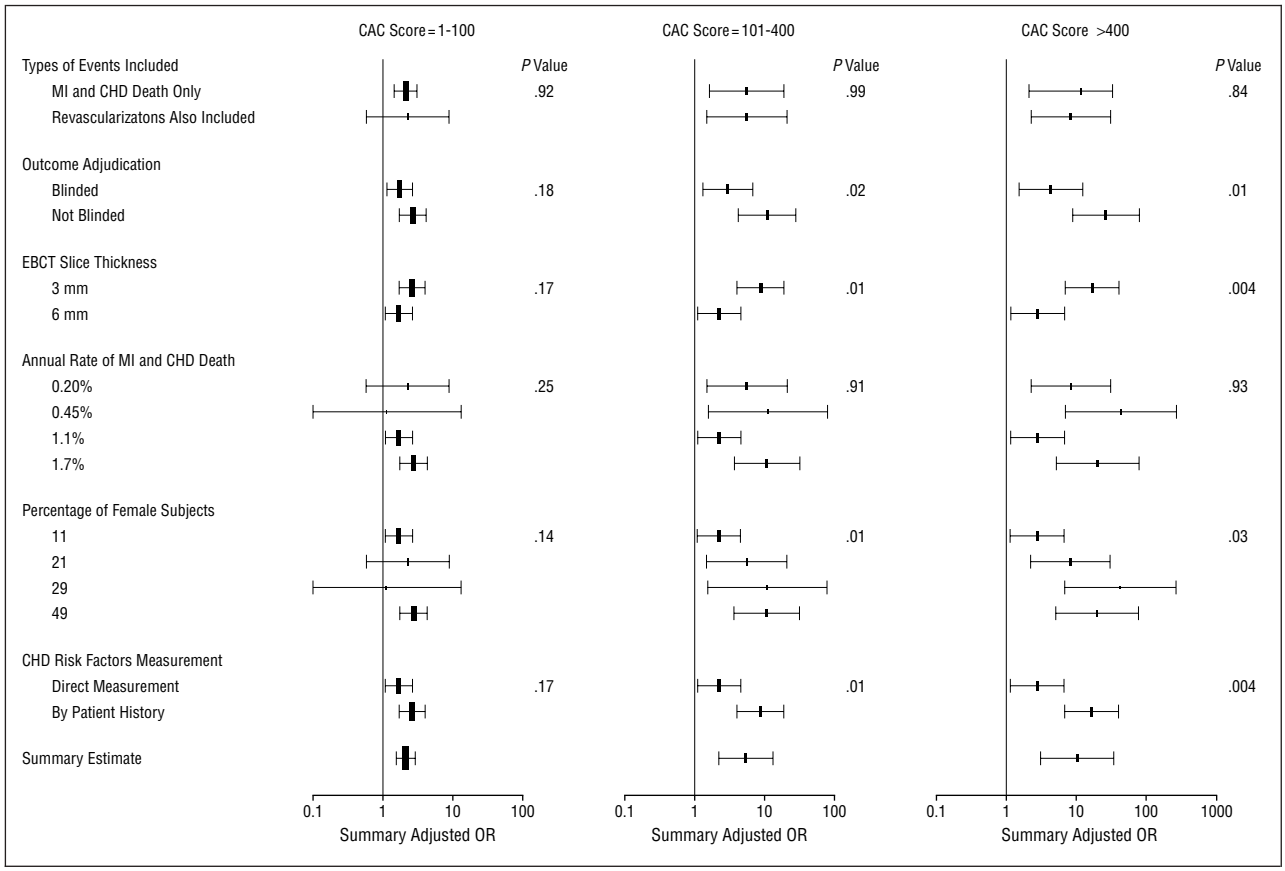

Figure 2. Subgroup analysis: summary adjusted odds ratios (ORs) stratified by study characteristics. Summary adjusted ORs compare the risk of a coronary heart disease (CHD) event in persons with different coronary artery calcium (CAC) scores with the risk in a person without calcification. *P* values refer to a test for interaction between subgroups or to a test of linear association (for "annual rate of myocardial infarction (MI) and CHD death" and "percentage of female subjects." EBCT indicates electron-beam computed tomography. Error bars indicate 95% confidence interval.

come adjudication and those reporting indirect measurement of established CHD risk factors generally reported higher relative risk estimates, which could be consistent with bias from measurement error. On the other hand, differences in study results may also be explained by differences in EBCT scanning technique: the only study

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using a 6-mm EBCT slice technique found significantly lower relative risks, which could be consistent with lower scan sensitivity and less power to identify very low-risk individuals.

Unexpectedly, the proportion of female subjects in each study was also associated with study results: studies in which more women were enrolled showed larger relative risk estimates. Arad et al[10] commented on a small, insignificant trend in the opposite direction within their study; none of the other authors noted testing for such interaction. Previous comparisons between men and women in the sensitivity and specificity of the CAC score in predicting angiographic stenoses have shown mixed results, with 1 study finding higher specificity in women,[32] 1 finding lower sensitivity in women,[33] and 1 finding similar test characteristics in men and women.[34] While this effect could be the result of confounding by other differences in study characteristics, it highlights the importance of inclusion and separate analysis of women in future studies of CAC and CHD.

Our analysis has some limitations. First, the standardization process that was required to compare results between studies is in itself not standard or routine. The problem of standardizing disparately presented results for purposes of meta-analysis is not unique to this article[35]; such standardization often requires complex methodology and assumptions. We believe our methods and assumptions were necessary and generally defensible, and we have shown that modification of some of those assumptions produced minimal changes to our results (Table 4). Some might also argue with our categorization of CAC scores. While our categories were somewhat arbitrary and likely resulted in some loss of information, we believe that they provide an intuitive and useful way to think about a patient's score (none, low, medium, or high) and capture much of the important score variation in the middle-aged persons who are most likely to undergo careful CHD risk stratification.

Second, we are limited by the small number of studies available for analysis. With only 4 studies available for subgroup analyses, it is not possible to untangle the potential causes of observed differences in study results, especially given the fact that 1 study was an outlier in terms of both study results and many of the important study characteristics.[11] We are also unable to assess for publication bias, though we would not expect such bias given public interest in both positive and negative results.

Finally, no meta-analysis can overcome the limitations of source studies. Causal inference is always limited when interpreting the results of observational studies; accordingly, this analysis should not be interpreted as evidence that CAC causes CHD events, only that it predicts them. Generalizability of our results is limited by the age, sex, and ethnic composition of study samples. Follow-up is generally limited to 3 or 4 years, leading to uncertainty regarding how long the relative protection from CHD events implied by a CAC score of 0 will endure. None of the articles described blinding of participants and their physicians to the CAC score, and only 1 study directly measured established risk factors such as hypertension and cholesterol.

Our principal finding, however, transcends these limitations: CAC scores *are* associated with CHD events, even when other CHD risk factors are accounted for. This has important implications for clinical practice. Consider the case of a 55-year-old woman with stage I hypertension, an HDL-C level of 40 mg/dL (1.0 mmol/L), an LDL-C level of 155 mg/dL (4.0 mmol/L) despite diet therapy, and no other CHD risk factors. According to current guidelines, this 55-year-old woman, whose 10-year CHD risk estimate is about 13%,[22] should probably receive both aspirin and cholesterol-lowering drug therapy, aiming for a goal LDL-C level of 130 mg/dL (3.4 mmol/L).[1,2] Using age- and sex-adjusted estimates of this woman's predicted CAC score,[12] we estimate her "post-test" CHD risk to be 6% if her CAC score = 0; 12% if CAC score = 1-100; 29% if CAC score = 101-400; or 48% if CAC score >400, using the summary adjusted relative risk estimates from all 4 studies (Figure 1). A 0 score, which about half of such women will have, might therefore lead us to recommend against cholesterol-lowering drug therapy (given the cost[36]) and aspirin therapy (given the risk of hemorrhagic stroke associated with aspirin use[2]). A score higher than 100, however, might lead us to recommend both continued aspirin use and more aggressive lipid control aiming for a goal LDL-C level of less than 100 mg/dL (<2.6 mmol/L).[1] Using the more conservative estimates reported in our analysis from the 2 studies using blinded outcome adjudication, her post-test CHD risk estimates change somewhat (8%, 14%, 23%, and 31%), but the clinical implications are the same. Deciding when and in whom such risk stratification might be worthwhile and cost-effective requires formal decision analysis and economic modeling, but this analysis suggests that measuring a patient's CAC score may sometimes provide valuable information for clinicians.

Several ongoing cohort studies, such as the Multi-Ethnic Study of Atherosclerosis,[37] the St Francis Heart Study,[38] and the Coronary Artery Risk Development in Young Adults (CARDIA) Study,[39] will address many of the problems inherent in earlier studies. We believe, however, that our meta-analysis has already answered 1 important, unresolved question: Does the CAC score predict coronary events even when standard CHD risk factors are taken into account? The answer, at least among the populations represented in these studies, is yes. Whether these results are valid in other populations and whether the added predictive value of the CAC score is worth the cost of a computed tomographic scan are important questions for further study.

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REFERENCES

1. 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;285:2486-2497.
2. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med.* 2002;136:161-172.
3. Blankenhorn D. Coronary arterial calcification: a review. *Am J Med Sci.* 1961; 242:1-9.
4. Lee TH, Brennan TA. Direct-to-consumer marketing of high-technology screening tests. *N Engl J Med.* 2002;346:529-531.
5. Doherty TM, Wong ND, Shavelle RM, Tang W, Detrano RC. Coronary heart disease deaths and infarctions in people with little or no coronary calcium. *Lancet.* 1999;353:41-42.
6. O'Malley P, Taylor AJ, Jackson JL, Doherty TM, Detrano RC. Prognostic value of coronary electron-beam computed tomography for coronary heart disease events in asymptomatic populations. *Am J Cardiol.* 2000;85:945-948.
7. 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;86:495-498.
8. Rumberger JA, Brundage BH, Rader DJ, Kondos G. Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. *Mayo Clin Proc.* 1999;74:243-252.
9. 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;101:850-855.
10. 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: 1253-1260.
11. Yang T, Doherty TM, Wong ND, Detrano RC. Alcohol consumption, coronary calcium, and coronary heart disease events. *Am J Cardiol.* 1999;84:802-806.
12. Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J.* 2001;141:375-382.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7:177-188.
14. Petitti DB. Approaches to heterogeneity in meta-analysis. *Stat Med.* 2001;20: 3625-3633.
15. 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;93:1951-1953.
16. Secci A, Wong N, Tang W, Wang S, Doherty T, Detrano R. Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. *Circulation.* 1997;96:1122-1129.
17. 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; 99:2633-2638.
18. Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol.* 2002;39:225-230.
19. Wong N, Budoff MJ, Pio J, Detrano RC. Coronary calcium and cardiovascular event risk: Evaluation by age- and sex-specific quartiles. *Am Heart J.* 2002;143: 456-459.
20. 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;106:2073-2077.
21. Vliegenthart R, Oudkerk M, Song B, van der Kuip DA, Hofman A, Witteman JC. Coronary calcification detected by electron-beam computed tomography and myocardial infarction: the Rotterdam Coronary Calcification Study. *Eur Heart J.* 2002; 23:1596-1603.
22. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998; 97:1837-1847.
23. Redberg RF, Shaw LJ. A review of electron beam computed tomography: implications for coronary artery disease screening. *Prev Cardiol.* 2002;5:71-78.
24. 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;36:326-340.
25. Wong ND, Detrano RC, Abrahamson D, Tobis JM, Gardin JM. Coronary artery screening by electron beam computed tomography: facts, controversy, and future. *Circulation.* 1995;92:632-636.
26. Pitt B, Rubenfire M. Risk stratification for the detection of preclinical coronary artery disease. *Circulation.* 1999;99:2610-2612.
27. Schmermund A, Baumgart D, Erbel R. Potential and pitfalls of electron-beam computed tomography in detecting coronary atherosclerosis. *Basic Res Cardiol.* 1999; 94:427-444.
28. Raggi P. Coronary calcium on electron beam tomography imaging as a surrogate marker of coronary artery disease. *Am J Cardiol.* 2001;87(4A):27A-34A.
29. Rumberger JA. Electron beam CT and coronary calcium score. *Circulation.* 1998; 97:2095-2096.
30. Detrano R. Medicine based on scientific evidence versus medicine based on evangelical marketing. *Am J Cardiol.* 2001;88:409-410.
31. Arad Y. Beyond traditional risk factor analysis for coronary artery disease: the case for coronary artery calcium assessment with electron beam computed tomography. *Prev Cardiol.* 2002;5:62-67.
32. Budoff MJ, Shokooh S, Shavelle RM, Kim HT, French WJ. Electron beam tomography and angiography: sex differences. *Am Heart J.* 2002;143:877-882.
33. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ. Coronary calcium in adults with type 1 diabetes: a stronger correlate of clinical coronary artery disease in men then in women. *Diabetes.* 2000;49:1571-1578.
34. Rumberger JA, Sheedy PFI, Breen JF, Schwartz RS. Coronary calcium, as determined by electron beam computed tomography, and coronary disease on arteriogram: effect of patient's sex on diagnosis. *Circulation.* 1995;91:2995-2996.
35. Browner WS, Westenhouse J, Tice JA. What if Americans ate less fat? a quantitative estimate of the effect on mortality. *JAMA.* 1991;265:3285-3291.
36. Prosser LA, Stinnett AA, Goldman PA, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med.* 2000;132:769-79.
37. Multi-Ethnic Study of Atherosclerosis (MESA). Available at: http://www.mesa-nhlbi.org/. Accessed May 9, 2003.
38. Arad Y, Newstein D, Roth M, Guerci AD. Rationale and design of the St Francis Heart Study: a randomized clinical trial of atorvastatin plus antioxidants in asymptomatic persons with elevated coronary calcification. *Control Clin Trials.* 2001; 22:553-572.
39. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol.* 1988; 41:1105-1116.

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