Coronary Artery Calcium Score Combined With Framingham Score for Risk Prediction in Asymptomatic Individuals

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THE FRAMINGHAM RISK SCORE (FRS) is a multivariable statistical model that uses age, sex, smoking history, blood pressure, cholesterol, high-density lipoprotein cholesterol (HDL-C), and blood glucose levels or history of diabetes to estimate coronary event risk among individuals without previously diagnosed coronary heart disease (CHD). Although coronary risk stratification is widely recommended, prediction models based on CHD risk factors, such as the FRS, have limitations in their ability to discriminate individuals who will or will not experience CHD. Given the uncertainty of current predictive models, the search for new strategies to discriminate patients who would benefit most from intensive primary prevention efforts is a clinically important objective. Once suggested approach to improve risk prediction over the FRS is the quantification of coronary artery calcium score (CACS), most commonly using computed tomography (CT).

The objective of this study was to determine whether CACS assessment combined with FRS among asymptomatic adults provides prognostic information superior to either method alone and whether the combined approach can more accurately guide primary preventive strategies for patients with CHD risk factors.

Context Guidelines advise that all adults undergo coronary heart disease (CHD) risk assessment to guide preventive treatment intensity. Although the Framingham Risk Score (FRS) is often recommended for this, it has been suggested that risk assessment may be improved by additional tests such as coronary artery calcium scoring (CACS).

Objectives To determine whether CACS assessment combined with FRS in asymptomatic adults provides prognostic information superior to either method alone and whether the combined approach can more accurately guide primary preventive strategies in patients with CHD risk factors.

Design, Setting, and Participants Prospective observational population-based study, of 1461 asymptomatic adults with coronary risk factors. Participants with at least 1 coronary risk factor (>45 years) underwent computed tomography (CT) examination, were screened between 1990-1992, were contacted yearly for up to 8.5 years after CT scan, and were assessed for CHD. This analysis included 1312 participants with CACS results; excluded were 269 participants with diabetes and 14 participants with either missing data or had a coronary event before CACS was performed.

Main Outcome Measure Nonfatal myocardial infarction (MI) or CHD death.

Results During a median of 7.0 years of follow-up, 84 patients experienced MI or CHD death; 70 patients died of any cause. There were 291 (28%) participants with an FRS of more than 20% and 221 (21%) with a CACS of more than 300. Compared with an FRS of less than 10%, an FRS of more than 20% predicted the risk of MI or CHD death (hazard ratio [HR], 14.3; 95% confidence interval [CI]; 2.0-104; P=.009). Compared with a CACS of zero, a CACS of more than 300 was predictive (HR, 3.9; 95% CI, 2.1-7.3; P<.001). Across categories of FRS, CACS was predictive of risk among patients with an FRS higher than 10% (P<.001) but not with an FRS less than 10%.

Conclusion These data support the hypothesis that high CACS can modify predicted risk obtained from FRS alone, especially among patients in the intermediate-risk category in whom clinical decision making is most uncertain.

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study, and the demographics of participants have been described. The original cohort consisted of 1461 asymptomatic participants (>45 years) with at least 1 abnormal coronary risk factors (>10% estimated 8-year risk of developing CHD by an earlier version of the Framingham risk equation). Participants with electrocardiographic (ECG) evidence of myocardial infarction (MI) or clinical history of MI, coronary revascularization, or angina were excluded. Thirty months after enrollment, 1312 surviving participants underwent a second evaluation including fasting phlebotomy concurrent with CT examination for measurement of CACS. Participants gave written informed consent at both examinations. The Harbor UCLA Research and Education Institute Human Subjects Committee approved this study.

We excluded patients with diabetes because CACS has not been found to have prognostic value for such patients in this cohort and because patients with diabetes are considered to be at high risk of future coronary events based on the presence of diabetes. Participants were classified as having diabetes if they had a history of keeping a diet or taking medication for diabetes, had been diagnosed as having diabetes during a hospital admission and had been discharged with insulin or oral hypoglycemic medications or had a random plasma glucose level of at least 200 mg/dL (11.1 mmol/L) at the time of recruitment.

### Risk Factors and CACS Measurements

Risk factors for CHD (smoking; sex; family history of CHD; blood pressure; total cholesterol; HDL-C; and low-density lipoprotein cholesterol [LDL-C] levels; triglycerides; and body mass index as a measure of obesity) and ECG results were routinely obtained at both examinations by previously described methods. Computed tomographic scans were performed within 2 (±2) days after the second risk factor evaluation using a 6-mm slice thickness acquisition protocol, which has high rescan reliability and similar predictive capacity compared with the commonly used 3-mm slice thickness. Although we have found 6-mm slice scores to be equivalent to 3-mm slice scores in predicting future CHD events, CACS by the former method are slightly lower than 6-mm scan scores. A regression equation has been developed for comparing these 2 types of measurements.

Quality control included periodic checks of the scanner by a radiation physicist, use of a phantom to calibrate and evaluate noise artifact, and determination of retest reproducibility of the scanning protocol. A single cardiologist blinded to all clinical data interpreted the scans using scoring software identical to that used for the Multi-Ethnic Study of Atherosclerosis (MESA) with CACS calculated by the Agatston method.

### Clinical Follow-up

We contacted participants yearly for up to 8.5 years after CT examination (median, 7.0 years) and assessed cardiovascular events using questions about intervening hospital admissions. We reviewed medical records for hospitalizations related to a complaint of chest discomfort, dyspnea, vascular or cardiac problems, or any major surgery. A follow-up attempt was considered successful when surviving participants either returned to the clinic or completed a telephone interview, and all relevant medical records were obtained. For deceased participants, we defined successful follow-up as the procurement of relevant medical records, transcribed conversation with the next of kin, death certificate, or autopsy report. Overall, 99% of the participants completed the questionnaire at least once following the baseline CT scan. During the last contact attempt (2000-2002), with subsequent acquisition and adjudication of relevant medical records, the follow-up rate was 87.5%.

### CHD End Point

A committee of 3 board-certified cardiologists reviewed medical records and transcripts of conversations with next of kin, without knowledge of other data, and applied majority rule to determine the occurrence of study end points. For this report, we focused only on “hard” CHD end points to minimize bias related to procedures that may ensue after coronary calcium detection. The study end point included nonfatal MI or CHD death. We defined MI as the presence of 2 or 3 of the following: prolonged chest pain prompting hospital admission, diagnostic evolutionary ECG changes, and elevation of serum creatine kinase levels to twice the upper limits of normal or a positive serum creatine kinase-MB fraction or troponin. Death due to CHD was assigned by the adjudication committee if death proved to be due to coronary atherosclerosis at autopsy, had occurred within 1 hour after onset of prolonged severe chest pain, had occurred suddenly in the absence of another known cause, or had occurred during hospitalization for MI.

### Statistical Analysis

Analyses were conducted using P<.05 as the significance level and SAS statistical software version 9.0 (SAS Inc, Cary, NC). For Cox regression analyses, CACS was grouped into the following preselected categories: 0, 1 to 100, 101 to 300, and 301 or more. The FRS 10-year risk was calculated by age and risk factors at the time of CT scanning using the score derived from the third National Cholesterol Education Program report and grouped into the following preselected 10-year risk prediction categories: 0% to 9%, 10% to 15%, 16% to 20%, and 21% or higher. Univariate Cox regression analysis was used to assess the risk of CHD death or nonfatal MI for baseline CACS or FRS. Tests for trend across FRS and CACS (as continuous and categorical variables) were also conducted. Bivariate Cox regression analysis was used to assess risk for CHD death or nonfatal MI based on the joint relationship between the baseline CACS and FRS.

Finally, revised risk probabilities (FRS + CACS) were obtained using bivariate Cox regression with time to death or nonfatal MI as the dependent variable.
and FRS and CACS as continuous independent variables. The predicted survival probabilities at the median follow-up time were calculated for each participant. The FRS plus CACS for each participant was then calculated as (1 – predicted survival probability). The average FRS plus CACS was then computed for the 4 CACS groups within each of the 4 FRS groups. A 2-way factorial analysis of variance (factors=FRS, CACS, and FRS × CACS) was conducted to test for differences between CACS groups within each FRS group. Pairwise t tests were used to compare the highest CACS level (>300) with each of the lower CACS levels. To accommodate multiple comparisons within each FRS group, the significance level was set at .05/3 = .017 (Bonferroni adjustment). Receiver operating characteristic curves were then plotted, and the areas under the curves were compared for the FRS plus CACS score vs FRS alone as indexes of the discriminative ability of the FRS plus CACS vs FRS alone.

A secondary analysis was also conducted to assess predictive capability of CACS or FRS for all-cause mortality.

**RESULTS**

Of the 1312 participants with CT scan results, 269 had diabetes, an additional 12 had coronary events prior to the CT scan, and 2 participants had missing risk factor data. Thus, the study cohort consisted of 1029 participants. Characteristics of these participants stratified by CACS groups are shown in Table 1. Overall, the mean (SD) age at the time of the CT scan was 65.7 (7.8) years; 53 (5.2%) were Asian; 35 (3.3%), black; 46 (4.5%), Hispanic; 1 (0.1%), Native American; and 874 (84.9%), white. Over an average (SD) follow-up period of 75.9 (18.4) months (range, 1.4–101.9), 84 individuals experienced either a nonfatal MI (n=68) or CHD death (n=16).

**Univariate Analyses**

Table 2 presents event rates for CHD death or nonfatal MI and the results of the univariate Cox regression analyses relating likelihood of the CHD death or nonfatal MI end point according to increasing levels of CACS or increasing levels of FRS. The risk (hazard ratio [HR]) of a CHD death or nonfatal MI for participants with a CACS higher than 300 was 3.9 times that of participants with a CACS of zero (P<.001). The risk of a CHD death or nonfatal MI for participants in the highest FRS group (>20%) was 14.3 times that of participants with an FRS of less than 10% (P =.009). The risk of a CHD death or nonfatal MI across increasing categories of CACS was 1.6 (P <.001) and 1.7 across increasing categories of FRS (P <.001). When analyzed as continuous variables in univariate Cox regression models, the risk of a CHD death or nonfatal MI per 1-SD increase in CACS (399) and FRS (7.1) was 1.4 (P <.001) and 1.6 (P <.001), respectively.

**Bivariate Analyses**

Table 3 presents the bivariate Cox regression analyses relating the likelihood of a CHD death or nonfatal MI according to increasing levels of CACS and FRS.
also increasing levels of FRS. Shown are the distribution of coronary events and the HRs of CHD death or nonfatal MI across the 16 categories defined by CACS×FRS. The referent group has the lowest FRS (0%-9%) and a CACS of 300 or less or a low intermediate FRS (10%-15%) and a CACS of zero. These groups were chosen as the referents due to similar event rates. For FRS from 0% through 9%, there was no significant increased risk with a CACS of 301 or higher. For an FRS from 10% through 15%, the risk was significantly greater than 1.0 for a CACS of more than 100 (P<.05). The risk of FRS from 10% through 15% and a CACS of more than 300 (HR, 17.6) was comparable with the risk of an FRS of more than 20% and a CACS of more than 300 (HR, 19.1; P<.001). For an FRS from 16% through 20%, the risk was significantly greater than 1.0 for the upper 3 CACS groups (P<.05). When analyzed as continuous variables in a bivariate model, the adjusted risk of a CHD death or nonfatal MI per 1-SD increase in the CACS was 1.3 (95% confidence interval [CI], 1.2-1.5; P<.001) and in the FRS was 1.5 (95% CI, 1.2-1.9; P<.001).

**Predicted Event Rates**

**Figure 1** shows the mean predicted event rates (FRS+CACS) for CHD death or nonfatal MI stratified by CACS groups within FRS groups. Pairwise comparisons revealed a statistically significant difference between a CACS of more than 300 and each of the other 3 CACS groups for an FRS of 10% or more (P<.001), and between a CACS of more than 300 and a CACS of zero for an FRS of less than 10% (P=.01). **Figure 2** displays receiver operating characteristic curves for prediction of CHD death or nonfatal MI. The mean (SD) area under the curve for the receiver operating characteristic curve for FRS plus CACS was 0.68 (0.03), significantly greater than that of the FRS alone (0.63 [0.03]; P<.001).

**All-Cause Mortality**

A univariate Cox regression analysis was performed to determine whether the CACS and the FRS predicted all-cause mortality (Table 4). Hazard ratios for all levels of CACS greater than zero were not significantly greater than 1.0. In contrast, the risk of all-cause mortality for an FRS of more than 20% was significantly greater than 1.0 (P=.03).

**COMMENT**

In this report from a large prospective study with a median follow-up of 7 years, we found that in asymptomatic participants without diabetes and at least 1 risk factor for CHD but no prior clinical CHD, the FRS alone was able to rank participants according to CHD event risk in a graded fashion, as expected. Coronary artery calcium scores alone were also able to rank CHD event risk independently of the FRS. The CACS significantly modified the risk prediction in all categories of an FRS of at least 10% but not when the FRS was less than 10%. The increment in predicted risk was equal to a 3% to 9% increase in 10-year event risk compared with FRS alone for every category of FRS estimate when the CACS was more than 300. Additionally, among the 316 participants with a CACS of zero, 14 coronary events were observed (4.4%); thus, absence of CACS did not preclude risk of a CHD event as has been reported in some other studies.

**Comparison With Previous Studies**

Studies comparing the prognostic accuracy of coronary calcium measurement by CT vs the FRS alone, or risk factors alone, have yielded somewhat conflicting results. For example, in an earlier report based on the 3-year follow-up from the South Bay Heart Watch, CACS results added little overall predictive capability for definite coronary events beyond that available by the FRS. However, other studies found that CACS results added to risk prediction beyond that attributable to traditional risk factors.
Variability in study results may be related to differences in patient characteristics, lengths of follow-up, numbers and types of defined CHD events, or differences in measurement of CHD risk factors. The purpose of this study was to reevaluate the additive predictive capability of CACS in the South Bay Heart Watch in light of the availability of a median follow-up of 7 years, the routine availability of measured coronary risk factors, and the occurrence of a considerable number of definite coronary events (MI or coronary death) during the follow-up period.

**Study Strengths**

This report is unique in several ways in comparison with other studies on the prognostic value of CT-derived coronary calcium scores in asymptomatic people. Previous reports\(^{10-13}\) included participants who were either self-referred or both self-referred and physician-referred, suggesting the possibility that these patients represented a biased group. In contrast, all participants in the South Bay Heart Watch were recruited and assessed to be asymptomatic before enrollment, suggesting that they may be more representative of the general population of asymptomatic individuals with CHD risk factors. Also, in other studies, coronary risk factors were not actually measured but were estimated based on patient self-report.\(^{10-12}\) Self-reported risk factors are less accurate and precise than measured risk factors; therefore, it is likely that the predictive value of risk factors was artificially limited in other studies. This methodological issue would also tend to overestimate the incremental effect of coronary calcium scores since CACS was the only directly measured risk marker in the previous studies, rendering comparison of CACS with FRS hazardous. In 4 previously published reports, average follow-up was less than 4 years, and definite coronary events were often rare.\(^{10-13}\) Earlier reports also typically included revascularizations among the coronary events counted to increase study power.\(^{10-13}\) This practice could also lead to overestimation of the value of CACS since the calcium score may have influenced the likelihood of a patient seeking revascularization.\(^{22}\)

Therefore, the current data derive from the only prospective study to measure all risk factors required to calculate the FRS in addition to measuring the CACS. Based on these unique aspects of the South Bay Heart Watch, it may be considered the only study to demonstrate conclusively that CACS can add to coronary event risk prediction over and above that determined by the FRS. Alexopoulos et al\(^{23}\) measured the coronary risk factors of 435 research patients and determined clinical outcomes following coronary calcium estimation using digital cinefluoroscopy. However, there were too few definite MI and coronary deaths to ascertain whether coronary calcium measurement by this non-CT technique added to the FRS prediction. Shaw et al\(^{24}\) demonstrated the ability of CACS to predict all-cause mortality in a study of 10,377 asymptomatic people referred for CT scanning by primary care physicians; however, that study did not include direct measurement of risk factors included in the FRS.

The current results also demonstrated that a CACS of zero does not routinely exclude risk of future CHD events. A previous preliminary analysis from the South Bay Heart Watch similarly reported that coronary events can occur despite low or undetectable CACS.\(^{25}\) Our analysis, with longer follow-up and more coronary events, further supports this observation. Why individuals without detectable coronary calcium might experience coronary events is uncertain, but it appears consistent with the current concept that soft, lipid-filled plaques are most vulnerable, leading to subsequent clinical events.\(^{26,27}\) It might be anticipated that such lesions would contain lower amounts of radiographically detectable calcium.\(^{28,29}\) Therefore, for individuals with no detectable coronary calcium, FRS may be the more prudent guide to clinical management of risk.

**Study Limitations**

Although this study has unique strengths, it also has limitations. The South Bay Heart Watch comprises predominantly male participants with an average age of 62 years at enrollment. Some have suggested that this cohort is neither heterogeneous nor representative of the general population, thus possibly reducing generalizability of the study’s find-
ings. However, as shown, the FRS ranged from about a 9% to a more than 21% 10-year risk, suggesting that the cohort was moderately diverse from the perspective of overall risk, within a clinically relevant range. These data may also have limited applicability to women and nonwhite ethnic groups. It should also be noted that the study did not test whether CACS measurement allowed for improved clinical outcomes. Rather, this study examined only whether application of CACS measurements could modify risk estimation.

These results may have been affected by unmeasured variables such as motivation to alter lifestyles that might influence event rates after testing for risk factors or CACS. This concern applies also to all previous studies of the pre-fluence event rates after testing for risk ateration to lifestyles that might in- 34 modify risk estimation.

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Analysis by LC-MS of the sesquiterpene lactone fraction of each sample was performed to determine the presence of anisatin, neoanisatin, and veranisatins A, B, and C. Although I verum is considered safe for consumption, this species also contains the toxic compounds, veranisatin A, B, and C. Anisatin compounds are thought to act as picrotoxin-like noncompetitive γ-aminobutyric acid (GABA) antagonists. The mass spectral pattern of each sample was similar in the number, type, and concentration of these compounds. Extracts from the third case, however, suggested the presence of an Illicium species other than I verum.

Comment. Given our laboratory findings, the symptoms we have described may be attributed to an overdose of I verum, contamination with I anisatum, or a combination of both. Illicium verum has been considered safe because it contains veranisatins in low concentrations. However, relatively small quantities in infants may be sufficient to produce adverse neurologic reactions.

Ingestion of star anise should be considered in the differential diagnosis of infants presenting with acute-onset irritability, vomiting, and seizures. Based on these cases and the finding of I verum contamination, we recommend against administering star anise to infants. Stricter regulation may also be warranted.

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CORRECTIONS


Incorrect Byline Order: In the Research Letter entitled “Adipocytokines in Synovial Fluid” published in the October 1, 2003, issue of THE JOURNAL (2003;290:1709-1710), the order of authors listed in the byline was incorrect. Ulf Müller-Ladner, MD, should have been listed in the final position.