

Combined Use of Computed Tomography Coronary Calcium Scores and C-Reactive Protein Levels in Predicting Cardiovascular Events in Nondiabetic Individuals

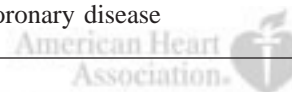
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Background—The South Bay Heart Watch is a prospective cohort study designed to appraise the value of coronary calcium and risk factors for predicting outcomes in asymptomatic adults. Two factors that may be related to subsequent cardiovascular events are coronary calcium (CAC, a manifestation of subclinical atherosclerosis) and high-sensitivity C-reactive protein (CRP, a measure of chronic inflammation).

Methods and Results—Between December 1990 and December 1992, 1461 participants without coronary heart disease underwent baseline risk factor screening, computed tomography for CAC, and measurement of CRP. Participants were followed up for 6.4 ± 1.3 years. Cox regression analyses were conducted for the 967 nondiabetics with CRP levels ≤ 10 mg/L to estimate the risk-factor-adjusted relative risks of CAC and CRP for the occurrence of (1) nonfatal myocardial infarction (MI) or coronary death and (2) any cardiovascular event (MI, coronary death, coronary revascularization, or stroke). CAC was a predictor of both end points ($P < 0.005$), and CRP was a predictor of any cardiovascular event ($P = 0.03$). Risk group analysis defined by tertiles for CAC (< 3.7 , 3.7 to 142.1 , > 142.1) and the 75th percentile for CRP (> 4.05 mg/L) indicated that there was increasing risk with increasing calcium and CRP. Relative risks for the medium-calcium/low-CRP risk group to high-calcium/high-CRP risk group ranged from 1.8 to 6.1 for MI/coronary death ($P = 0.003$) and 2.8 to 7.5 for any cardiovascular event ($P < 0.001$).

Conclusions—Participants without diabetes and those at intermediate risk may benefit from risk stratification based on high-sensitivity CRP levels and CAC, because both factors contribute independently toward the incidence of cardiovascular events. (*Circulation*. 2002;106:2073-2077.)

Key Words: C-reactive protein ■ calcium ■ coronary disease



Despite the availability of effective preventive therapies, cardiovascular disease remains a leading cause of morbidity and mortality. In addition to elevated lipoproteins and various coagulation and inflammatory factors, baseline levels of atherosclerotic disease assessed with noninvasive means also contribute to the risk of cardiovascular events.¹⁻³ A recent meta-analysis reported a pooled 4-fold relative risk (RR) for computed tomographic (CT) coronary calcium as a predictor of myocardial infarction (MI) or coronary death.⁴ In addition, serum levels of C-reactive protein^{5,6} (CRP) in the highest tertile predict future coronary events in asymptomatic men⁷ and postmenopausal women.^{8,9} Moreover, CRP has been shown to add to the predictive value of lipid testing alone.^{6,7} RRs have varied, but in general, elevated CRP levels impart an approximately 2-fold risk of coronary events after adjustment for demographic and risk factors. CRP levels have been shown to be associated with progression of carotid intimal-medial thickness,¹⁰ although not with baseline values of this measure of subclinical atherosclerosis. Finally, 2 studies did not reveal an association between CRP levels and CT

calcium scores in cohorts of postmenopausal women¹¹ and middle-aged men.¹² These findings suggest that inflammation and baseline atherosclerosis may contribute independently and in a complementary fashion to the risk of coronary events.

The South Bay Heart Watch (SBHW) is a prospective cohort study designed to appraise the value of coronary calcium and both traditional and nontraditional risk factors for predicting cardiovascular outcomes and calcium progression in asymptomatic adults. The objective of this investigation was to utilize the SBHW cohort of nondiabetics to evaluate prospectively the combined use of CT coronary calcium scores and high-sensitivity CRP in the prediction of cardiovascular events.

Methods

Study Design

The study design of the SBHW has been described previously.¹³ Briefly, the SBHW cohort comprises respondents to a community-based mailing campaign. The cohort consists of 1461 asymptomatic participants ≥ 45 years old with multiple cardiac risk factors ($\geq 10\%$ 8-year risk of developing coronary heart disease by Framingham risk

Received June 6, 2002; revision received July 31, 2002; accepted August 2, 2002.

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000033819.29662.09

equation) without evidence of coronary heart disease at the time of enrollment. Participants were initially screened and enrolled between December 1990 and December 1992. Participants with ECG evidence of infarction or clinical history of infarction, revascularization, or typical angina were excluded.

Thirty months after enrollment, 1312 surviving participants underwent a second medical and risk factor evaluation that included fasting phlebotomy concurrent with CT examinations for coronary calcification. CT examinations were performed within 2 ± 2 days of the risk factor evaluations. Serum samples were stored at -70°C for subsequent analyses. All participants gave informed consent at the time of recruitment and again at the time of repeat risk factor assessment and CT scanning. The Harbor UCLA Research and Education Institute Human Participants Committee approved this study.

Because we have found that calcium scores do not have prognostic value in the diabetics in our cohort,¹⁴ we excluded diabetics for the purposes of this analysis. Participants were classified as having diabetes if the participant had a history of being on diet or medication for diabetes mellitus at the time of CT scanning and risk factor assessment or had a random blood sugar of ≥ 200 mg/dL at the time of recruitment into the cohort.

Coronary Calcium Scanning

CT scans were performed within 2 ± 2 days after risk factor evaluation with an Imatron C-100 scanner. The acquisition protocol consisted of 6-mm image slices¹⁵ obtained at 80% of the ECG RR interval during breath holding. In a subgroup of 286 participants who underwent both 6- and 3-mm scanning, we demonstrated that the 6-mm protocol has increased rescan reliability¹⁵ and has similar predictive value.¹⁶ The Spearman rank correlation coefficient between the calcium scores from the 2 methods was 0.94. All participants were scanned over a bone mineral density phantom (Image Analysis).

Coronary Calcium Scoring

A single cardiologist blinded to all clinical outcome and serologic data interpreted all scans. The scoring software used was the same as that used for the Multi-Ethnic Study of Atherosclerosis (MESA).¹⁷ This includes a pixel adjustment that uses the formula new pixel value = (old pixel value - intercept)/slope, where slope and intercept refer to the results of a least-squares linear fit relating standard radiographic densities to the measured mean CT numbers in the calibration phantom scanned under the participants. The minimal calcific focus size was 4.1 mm^3 , chosen to be equivalent to that used in the ongoing MESA¹⁷ and CARDIA¹⁸ studies. The coronary calcium score was calculated according to the method of Agatston.¹⁹

Risk Factor and CRP Determinations

Smoking, blood pressure measurements, lipoprotein measurements (total cholesterol, HDL and LDL cholesterol, and triglycerides), and ECGs for left ventricular hypertrophy were all obtained within 2 days of CT scanning. A nurse performed phlebotomy for these determinations while the participant was fasting. Analysis for lipoproteins was done as described previously.¹⁶ After thawing of frozen serum²⁰ collected at the time of CT acquisition, measurements of CRP were performed with an ultrasensitive latex-enhanced immunoturbidimetric assay with a detection threshold of 0.01 mg/L (Playmedco). CRP assay was calibrated to International Federation of Clinical Chemistry reference standards. Testing was performed by a technician who was blinded to the clinical outcomes and CT data. In a reliability study of 27 duplicate CRP determinations, the coefficient of variation of the average determination was equal to 0.89. No significant difference between duplicate determinations was found ($P > 0.10$); the correlation between pairs of determinations was 0.99 ($P < 0.0001$). Participants with CRP levels > 10 mg/L were assumed to have an exogenous acute-phase stimulus and excluded from further analysis.

Evaluation of Study End Points

We contacted participants every year for 7 years after CT examinations. At that time, we assessed cardiovascular disease using questions about intervening hospital admissions. We reviewed medical records for any hospitalization related to a complaint of chest discomfort, dyspnea,

vascular or cardiac problems, or admissions for major cardiac or noncardiac surgeries. We considered a follow-up attempt 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.

A committee of 3 board-certified cardiologists reviewed medical records and transcripts of conversations with next of kin, without knowledge of other data. They applied majority rule to determine the occurrence of the end points of MI, stroke, or coronary death. End points of coronary revascularization with either CABG surgery or percutaneous coronary intervention (PTCA) and stroke were ascertained by records review by a cardiologist investigator.

We defined MI as the presence of 2 of the following 3 factors: prolonged chest pain prompting hospital admission, diagnostic evolutionary ECG changes, and elevation of serum creatine kinase to twice the upper limits of normal or a positive serum creatine kinase-MB fraction or troponin.

The research team confirmed all deaths with transcriptions of conversations with next of kin, medical records, or death certificates. The committee reviewing medical records considered coronary heart disease death to have occurred if the death was proved to be due to coronary atherosclerosis by autopsy, occurred within 1 hour after the onset of prolonged severe chest pain, occurred suddenly in a participant for whom there was no other known cause, or occurred during hospital admission for acute MI. The committee considered stroke to be present if there was a persistent neurological deficit (> 48 hours) with corroborative imaging evidence by computed tomography or MRI. Coronary revascularization with either CABG surgery or percutaneous coronary intervention was ascertained by review of operative and cardiac catheterization reports.

Two study end points were defined. The MI/coronary death end point was the occurrence of nonfatal MI or coronary heart disease death; the "any cardiovascular event" end point was the occurrence of nonfatal MI, coronary death, stroke, or coronary revascularization. Abnormal angiographic findings not treated with revascularization were not regarded as events.

Statistical Analysis

Statistical analyses were conducted for the subgroup of nondiabetic participants with CRP levels ≤ 10 mg/L. Baseline characteristics were compared between participants experiencing and not experiencing each of the 2 end points by 2-sample *t* tests for continuous measures and χ^2 tests for discrete measures.

Cox regression analyses were utilized to evaluate the adjusted RR of the calcium score and CRP with each of the study end points. For these analyses, the 2 dependent variables were the time to nonfatal MI/coronary death and the time to any cardiovascular event. The calcium score (log transformed to satisfy the Cox regression proportional hazard requirement) and CRP were treated as continuous, independent variables. Covariates were variables found to be statistically significant between participants with and without cardiovascular events. Candidate covariates were age, sex, total cholesterol, HDL, systolic blood pressure, diastolic blood pressure, ever smoked, currently taking aspirin, and currently taking a HMG-CoA reductase inhibitor. Likelihood ratio tests for trends in coronary event rates, hazard ratios (as estimators of RR), and 95% CIs were calculated.

Bivariate Cox regression analyses were also conducted for risk groups defined by the tertiles of the distribution of calcium scores and the 75th percentile of the distribution of CRP. Calcium score and CRP risk groups were determined from the subgroup of participants without any cardiovascular event. These analyses were also adjusted for the significant risk factor covariates. Likelihood ratio tests for trends in coronary event rates across risk groups and hazard ratios (as estimators of RR) for each risk group were calculated relative to the reference group (1st tertile calcium score and < 75 th percentile CRP). Bivariate Cox regression analyses were also conducted adjusting for the Framingham risk score. All analyses were conducted at the 0.05 significance level and used SAS software.

TABLE 1. Baseline Characteristics of Study Participants With or Without the MI/Coronary Death End Point or any Cardiovascular Event End Point (Nonfatal MI or Cardiac Death, PTCA or CABG, or Stroke)

	MI/Coronary Death End Point			Any Cardiovascular Event		
	Yes (n=50)	No (n=917)	<i>P</i> *	Yes (n=104)	No (n=863)	<i>P</i>
Age, y	67 (8)	66 (8)	0.16	68 (7)	66 (8)	0.02
Male sex, n (%)	46 (92)	829 (90)	0.71	95 (91)	780 (90)	0.75
Race, n (%)			0.67			0.33
Asian	3 (6)	49 (5)	...	6 (6)	46 (5)	...
African American	4 (8)	46 (5)	...	5 (5)	45 (5)	...
Hispanic	1 (2)	42 (5)	...	1 (1)	42 (5)	...
White	42 (84)	780 (85)	...	92 (88)	730 (85)	...
Ever smoked, n (%)	34 (68)	666 (73)	0.48	67 (64)	633 (73)	0.05
Taking aspirin, n (%)	14 (28)	293 (32)	0.56	43 (41)	264 (31)	0.03
Taking statins, n (%)	6 (12)	95 (10)	0.72	10 (10)	91 (11)	0.76
Blood pressure, mm Hg						
Systolic	149 (24)	140 (19)	0.01	146 (21)	140 (19)	0.007
Diastolic	80 (13)	80 (10)	0.95	80 (11)	80 (10)	0.53
Body mass index, kg/m ²	29 (6)	27 (4)	0.15	28 (5)	27 (4)	0.03
Total cholesterol, mg/dL	234 (37)	231 (41)	0.62	235 (39)	231 (41)	0.36
HDL cholesterol, mg/dL	40 (13)	47 (16)	0.006	43 (14)	47 (16)	0.01
Calcium score	431 (630)	205 (389)	0.0001	395 (571)	195 (378)	<0.0001
	208 (21–539)	43 (0–233)		203 (23–494)	37 (0–208)	
CRP	3.8 (2.2)	3.0 (2.0)	0.007	3.5 (2.0)	3.0 (2.0)	0.002
	3.3 (1.9–5.0)	2.5 (1.5–3.9)		3.2 (2.0–4.5)	2.5 (1.5–3.9)	

Discrete variables expressed as frequency (percent); continuous variables expressed as mean (SD). Calcium score and CRP expressed as mean (SD)/median (25th, 75th quartile range).

*Statistical testing utilized 2-sample *t* tests (for continuous variables), χ^2 tests (for discrete variables), and the Wilcoxon rank sum test for the calcium score and CRP. The Welch *t* test was utilized for variables with unequal variance (body mass index, systolic blood pressure, and diastolic blood pressure).

Results

A total of 967 (74%) of 1307 participants met the study criteria (nondiabetic and CRP ≤10 mg/L). Table 1 presents the baseline characteristics for the study participants stratified by each of the study end points. For each end point, baseline characteristics were contrasted between participants with and without the end point. Over an average ± SD follow-up period of 76.8±15.6 months, 50 participants experienced the MI/coronary death end point, and 104 participants experienced any cardiovascular event (MI, coronary death, revascularization, or stroke). For the MI/coronary death end point, significant differences between participants with and without events were found for systolic blood pressure and HDL cholesterol. Participants who experienced an MI or coronary death had higher systolic blood pressure (*P*=0.01) and lower HDL cholesterol (*P*=0.006). For any cardiovascular event, significant differences between participants with and without an event were found for age, smoking status, aspirin usage, systolic blood pressure, body mass index, and HDL cholesterol. Participants who experienced any cardiovascular event were significantly older (*P*=0.02), were less likely to have smoked (*P*=0.05), were more likely to take aspirin (*P*=0.03), had higher systolic blood pressure (*P*=0.005), had higher body mass index (*P*=0.03), and had lower HDL (*P*=0.002).

On the basis of these analyses, covariates used in the Cox regression analyses were age, systolic blood pressure, HDL cholesterol, currently taking aspirin, body mass index, race, and ever smoked.

For either end point, the median calcium score was ≈5 times greater in participants who had an event than in those who did not (*P*<0.0001). In addition, there were significantly larger CRP values for those who experienced end points (*P*=0.002).

Independent and Joint Effects of Calcium Score and CRP: Continuous Variable Analyses

Cox regression analyses of the calcium score and CRP (treated as continuous variables, log transformed and adjusted for the risk factor covariates) over the entire study cohort demonstrated that the calcium score was a statistically significant predictor of both end points (*P*<0.005). CRP was a marginally significant predictor of MI or coronary death (*P*=0.09) and a statistically significant predictor of any cardiovascular event (*P*=0.03). Stepwise Cox regression demonstrated that after adjustment for the risk factor covariates and the calcium score, CRP continued to contribute to the prediction of cardiovascular events (*P*=0.07 for MI/coronary death; *P*=0.02 for any cardiovascular event). Furthermore, after adjustment for the risk factor covariates, calcium score, and CRP, the interaction of calcium score and CRP was nonsignificant (*P*=0.46).

TABLE 2. RRs for Study End Points Associated With Calcium Scores and CRP (Treated as Continuous Variables)

End Point	Incidence Rate	RR	95% CI	P*
Independent effects of calcium scores and CRP				
MI/coronary death	50/967			
Calcium score		1.13	1.04–1.23	0.005
CRP		1.49	0.94–2.37	0.09
Any cardiovascular event†	104/967			
Calcium score		1.15	1.08–1.22	<0.0001
CRP		1.39	1.03–1.89	0.03
Joint effects of calcium scores and CRP				
MI/coronary death	50/967			
Calcium score		1.14	1.04–1.24	0.004
CRP		1.55	0.97–2.46	0.07
Calcium×CRP		0.95	0.83–1.09	0.46
Any cardiovascular event	104/967			
Calcium score		1.15	1.08–1.22	<0.0001
CRP		1.46	1.07–1.98	0.02
Calcium×CRP		0.99	0.90–1.09	0.84

*Cox regression analyses for independent effects of calcium and CRP; stepwise Cox regression analysis for the joint effects of calcium and CRP. Calcium score and CRP are log-transformed. Covariates=age, systolic blood pressure, HDL, currently taking aspirin, body mass index, race, and ever smoked.

†Any cardiovascular event: nonfatal MI, coronary death, PTCA, CABG, stroke.

Joint Effects of CRP and Calcium Score: Risk Group Analyses

For the calcium score, risk groups were defined by the subgroup of participants without events by tertiles as low (<3.7), medium (3.7 to 142.1), and high (>142.1). For CRP, risk groups were defined by the 75th percentile as normal (<4.05 mg/L) and abnormal (\geq 4.05 mg/L).

Figure 1 presents the adjusted RRs of the MI/coronary event end point according to the bivariate risk group categories of CRP and calcium score. Compared with participants in the low-risk group for both calcium score and CRP (reference group), there was increasing risk for MI/coronary events with increasing CRP level and increasing calcium score (range of RR 1.8 to 6.1; $P=0.003$ test for trend across the 6 risk groups). Compared with participants in the low-risk CRP and calcium score group (reference group), increased risk was found for the low-risk CRP and high-risk calcium group (RR=4.9) and the high-risk CRP and medium- and high-risk calcium groups (RR=4.3 and 6.1, respectively; $P<0.05$).

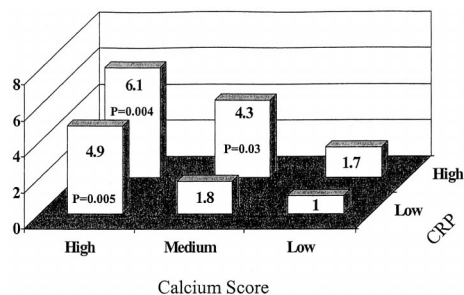


Figure 1. RRs of nonfatal MI or coronary death associated with high (\geq 75th percentile=4.05 mg/L) and low (<4.05 mg/L) levels of CRP and high (>142.1), medium (3.7 to 142.1), and low (<3.7) tertiles of calcium scores.

Figure 2 presents the adjusted RRs for any cardiovascular event according to the bivariate risk group categories of calcium score and CRP. Compared with participants in the low-risk group for both calcium score and CRP, there was increasing risk for any cardiovascular event with increasing CRP level and increasing calcium score (range of RR=2.8 to 7.5; $P<0.001$ test for trend across the 6 risk groups). Compared with participants in the low-risk CRP and calcium score group, increased risk was found for the low-risk CRP and medium- and high-risk calcium groups (RR=2.8 and 4.4, respectively) and the high-risk CRP and medium- and high-risk calcium groups (RR=3.4 and 7.5, respectively; $P<0.05$).

Prognostic Value of Calcium Score and CRP Adjusted for Framingham Risk Score

We also estimated the RRs for each of the end points according to the bivariate risk group categories of CRP and the calcium scores with adjustment for the Framingham risk score, instead of

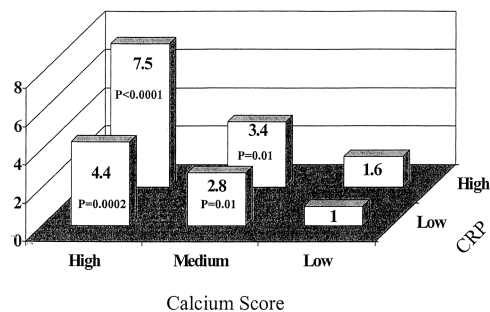


Figure 2. RRs of nonfatal MI, coronary death, PTCA, CABG, or stroke associated with high (\geq 75th percentile=4.05 mg/L) and low (<4.05 mg/L) levels of CRP and high (>142.1), medium (3.7 to 142.1) and low (<3.7) tertiles of calcium scores.

the significant risk factor covariates. Similar results were found. Compared with participants in the low-risk group for both the calcium score and CRP, there was increasing risk for MI/coronary death with increasing CRP level and increasing calcium score (range of RR=1.7 to 6.5; $P=0.0002$ test for trend across the 6 risk groups). Similarly, there was increasing risk for any cardiovascular event with increasing CRP levels and increasing calcium scores (range of RR=2.9 to 8.2; $P<0.0001$ test for trend across the 6 risk groups).

Discussion

Risk-adjusted analysis revealed that coronary calcium and CRP levels are associated with ischemic cardiovascular events in previously asymptomatic nondiabetic adults. Furthermore, calcium and CRP appear to be complementary for risk prediction of cardiovascular events. Our analysis using the combination of coronary calcium score tertiles and elevated CRP levels (defined by the 75th quartile) discriminated approximately a 6-fold difference in risk of MI and cardiac death and a 7-fold difference in the risk of any cardiovascular event between the lowest-risk (lowest tertile calcium score and normal CRP levels) and the highest-risk (highest tertile of calcium score and elevated CRP levels) groups. The highest-tertile coronary score group was at significantly increased risk regardless of CRP levels.

The lack of interaction in nondiabetics between CRP levels and coronary calcium scores along with the complementary predictive power of the 2 tests suggests that they assess different aspects or mechanisms that result in cardiovascular events. Coronary calcium is a surrogate marker of the presence and amount of coronary atherosclerosis, whereas CRP appears to provide an assessment of overall atherosclerotic activity and stability. Inflammation appears to be an important component of vulnerable plaques that are likely to rupture or erode and cause coronary events.^{21,22} Therefore, it is likely that combined, the 2 studies provide an assessment as to the presence, amount, and stability of potential coronary atherosclerosis.

The main limitation of the present study is that participants were relatively homogeneous, mostly older men with coronary heart disease, which limits the generalizability of the study. Another limitation is that the statistical analyses could not control for all possible relevant confounders (eg, physical activity). Also noteworthy is that CRP levels in the present study were greater than those derived from a meta-analysis based on 14 population-based studies.⁹ Nevertheless, the discriminating power of combined use of CRP and CT is more noteworthy given the wide range of RRs produced even when applied to a relatively homogeneous population.

Clinically, the combined use of calcium scores and CRP helps to risk-stratify participants without diabetes. Nondiabetics are at more variable risk for the development of cardiovascular events even among those with multiple cardiac risk factors. Although the exact role of both calcium scores and CRP awaits more definitive studies such as the ongoing MESA trial (a National Institutes of Health-sponsored trial assessing the predictive value of CT coronary calcium), the present study indicates that the use of combined testing with CT and CRP appears to be complementary and promising, at least among those without diabetes.

Acknowledgment

Supported by grant No. HL63963-01A1 from the National Heart, Lung, and Blood Institute.

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