

# Relationship and prognostic value of coronary artery calcification by electron beam computed tomography to stress-induced ischemia by single photon emission computed tomography

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**Background** Stress single photon emission computed tomography (SPECT) is commonly performed in patients with abnormal electron beam computed tomography (EBCT) to define risk stratification, but the published prognostic data for patients undergoing both SPECT and EBCT are limited. The objective of the study was to examine the association and prognostic value between EBCT, coronary artery calcium score (CACS), and stress SPECT imaging.

**Methods** We identified 835 patients (age  $54.8 \pm 10.0$  years, 77% male) who underwent EBCT and stress SPECT within a 3-month period. Coronary artery calcium score was categorized as normal (0), minimal (1-10), mild (11-100), moderate (101-400), and severe ( $>400$ ). Single photon emission computed tomography summed stress score (SSS) was categorized as normal, low risk, intermediate risk, and high risk per Cedar Sinai criteria. Average follow-up was  $4.8 \pm 3.2$  years. End points were all-cause death, death/myocardial infarction (MI), and death/MI/late revascularization.

**Results** The correlation of CACS to SSS was weak but statistically significant ( $r = +0.19$ ,  $P < .001$ ). The percentage of high-risk SSS increased with higher CACS scores; 4% of patients with normal EBCT and 18% with severe CACS had high-risk SSS. Coronary artery calcium score ( $\chi^2 = 11.4$ ,  $P < .001$ ), diabetes mellitus ( $\chi^2 = 4.6$ ,  $P = .031$ ), and chest pain class ( $\chi^2 = 8.7$ ,  $P = .003$ ) were independently associated with high-risk SPECT. The SSS ( $\chi^2 = 6.9$ ,  $P = .009$ ) and CACS ( $\chi^2 = 7.8$ ,  $P = .005$ ) were independently associated with mortality, as well as with both secondary end points of death/MI and death/MI/late revascularization. Only CACS predicted mortality in the 408 asymptomatic patients ( $\chi^2 = 5.2$ ,  $P = .02$ ), but these patients had an annual mortality of only 0.4% over the next 5 years.

**Conclusions** In selected patients undergoing both EBCT and SPECT, CACS is weakly correlated with SPECT SSS, likely reflecting the different information provided by EBCT and SPECT. Coronary artery calcium score is independently associated with high-risk SPECT after adjustment for clinical variables. Coronary artery calcium score and SSS are complementary for the prediction of mortality in symptomatic patients. Only CACS predicted mortality in the asymptomatic patients, but they had a low annual mortality. (*Am Heart J* 2007;153:807-14.)

Previous histopathologic studies have demonstrated that the extent of coronary artery calcification determined by electron beam computed tomography (EBCT) correlates well with coronary artery atherosclerotic plaque burden.<sup>1</sup> However, studies comparing EBCT

results with lumen stenoses by angiography and/or plaque calcification by intracoronary ultrasound demonstrated that very elevated calcium scores are specific for obstructive coronary lesions, but sensitivity is compromised; conversely, low calcium scores are sensitive for obstructive disease, but specificity is reduced.<sup>2,3</sup> Furthermore, patients with no detectable calcification by EBCT may still harbor soft coronary plaque; conversely, patients with no luminal stenosis may in fact have calcification in the setting of positive remodeling.<sup>4</sup>

Because the relationship between coronary artery calcium and high-grade coronary artery stenoses is uncertain, clinicians may refer patients with positive EBCT for nuclear stress testing. Although prior studies have examined the relationship between EBCT and

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**Table I.** Demographic and clinical characteristics grouped by CACS (n = 835)

Parameter	Overall	CACS $\leq$ 400 (n = 615)	CACS $>$ 400 (n = 220)	P
Age (y)	54.8 $\pm$ 10.0	52.3 $\pm$ 9.3	62.7 $\pm$ 8.6	<.001
Male	641 (76.8%)	446 (72.5%)	195 (88.6%)	<.001
Diabetes mellitus	115 (13.8%)	62 (10.1%)	53 (24.1%)	<.001
Smoking	393 (47.1%)	269 (43.7%)	124 (56.4%)	.001
Hypercholesterolemia	562 (67.3%)	396 (64.4%)	166 (75.5%)	.003
Hypertension	353 (42.3%)	245 (39.8%)	108 (49.1%)	.02
Symptom status				
Asymptomatic	408 (48.9%)	271 (44.1%)	137 (62.3%)	<.001
Typical angina	66 (7.9%)	51 (8.3%)	15 (6.8%)	.49
Atypical/Noncardiac chest pain	312 (37.4%)	266 (43.3%)	46 (20.9%)	<.001
Dyspnea	49 (5.9%)	27 (4.4%)	22 (10.0%)	.002

single photon emission computed tomography (SPECT) results,<sup>5-7</sup> they have not included subsequent patient outcomes. The objectives of this study were (1) to examine the associations between coronary artery calcium score (CACS) as determined by EBCT and findings on SPECT and (2) to examine the prognostic value of these techniques.

## Methods

### Patient population

The study protocol was approved by the Mayo Foundation Institutional Review Board. Imaging data from all patients who undergo SPECT imaging or EBCT are stored in separate electronic databases. We retrospectively identified patients who underwent both EBCT and stress SPECT within a 3-month interval (mean 3.2  $\pm$  2.1 days; EBCT performed 90 days pre-SPECT to 86 days post-SPECT) from February 1989 to October 2002. Twelve hundred thirty patients met this criteria.

Patients were then excluded for the following reasons (some patients met  $\geq$ 1 criterion): (1) established coronary artery disease on the basis of history of prior myocardial infarction (MI) or previous percutaneous or surgical revascularization (n = 234); (2) significant valvular heart disease (n = 55); (3) left bundle-branch block or paced ventricular rhythm (n = 27); (4) lack of consent to research participation (n = 25); or (5) incomplete data in the EBCT database before 1995 (n = 134). The final study population consisted of 835 patients, all of whom gave consent to use their data for research purposes.

Demographic and clinical data were collected on each patient at the time of stress SPECT. Age, sex, body mass index (BMI), symptom status (asymptomatic vs chest pain or dyspnea), smoking status, family history of premature coronary artery disease, history of hypercholesterolemia, diabetes, and hypertension were recorded. Chest pain was categorized as typical angina, atypical angina, or noncardiac chest pain.

### Electron beam computed tomography

This methodology has been previously described.<sup>8</sup> All patients underwent 2 consecutive scans approximately 1 minute apart on the same EBCT machine (Imatron C-150, San Francisco, CA) with electrocardiographic triggering at 60% of

the R-R interval. Approximately forty 3-mm-thick slices with 100-millisecond acquisition times were obtained. Imaging was performed without intravenous contrast over 30 to 40 seconds during 1 to 3 breath holds.

The major epicardial arteries were inspected for the presence of calcium. Each scan was interpreted and verified by an experienced radiologist blinded to the patient's clinical care. Semiautomated computer software calculated the calcium score according to the method of Agatston et al for each vessel.<sup>9</sup> Foci of calcific plaque(s) with 3 contiguous pixels  $\geq$ 1 mm<sup>2</sup> in area and peak density  $\geq$ 130 Hounsfield units (HU) were identified for each epicardial vessel. The product of the area and respective density factor (1 = 130-199 HU, 2 = 200-299 HU, 3 = 300-399 HU, and 4 if  $\geq$ 400 HU) constituted the vessel-specific CACS.

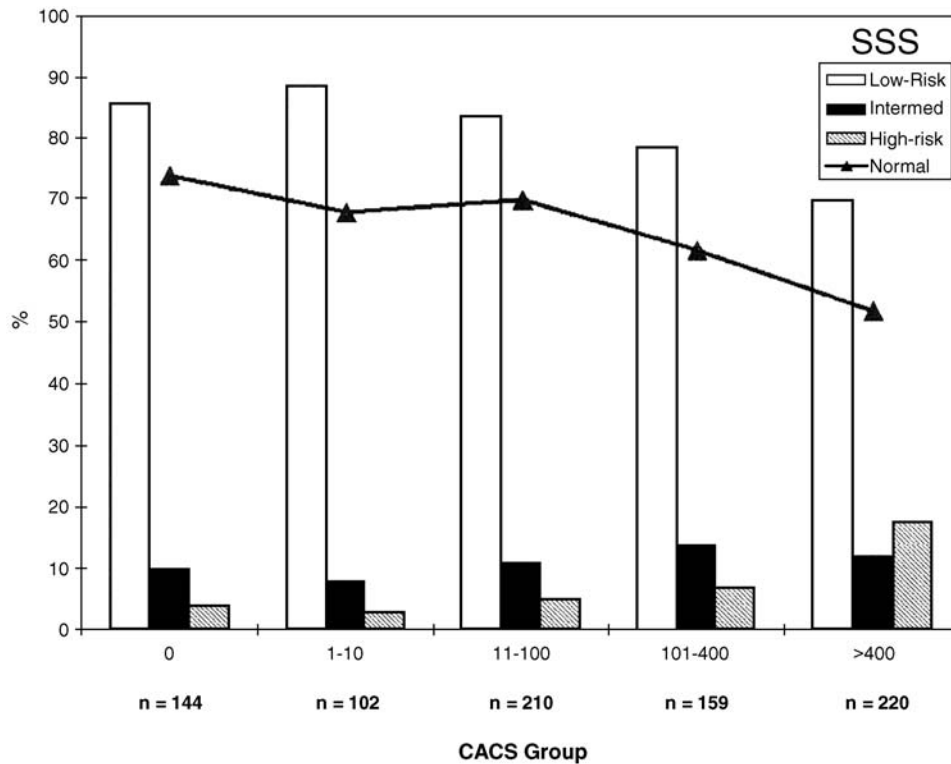
The total CACS was computed as the sum of the calcium scores for all epicardial vessels. Total CACS was stratified into 5 categories: 0 (none), 1 to 10 (minimal), 11 to 100 (mild), 101 to 400 (moderate), and  $>$ 400 (severe), based on previous studies.<sup>5-7</sup> Previous studies have demonstrated that CACS increases with age and varies in prevalence by sex.<sup>10,11</sup> Thus, we also analyzed CACS according to age- and sex-adjusted percentile score derived from a subpopulation of asymptomatic patients in the Rochester Family Heart Study.<sup>12</sup>

### Stress SPECT

Most patients underwent exercise treadmill testing with the Bruce protocol (n = 735, 88.0%). Other stress modalities included treadmill testing with modified exercise protocols (n = 12, 1.4%) or pharmacologic stress tests with adenosine (n = 75, 8.9%), dipyridamole (n = 6, 0.7%), or dobutamine (n = 4, 0.5%). Adenosine, dipyridamole, and dobutamine stress tests were performed according to standard protocols.

The SPECT images were acquired and processed as previously described.<sup>13</sup> Patients imaged with Tl-201 underwent a same-day stress (3-4 mCi Tl-201 based on patient weight injected at peak stress) and delayed imaging (3-4 hours later) protocol. Patients injected with technetium Tc 99m sestamibi underwent either a same-day (approximately 10 mCi technetium Tc 99m rest and 40 mCi technetium Tc 99m peak stress) or 2-day protocol (consisting of approximately 25 mCi technetium Tc 99m injection at both rest and peak stress).

**Figure 1**



Distribution of SSS strata by CACS group ( $P < .001$  for  $3 \times 5 \chi^2$  comparison). The solid line shows the percentage of patients with normal SPECT scans.

Perfusion in each segment on standard views during rest and stress was graded by consensus of 2 experienced observers. Traditionally, our laboratory reports wall segment perfusion based on a 5-point scoring system ranging from 0 (absent perfusion) to 4 (normal). To be consistent with previous studies, SPECT perfusion scores were recoded using a previously described 5-point scoring system: 0(normal), 1 (mildly diminished), 2 (moderately diminished), 3 (severely diminished), and 4 (absent).<sup>13</sup> Mild fixed defects (segment scores of 3 on both rest and stress images) were recoded to 0 (normal) because most mild fixed defects represent soft tissue attenuation.

The summed stress score (SSS) is the total of all segment scores based on a 14-segment short axis model. A normal study is an SSS of 0 (14 segments  $\times$  0 [normal]). The SSS was analyzed as a continuous and categorical variable for risk assessment based upon previously published criteria: SSS 0 to 3 (low risk), SSS 4 to 8 (intermediate risk), and SSS  $>8$  (high risk).<sup>14</sup>

### Outcome measures

All patients, except those who lived outside the United States or Canada, were mailed a survey questionnaire. The primary end point was mortality from any cause. Secondary end points included mortality/nonfatal MI and mortality/nonfatal MI/late coronary revascularization. Percutaneous coronary

**Table II.** Associations of CACS and clinical variables to high-risk SSS

Variable	Univariate		Multivariate	
	$\chi^2$	P	$\chi^2$	P
CACS	12.5	<.001	11.4	<.001
BMI (kg/m <sup>2</sup> )	8.0	.005		
Diabetes mellitus	7.2	.008	4.6	.031
Chest pain class*	6.0	.01	8.7	.003
Symptom status†	2.0	.15		
Hypertension	1.5	.22		
Age	1.2	.28		
Sex	0.8	.37		
Hypercholesterolemia	0.2	.68		
Smoking	0.1	.70		
Family history	0.01	.91		

\*Chest pain classification: 0 = no chest pain, 1 = noncardiac, 2 = atypical, 3 = typical angina.

†Symptomatic (chest pain/dyspnea) versus asymptomatic.

intervention (PCI) or coronary artery bypass grafting (CABG) performed  $\leq 3$  months from SPECT was defined as *early* and  $>3$  months as *late* revascularization.

**Table III.** Univariate associations of CACS, SSS, and clinical variables to outcome

Variable	Death			Death/MI			Death/MI/Late revascularization		
	$\chi^2$	P	HR	$\chi^2$	P	HR	$\chi^2$	P	HR
Diabetes mellitus	28.1	<.001	7.44	19.9	<.001	6.14	18.5	<.001	3.75
CACS (100-unit increase)	23.3	<.001	1.05	19.4	<.001	1.05	19.8	<.001	1.04
Hypertension	16.6	<.001	6.53	11.1	<.001	4.10	15.1	<.001	3.05
SSS	11.1	<.001	1.07	14.7	<.001	1.08	16.9	<.001	1.07
Age (10-y increase)	9.7	.002	1.84	4.4	.04	1.53	5.3	.02	1.38
BMI (kg/m <sup>2</sup> )	8.0	.005	1.09	8.4	.004	1.09	2.6	.11	1.04
Hypercholesterolemia	7.1	.008	0.36	5.6	.02	0.39	1.6	.2	0.7
Family history	6.7	.01	0.33	3.8	.05	0.44	0.7	.39	0.79
Symptom status*	5.0	.03	3.04	2.5	.12	2.01	1.6	.21	1.43
Sex (male)	3.6	.06	0.49	4.9	.03	0.42	0.3	.56	1.21
Chest pain class†	1.6	.21	1.23	2.7	.10	1.34	2.3	.13	1.21
Smoking	1.0	.33	1.45	0.1	.75	1.13	0.6	.45	1.23

HR, Hazard ratio.

\*Symptomatic (chest pain/dyspnea) versus asymptomatic.

†Chest pain class: 0 = no chest pain, 1 = noncardiac, 2 = atypical, 3 = typical angina.

Medical records/autopsy/coroner reports and/or death certificates were used to verify mortality. Review of all records was performed by 2 persons (an experienced data abstracter and a physician) blinded to EBCT CACS and SPECT perfusion data to confirm MI (American College of Cardiology/European Society of Cardiology definition), PCI, and CABG.

Follow-up was 80.2% complete at a mean of  $4.8 \pm 3.2$  years. Patients were excluded from follow-up analyses for the following reasons: (1) address of record outside the United States or Canada ( $n = 80$ , 9.6%), (2) refused consent to participate in the follow-up portion of the study ( $n = 54$ , 6.5%), and (3) current mailing address not known ( $n = 31$ , 3.7%). Excluding patients from outside the United States or Canada, follow-up was 88.8% complete.

### Statistical analysis

Descriptive data were summarized with count and percentage data or as mean  $\pm$  SD for continuous variables. The correlation of CACS results for the 2 serial EBCT scans was excellent ( $r^2=0.96$ ,  $P < .0001$ ); we chose the higher CACS in all analyses. The correlation between CACS and SSS was tested with the Spearman correlation coefficient. Univariate logistic regression analysis was performed to test the associations of clinical risk variables with high-risk SPECT results (ie, SSS  $>8$ ). The  $\chi^2$  test was applied for dichotomous variables and the Wilcoxon rank-sum test for continuous variables. Multivariable logistic regression analysis identified variables with the strongest independent association with high-risk SPECT in a stepwise fashion.

Kaplan-Meier methods were used to estimate mortality and combined end points. For the end point of mortality/nonfatal MI, patients who underwent any coronary revascularization were censored. For the end point of mortality/nonfatal MI/late revascularization, patients who underwent early coronary revascularization were censored. Cox regression analysis was used to assess the relative risk of CACS and SSS (both as continuous variables) to the occurrence of the

various end points. The number of clinical covariates entered into these models was limited to avoid overfitting. Differences between Kaplan-Meier event-free survival curves were assessed with the log rank test statistic.

The SAS Proprietary Software Release 8.2 (1999-2000, SAS Institute, Inc, Cary, NC) was used for all analyses.

## Results

### Patient characteristics (Table I)

Patients with severe CACS (ie,  $>400$ ) were significantly more likely to be male; be older; and have a clinical history of diabetes mellitus, smoking, hypercholesterolemia, and systemic hypertension (Table I). Approximately half of the study group was asymptomatic (49%). These patients were more likely to have severe CACS (reflecting selective referral to SPECT).

### EBCT and SPECT results

The EBCT CACS ranged from 0 to 9388 (median 69.3). The distribution of patients by CACS group was weighted toward more abnormal studies: 0 ( $n = 144$ , 17%), 1 to 10 ( $n = 102$ , 12%), 11 to 100 ( $n = 210$ , 25%), 101 to 400 ( $n = 159$ , 19%), and  $>400$  ( $n = 220$ , 26%). The SPECT SSS ranged from 0 to 40 (median 0), but was dominated by low-risk studies: low risk ( $n = 671$  [80.3%], including 537 [64.3%] patients with normal SPECT), intermediate risk ( $n = 95$  [11.4%]), and high risk ( $n = 69$  [8.3%]). The overall correlation of CACS to SSS was weak but statistically significant ( $r = +0.19$ ,  $P < .001$ ).

The distribution of SPECT SSS risk categories by CACS group is depicted in Figure 1. The percentage of high-risk SPECT (SSS  $>8$ ) increased modestly with

higher CACS group, but 4% of patients with normal EBCT and only 18% with severe CACS (>400) had high-risk SPECT. Conversely, 70% of patients with severe CACS had low-risk SPECT. The median CACS percentile score was 75% (25%-75% interquartile range 49.3-90.1). The distribution of SSS strata by percentile score was similar to that observed with total CACS; a greater percentage of high-risk scans was noted in the higher-percentile score groups, but even in patients with severe percentile score (ie, PS>75%), 59% of patients had normal SPECT.

### Association of clinical risk variables and CACS to high-risk SPECT

We tested the association of 10 clinical risk variables and CACS with high-risk SPECT (Table II). By univariate analysis, CACS demonstrated the strongest association. Body mass index, diabetes mellitus, and chest pain class (none, noncardiac pain, atypical angina, typical angina) were also associated with high-risk SPECT.

Although the presence or absence of symptoms was not associated with high-risk SPECT, symptomatic patients with severe CACS were significantly more likely to have high-risk SPECT (59% vs 41%,  $P = .003$ ).

In multivariate analysis, CACS (adjusted  $\chi^2 = 11.4$ ,  $P < .001$ ), diabetes mellitus ( $\chi^2 = 4.6$ ,  $P = .031$ ), and chest pain class ( $\chi^2 = 8.7$ ,  $P = .003$ ) were independently associated with high-risk SPECT.

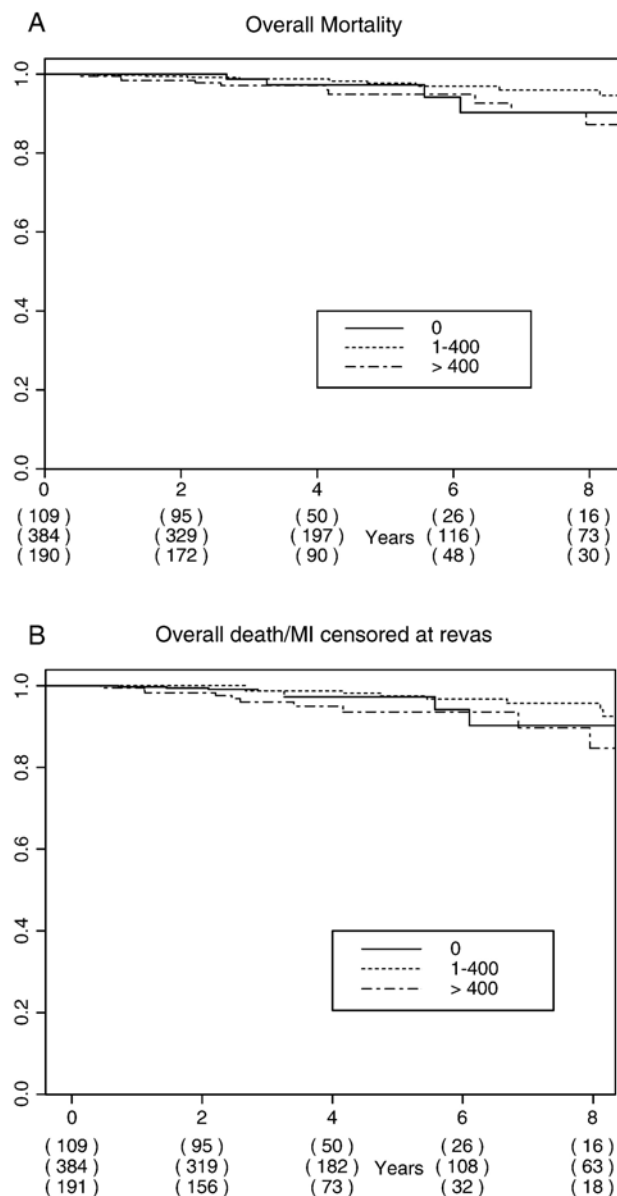
In a multivariate model without CACS, BMI ( $\chi^2 = 5.7$ ,  $P = .017$ ), diabetes mellitus ( $\chi^2 = 4.7$ ,  $P = .03$ ), and chest pain class ( $\chi^2 = 6.3$ ,  $P = .01$ ) were independently associated with high-risk SPECT. However, after adjusting for BMI, diabetes mellitus, and chest pain class, the addition of CACS to the model remained independently associated with high-risk SPECT ( $\chi^2 = 10.9$ ,  $P < .001$ ).

### Prognosis

Compared with the 670 patients who were included, the 165 patients who were excluded from the follow-up analysis were younger (52.8 years vs 55.3 years,  $P = .004$ ) and had lower SSS (55 vs 54,  $P = .006$ ), lower SRS (1 vs 2,  $P = .01$ ), and lower CACS (245 vs 418,  $P < .001$ ). There were no other significant clinical differences.

Of the 670 patients in the follow-up analyses, there were 29 deaths, 6 nonfatal MIs, 22 early PCI/CABG, and 35 late PCI/CABG. The CACS, SSS, and multiple clinical variables (Table III) were significantly associated with adverse outcomes. Patients with severe CACS compared with patients with lower CACS or no calcium tended to have lower 8-year survival (Figure 2, A,  $P = .09$ ). Annual mortality over the next 5 years was 0.5% and 1.0% in patients with CACS <400 and >400, respectively. The end point of death/MI showed a similar but stronger trend ( $P = .04$ ). Risk categories of SSS were

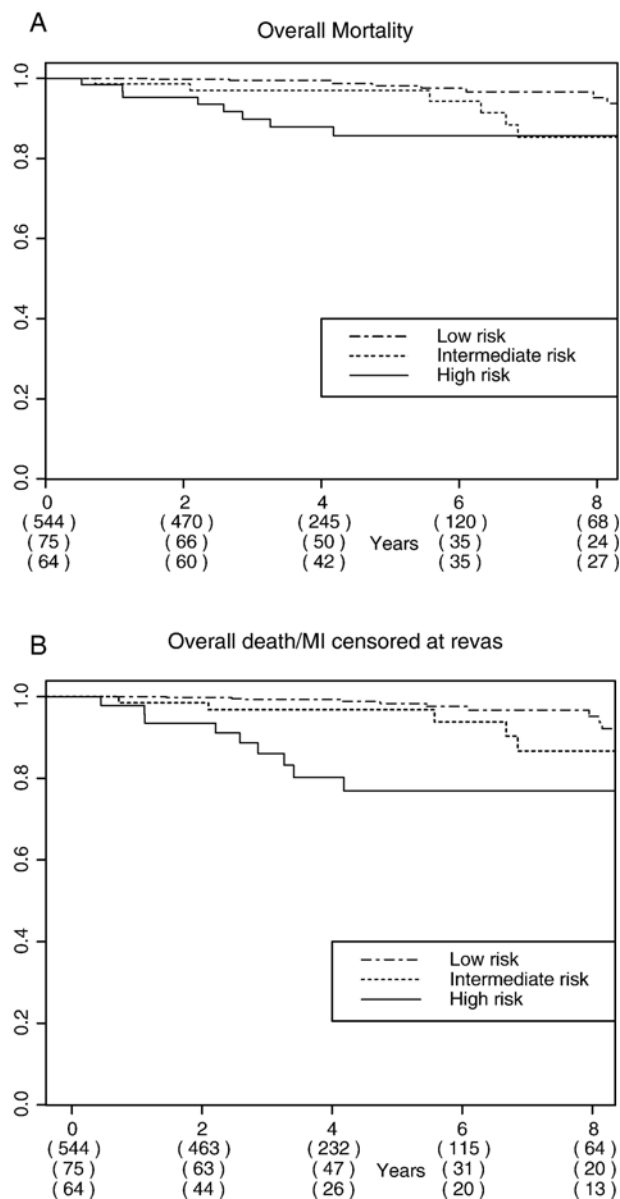
Figure 2



**A**, Survival stratified by CACS ( $P = .09$  by log rank test). **B**, Survival free of death/MI stratified by CACS ( $P = .04$  by log rank test).

associated with overall mortality (Figure 3, A,  $P < .001$ ; death/MI, Figure 3, B,  $P \leq .001$ ). Patients with high-risk SSS had a 2.9% annual mortality over the next 5 years in contrast to 0.6% for intermediate-risk SSS and 0.4% for low-risk SSS.

On multivariable analysis, considering them as continuous variables, CACS ( $\chi^2 = 7.8$ ,  $P = .005$ ) and SSS ( $\chi^2 = 6.9$ ,  $P = .009$ ) were independently associated

**Figure 3**

**A**, Survival stratified by SSS ( $P = .001$  by log rank test). **B**, Survival free of death/MI stratified by SSS ( $P < .001$  by log rank test).

with mortality, as well as with death/MI and death/MI/late revascularization (Table IV). The presence or absence of symptoms was not significant in any of these analyses.

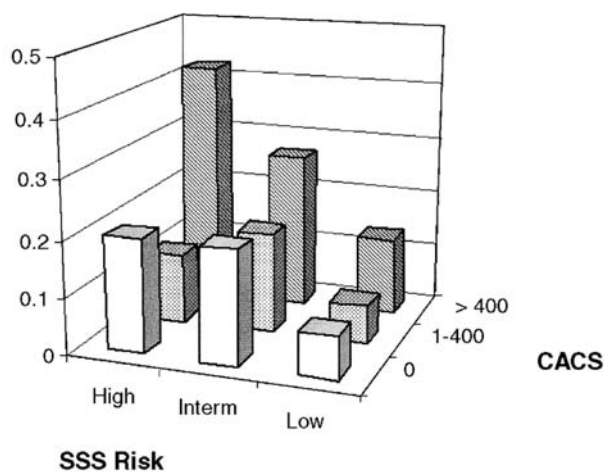
Patients with the combination of CACS and high-risk SPECT had a higher 10-year mortality (42%) than patients in lower CACS and lower-risk SPECT groups (Figure 4).

**Table IV.** Independent associations of CACS and SSS to outcome

Variable	Death		Death/MI		Death/MI/Late revascularization	
	$\chi^2*$	<i>P</i>	$\chi^2*$	<i>P</i>	$\chi^2\dagger$	<i>P</i>
SSS	6.9	.009	11.4	<.001	12.8	<.001
CACS	7.8	.005	4.6	.03	7.0	.008

\*Adjusted for diabetes and hypertension.

†Adjusted for diabetes, hypertension, and hypercholesterolemia.

**Figure 4**

Ten-year rates of death stratified by CACS and SSS.

#### Analysis in asymptomatic patients

The distribution of CACS in asymptomatic patients was also weighted toward more abnormal studies: 0 ( $n = 53$ , 13.0%), 1 to 10 ( $n = 39$ , 9.6%), 11 to 100 ( $n = 98$ , 24%), 101 to 400 ( $n = 81$ , 19.9%), and  $>400$  ( $n = 137$ , 33.6%). This subgroup of patients had a similar predominance of low-risk SPECT studies: low risk ( $n = 350$ , 86%), intermediate risk ( $n = 30$ , 7%), and high risk ( $n = 28$ , 7%). Among asymptomatic patients with CACS  $<100$ , 90% had low-risk SPECT and 4% had high-risk SPECT. Among patients with severe CACS, 80.3% had low-risk SPECT and 11.7% had high-risk SPECT.

In this subgroup, there were only 5 deaths, 2 nonfatal MIs, and 13 late revascularizations; annual mortality was only 0.4% over the next 5 years. Only CACS predicted mortality ( $\chi^2 = 5.2$ ,  $P = .02$ ).

Annual event rates for the next 5 years for asymptomatic patients with severe CACS were 0.4% for death,

0.9% for death/nonfatal MI, and 2.1% for death/nonfatal MI/late revascularization. Annual event rates for the next 5 years for asymptomatic patients with high-risk SSS were 1.0% for death, 2.3% for death/nonfatal MI, and 3.7% for death/nonfatal MI/late revascularization.

Asymptomatic patients with both severe CACS and high-risk SPECT ( $n = 15$ ) had no deaths during follow-up.

## Discussion

This study demonstrates that both EBCT CACS and SSS by SPECT were independently associated with all-cause mortality, as well as the secondary end points of death/MI and death/MI/late revascularization. Patients with both severe CACS and high-risk SPECT had higher 10-year mortality than any other patient subgroup. There was a statistically significant but weak correlation between increasing CACS by EBCT and SSS by SPECT. Discordant findings were present at both ends of the CACS spectrum. For patients with no calcification, 4% had high-risk SPECT; for patients with CACS  $>400$ , 70% had low-risk SPECT. Nonetheless, EBCT CACS was independently associated with high-risk SPECT after adjusting for clinical variables.

The weak correlation between CACS and SSS is likely related to the different types of information that EBCT and SPECT provide.<sup>15</sup> Coronary calcification is a highly sensitive indicator of the overall burden of coronary artery atherosclerosis but is much less specific for hemodynamically significant coronary artery stenoses. Conversely, stress SPECT is suited for detecting hemodynamically significant coronary artery lesions; but non-flow-limiting lesions may be missed.

### Prior studies

Three studies have compared stress SPECT and EBCT.<sup>5-7</sup> In the study of He et al of 411 primarily asymptomatic patients, 46% of patients (comparable with the 48% of patients in our study) with severe CACS had an abnormal SPECT.<sup>5</sup> Anand et al prospectively performed stress SPECT on 220 asymptomatic patients with CACS  $\geq 100$  and found that 18% and 45% of patients with moderate and severe CACS, respectively, had inducible ischemia. In our study, 21% and 30% of patients with moderate and severe CACS, respectively, had an intermediate- or high-risk SSS. In a study of 1195 patients (51% asymptomatic) who underwent both SPECT and EBCT or multislice CT, Berman et al reported that 13% of patients with CACS  $\geq 400$  had ischemic SPECT studies (in our study, 18% of patients with severe CACS had high-risk SPECT).<sup>7</sup>

Overall, results in this study are similar to previous reports with the exception of the prevalence of abnormal SPECT in patients with no calcification. In these patients, Berman et al<sup>7</sup> reported that 0.4% had moderate or severe ischemia and He et al<sup>5</sup> reported that

no patients had abnormal SPECT. In our study, 4% of patients with CACS = 0 had high-risk SPECT. However, because this 4% prevalence only represented 6 patients out of 144, it might reflect the play of chance.

### Prognosis

The prognostic ability of stress SPECT has been well established.<sup>16</sup> Several studies have now demonstrated that EBCT CACS also provides prognostic information.<sup>17-19</sup> The most original aspect of this study is the assessment of the prognostic value of both EBCT and SPECT performed in the same patient. In this study, CACS and SSS were independently associated with patient outcomes. The strength of the association with mortality was similar for each variable. The 10-year mortality rate for patients with both severe CACS and high-risk SPECT was 42%, compared with 27% and 31% for patients with only severe CACS and only high-risk SPECT, respectively.

The SSS tended to have a stronger association than CACS with the combined end points. However, only CACS was predictive of mortality in asymptomatic patients. There were only 5 deaths in this subgroup, which had an annual mortality of only 0.4% over the next 5 years. Given this low mortality rate, it will be difficult to demonstrate independent prognostic significance for these 2 variables without a much larger study population. Adequate power would likely require at least 20 deaths. This would require a study population of at least 1632 patients with a similar length of follow-up.

### Limitations

The major limitation is the retrospective study design. The study group was highly selected; the results may not be applicable to other patient populations. There was verification or posttest referral bias<sup>20</sup>; patients with elevated CACS were more likely to have undergone stress SPECT. The CACS is subject to interscan variability, especially in patients with low scores.<sup>21</sup> However, the correlation in CACS between serial EBCTs in our patient population was excellent ( $r^2 = 0.96$ ,  $P < .0001$ ).

Moreover, even in the presence of a severe CACS, a high-risk SSS, or both, the annual mortality rate in asymptomatic patients remained low. Such patients certainly merit appropriate risk factor modification. However, these data suggest that it is unlikely that any strategy of additional testing and/or treatment will improve their survival further.

We used a 14-segment model rather than the 20-segment model used by others<sup>7</sup> to measure SSS. However, this model has shown prognostic utility in multiple previous studies from our laboratory.

Lastly, follow-up data were unavailable in 19.8% of patients, although almost one half of these lived outside

North America. The excluded patients had significantly less abnormality on both EBCT and SPECT.

### Conclusions

Electron beam computed tomography and SPECT provide different but complementary types of information with respect to diagnosis and risk stratification. Coronary artery calcium score is associated with SPECT SSS, but the strength of the correlation is weak. Stress SPECT in patients with CACS >0 yields normal results in most patients, even those with CACS  $\geq$ 400. By multivariate analyses, CACS and SSS were comparable for prediction of mortality; SSS was a stronger variable for predicting combined end points. However, only CACS predicted mortality in asymptomatic patients in whom the mortality was low even for CACS >400. Further prospective studies of large cohorts of patients are necessary to define the use of EBCT testing.

### References

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