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Cardiac Imaging

The Coronary Artery Calcium Score and Stress Myocardial Perfusion Imaging Provide Independent and Complementary Prediction of Cardiac Risk

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Objectives This study sought to examine the relationship between coronary artery calcium score (CACS) and single-photon emission computed tomography (SPECT) results for predicting the short- and long-term risk of cardiac events.

Background The CACS and SPECT results both provide important prognostic information. It is unclear whether integrating these tests will better predict patient outcome.

Methods We followed-up 1,126 generally asymptomatic subjects without previous cardiovascular disease who had a CACS and stress SPECT scan performed within a close time period (median 56 days). The median follow-up was 6.9 years. End points analyzed were total cardiac events and all-cause death/myocardial infarction (MI).

Results An abnormal SPECT result increased with increasing CACS from <1% (CACS ≤10) to 29% (CACS >400) ($p < 0.001$). Total cardiac events and death/MI also increased with increasing CACS and abnormal SPECT results ($p < 0.001$). In subjects with a normal SPECT result, CACS added incremental prognostic information, with a 3.55-fold relative increase for any cardiac event (2.75-fold for death/MI) when the CACS was severe (>400) versus minimal (≤10). Separation of the survival curves occurred at 3 years after initial testing for all cardiac events and at 5 years for death/MI.

Conclusions The CACS and SPECT findings are independent and complementary predictors of short- and long-term cardiac events. Despite a normal SPECT result, a severe CACS identifies subjects at high long-term cardiac risk. After a normal SPECT result, our findings support performing a CACS in patients who are at intermediate or high clinical risk for coronary artery disease to better define those who will have a high long-term risk for adverse cardiac events. (J Am Coll Cardiol 2009;54:1872–82) © 2009 by the American College of Cardiology Foundation

The coronary artery calcium score (CACS) severity, defined by noncontrast cardiac computed tomography, is known to predict subsequent patient outcome (1,2). Likewise, stress-induced perfusion defects on single-photon emission computed tomography (SPECT) identify low- and high-risk groups among heterogeneous populations of both symptomatic (3) and asymptomatic (4) patients. However, both testing modalities are imprecise in risk stratification in that patients with a normal stress SPECT result still have a low but well-defined annual risk of cardiac death and/or myocardial infarction (MI), whereas most patients with a moderate or severe CACS do not develop a subsequent cardiac event.

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Thus, the purpose of this study was to examine whether integration of CACS results with those of stress SPECT could improve risk prediction in a group of generally asymptomatic patients without clinically apparent coronary artery disease (CAD).

Methods

Study population. From December 1995 to May 2006, 1,175 subjects without a previous history of CAD underwent both a CACS determination by electron beam computed tomography and stress SPECT imaging (within a median of 56 days) for clinically indicated reasons. The clinically indicated reason for performing a CACS was to determine the presence and extent of atherosclerotic plaque burden among asymptomatic subjects with risk factors for CAD and in those with atypical chest pain symptoms and/or a normal SPECT study result. The SPECT study was performed to evaluate chest pain symptoms and/or to determine whether myocardial ischemia was present in

subjects who had an abnormal CACS result. No one had coronary revascularization between tests. Of these 1,175 subjects, 1,126 (95.8%) were included in the final risk analyses because they had complete clinical follow-up and also had assessment of their vital status through the Social Security Death Index.

Electron beam computed tomography. Electron beam computed tomography was performed on an Imatron C-150 (Imatron, Inc., South San Francisco, California) computed tomography scanner with a 100-ms exposure time and a 30-cm field of view. With electrocardiographic (ECG) gating, 32 consecutive images were obtained in diastole at 3-mm intervals. Coronary calcification was defined as a hyperattenuating lesion of >130 Hounsfield units with an area equal to 3 pixels (>1.02 mm^2). The CACS was calculated using the standard Agatston criteria (5) and was reported as normal (CACS ≤10), mild (CACS 11 to 100), moderate (CACS 101 to 400), or severe (CACS >400) (6).

Stress SPECT imaging. Stress and rest SPECT imaging were performed with thallium-201 (67%), technetium-99m sestamibi (21%), or technetium-99m tetrofosmin (12%) according to standard American Society of Nuclear Cardiology guidelines (7). Most subjects (84%) underwent exercise stress, but 14.1% received adenosine and 1.9% had dobutamine using standard infusion protocols (7). Medications such as nitrates and beta-blockers were stopped at least 12 h before testing. An ischemic ECG response was defined as a ≥1-mm ST-segment depression occurring >80 ms after the J point. All exercise ECGs were interpreted by researchers who had no knowledge of CACS or SPECT results. The Duke treadmill score was calculated in all subjects undergoing exercise stress and was defined as low (≥5), intermediate (−10 to 4), or high (≤−11) risk (8).

The SPECT images were visually interpreted in all 3 standard projections, along with the gated SPECT and raw image data to assess for study normalcy/abnormalcy and to determine whether perfusion defects were fixed, partially reversible, or completely reversible. Quantitative SPECT was performed by a single investigator (J.J.M.) using a previously validated automated program to determine the extent and severity of left ventricular (LV) perfusion defect size (PDS) and the extent of scintigraphic scar and ischemia (9). The ischemic PDS was calculated based on the change in counts from the stress to the rest images. A stress-induced total PDS ≥15% or an ischemic PDS ≥10% defined high risk for cardiac events (9,10).

Follow-up and outcomes. Clinical follow-up was prospectively obtained in years 1998, 2002, 2005, and 2008 by questionnaire, telephone interviews, and review of medical records in 1,126 of 1,175 subjects (95.8%). Median follow-up was 6.9 years (25th and 75th percentiles, 4.7 and 8.8 years). All events were corroborated by a physician blinded to CACS and SPECT results. The cause of death was determined by review of medical records, death certificates, and/or telephone interviews with family members or referring physicians. In May 2008, all subjects had assessment of their vital status through the Social Security Death Index.

The total cardiac events of cardiac death, nonfatal MI, and coronary revascularization with bypass surgery or percutaneous approaches were defined as primary events. The events of all-cause mortality and nonfatal MI were defined as secondary events. Cardiac death was defined as death of any cardiac cause, including a fatal MI, sudden arrhythmic death, or heart failure. An MI was defined by standard clinical, ECG, and enzymatic criteria (9,11).

Abbreviations and Acronyms

CACS = coronary artery calcium score
CAD = coronary artery disease
ECG = electrocardiogram/electrocardiographic
LV = left ventricular
MI = myocardial infarction
PDS = perfusion defect size
SPECT = single-photon emission computed tomography

Statistical analysis. Continuous variables are expressed as mean ± SD, and categorical variables are expressed as frequency (percentage). Independent 2-group hypothesis testing was performed using Wilcoxon rank sum (Mann-Whitney *U*) tests to compare central tendencies for clinical variables and CACS results in subjects who did or did not have clinical follow-up data. Baseline characteristics of the population were examined by CACS category and SPECT results. The Framingham risk score was calculated in all subjects based on standard criteria (12). Because absolute cholesterol and blood pressure measurements were not available, we calculated the Framingham risk score using a conservative definition for hyperlipidemia (cholesterol 200 to 239 mg/dl) and hypertension (systolic blood pressure 140 to 159 mm Hg). The Kruskal-Wallis analysis of variance was used to identify significant differences in central tendencies of continuously scaled variables over CACS categories and SPECT results. Contingency table analysis was performed using chi-square tests. Kaplan-Meier analysis of primary and secondary events was based on discrete CACS categories (0 to 10, 11 to 100, 101 to 400, and >400) and SPECT categories (normal, total LV PDS dichotomized at 15%, ischemic PDS dichotomized at 10%). The date of the first test (either electron beam tomography or SPECT) was used as time 0. Two-sided log-rank tests were used to determine significance. Univariate and multivariate Cox proportional hazards models were used to identify the association between time-to-event and baseline clinical characteristics and the CACS and SPECT results. The clinical characteristics included in the model were age, sex, smoking status, history of hyperlipidemia, history of hypertension, chest pain, abnormal resting ECG, family history of CAD and diabetes mellitus, and whether exercise was used as the stress modality with SPECT. Interactions between CACS, SPECT, and baseline characteristics were assessed for subjects with varying CACS and SPECT time intervals. The proportionality assumption of the Cox models was assessed by including time-dependent interactions of each covariate with survival time in the model. There was no evidence of violation of

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this assumption for any covariate. Multivariate likelihood ratio tests were performed to assess entry of clinical, SPECT, and CACS variables into Cox proportional hazard models. A type I error rate of alpha = 0.05 was used for all hypothesis tests. The relationship between CACS and SPECT results was determined in the 717 subjects who underwent both tests within 6 months. All statistical analyses were performed with Stata version 10 (Stata Statistical Software, College Station, Texas).

Results

Baseline characteristics. The baseline characteristics are shown in Table 1. For the entire cohort of 1,175 subjects, the mean age was 58.1 ± 9.8 years, 73% were male, and 10% were diabetic. Most subjects (83%) were entirely asymptomatic at the time of initial baseline testing, whereas 17% had various atypical chest pain symptoms. The mean number of cardiac risk factors was 2.05 ± 1.08. The Framingham risk score was low in 191 subjects (16.2%), intermediate in 915 subjects (77.9%), and high in 69 subjects (5.9%). The median CACS was 127, with interquartile ranges as follows: first (0 to 14), second (15 to 127), third (128 to 440), and fourth (441 to 6,413). An abnormal SPECT result was observed in 151 of 1,175 subjects (13%); 44 (4.0%) had a total PDS ≥15% and 35 (3.0%) had an ischemic PDS ≥10%. In the 151 subjects with an abnormal SPECT result, 21 (14%) had a fixed defect, 94 (62%) had a partially reversible defect, and 36 (24%) had a completely reversible defect.

The baseline characteristics of subjects with and without clinical follow-up were not significantly different, except that those with follow-up were slightly older (58.4 years of age vs. 52.4 years of age, p = 0.001), had a higher Framingham risk score (11.4 ± 6.6 vs. 7.1 ± 3.5, p < 0.001), and were more likely to have hypertension (52% vs. 37%, p = 0.04).

Baseline characteristics in subjects with follow-up by CACS and SPECT category. Subjects with a higher CACS were older, were more frequently male, and had a greater frequency of diabetes and hypertension (Table 2). The mean number of cardiac risk factors and the Framingham risk score significantly increased with increasing CACS. In subjects undergoing exercise stress, the Duke treadmill score did not significantly differ across CACS categories.

As shown in Table 3, subjects with a large total (≥15%) or ischemic (≥10%) PDS were older, were more frequently male, and had a higher incidence of diabetes and hypertension compared with those with a normal SPECT result.

Table 1 Baseline Demographic, CACS, and Stress SPECT Results

	Total (n = 1,175)	Follow-Up (n = 1,126)	No Follow-Up (n = 49)	p Value
Age, yrs	58.1 ± 9.8	58.4 ± 9.8	52.4 ± 10.7	0.001
Male sex	855 (73%)	816 (73%)	39 (80%)	0.36
Cardiac risk factors				
Diabetes	117 (10%)	114 (10%)	3 (6%)	0.5
Hypertension	601 (51%)	583 (52%)	18 (37%)	0.04
Hyperlipidemia	650 (55%)	624 (55%)	26 (53%)	0.86
Smoking history	558 (47%)	532 (47%)	26 (53%)	0.52
Family history of CAD	488 (42%)	473 (42%)	15 (31%)	0.15
Number of cardiac risk factors	2.05 ± 1.08	2.06 ± 1.08	1.8 ± 1.08	0.12
Framingham risk score	11.2 ± 6.5	11.4 ± 6.6	7.1 ± 3.5	<0.001
Atypical chest pain	203 (17%)	199 (18%)	4 (8%)	0.13
CACS, median (25th–75th percentile)	127 (15–440)	127 (14–442)	138 (15–358)	0.99
CACS results				
0–10	276 (24%)	266 (24%)	10 (20%)	0.73
11–100	250 (21%)	240 (21%)	10 (20%)	0.98
101–400	334 (28%)	316 (28%)	18 (37%)	0.25
>400	315 (27%)	304 (27%)	11 (22%)	0.59
Ischemic exercise ECG	122 (10%)	116 (12%)	6 (12%)	0.84
Abnormal stress SPECT	151 (13%)	149 (13%)	2 (4%)	0.1
Fixed defect	21 (2%)	21 (2%)	0 (0%)	
Partially reversible defect	94 (8%)	93 (8%)	1 (2%)	
Completely reversible defect	36 (3%)	35 (3%)	1 (2%)	
Quantitative SPECT results				
Total PDS (% LV)	1.89 ± 5.8	1.9 ± 5.9	1.5 ± 5.8	0.97
Ischemic PDS (% LV)	0.8 ± 3.1	0.8 ± 3.2	0.8 ± 4.7	0.66
Total PDS ≥15%	44 (4%)	43 (4%)	1 (2%)	0.8
Ischemic PDS ≥10%	35 (3%)	34 (3%)	1 (2%)	0.97

CACS = coronary artery calcium score; CAD = coronary artery disease; ECG = electrocardiogram; LV = left ventricular; PDS = perfusion defect size; SPECT = single-photon emission computed tomography.

Table 2 Baseline Demographic and Stress Test Differences by CACS Severity in Subjects With Follow-Up

	CACS Severity Groups				
	0–10 (n = 266)	11–100 (n = 240)	101–400 (n = 316)	>400 (n = 304)	p Value
Mean CACS	1 ± 2	49 ± 26	210 ± 81	1,082 ± 832	<0.001
Age, yrs	54 ± 9.7	56 ± 9.6	59.6 ± 8.2	62.5 ± 9.6	0.0001
Male sex	135 (51%)	169 (70%)	254 (80%)	258 (85%)	<0.001
Cardiac risk factors					
Diabetes	11 (4%)	27 (11%)	36 (11%)	40 (14%)	0.002
Hypertension	111 (42%)	113 (47%)	172 (54%)	187 (62%)	<0.001
Hyperlipidemia	130 (49%)	137 (57%)	184 (58%)	173 (57%)	0.1
Smoking history	119 (45%)	103 (43%)	156 (49%)	154 (51%)	0.22
Family history of CAD	116 (44%)	91 (38%)	129 (41%)	137 (45%)	0.35
Mean number of risk factors	1.83 ± 1.0	1.96 ± 1.0	2.14 ± 1.1	2.27 ± 1.1	<0.001
Framingham risk score	8.01 ± 4.3	10.1 ± 6.2	12.4 ± 6.5	14.2 ± 7.1	<0.001
Low	75 (28%)	52 (22%)	26 (8%)	20 (7%)	
Intermediate	189 (71%)	179 (75%)	267 (84%)	249 (82%)	
High	2 (1%)	9 (4%)	23 (7%)	35 (12%)	
Atypical chest pain	83 (31%)	41 (17%)	44 (14%)	32 (11%)	0.001
Exercise stress with SPECT	229 (86%)	205 (85%)	274 (87%)	238 (78%)	0.01
Duke treadmill score group*					0.33
Low (n = 795)	190 (83%)	187 (91%)	231 (84%)	187 (79%)	
Intermediate (n = 143)	38 (16%)	17 (8%)	43 (16%)	45 (19%)	
High (n = 8)	1 (1%)	1 (1%)	0 (0%)	6 (2%)	

*Group consists of 946 subjects who had treadmill exercise as part of their SPECT study.
Abbreviations as in Table 1.

The mean number of cardiac risk factors and the Framingham risk score significantly increased based on total and ischemic PDS. Most of the 977 subjects (83.2%) with a normal SPECT result had either an intermediate (78.3%) or a high (4.9%) Framingham risk score.

SPECT results and CACS severity. The prevalence of an abnormal SPECT result increased significantly with the CACS ($p < 0.001$). Although an abnormal SPECT result was seen in <2% of subjects with a CACS ≤100, this increased to 9.8% and 31% among those with CACS 101 to

Table 3 Baseline Demographic and Stress Test Differences by SPECT Results in Subjects With Follow-Up

	Normal (n = 977)	PDS <15% (n = 106)	PDS ≥15% (n = 43)	p Value	IPDS <10% (n = 115)	IPDS ≥10% (n = 34)	p Value*
Age, yrs	57.7 ± 9.6	62.4 ± 10	65 ± 8.7	<0.001	62.8 ± 9.8	64 ± 9.1	<0.001
Male sex	684 (70%)	93 (88%)	39 (91%)	<0.0001	101 (88%)	31 (91%)	<0.0001
Cardiac risk factors							
Diabetes	89 (9%)	15 (14%)	10 (23%)	0.004	15 (13%)	10 (29%)	<0.0001
Hypertension	492 (50%)	62 (59%)	29 (67%)	0.031	69 (60%)	22 (65%)	0.046
Hyperlipidemia	540 (55%)	57 (54%)	27 (63%)	0.59	60 (52%)	24 (71%)	0.16
Smoking history	451 (46%)	63 (59%)	18 (42%)	0.11	64 (56%)	17 (50%)	0.23
Family history of CAD	410 (41%)	48 (45%)	15 (35%)	0.51	52 (45%)	11 (32%)	0.41
Mean number of risk factors	2.03 ± 1.08	2.31 ± 1/08	2.30 ± 1.17	0.01	2.26 ± 1.08	2.47 ± 1.19	0.008
Framingham risk score	10.8 ± 6.2	14.4 ± 7.0	17.3 ± 8.1	<0.001	14.6 ± 7.0	17.6 ± 8.5	<0.001
Low	164 (17%)	7 (7%)	2 (5%)		7 (6%)	2 (6%)	
Intermediate	765 (78%)	88 (83%)	31 (72%)		95 (83%)	24 (71%)	
High	48 (5%)	11 (10%)	10 (23%)		13 (11%)	8 (23%)	
Atypical chest pain	183 (19%)	11 (10%)	5 (12%)	0.06	14 (12%)	2 (6%)	0.04
Exercise stress with SPECT	843 (86%)	77 (73%)	26 (61%)	<0.001	82 (71%)	21 (62%)	0.0001
Duke treadmill score group†				<0.0001			0.005
Low (n = 795)	715 (84%)	58 (75%)	22 (85%)		65 (79%)	15 (71%)	
Intermediate (n = 143)	124 (15%)	15 (20%)	4 (15%)		14 (17%)	5 (24%)	
High (n = 8)	4 (1%)	4 (5%)	0 (0%)		3 (4%)	1 (5%)	

*Normal SPECT versus IPDS <10%, IPDS >10%. †Group consists of 946 subjects who had treadmill exercise as part of their SPECT study.
IPDS = ischemic perfusion defect size; other abbreviations as in Table 1.

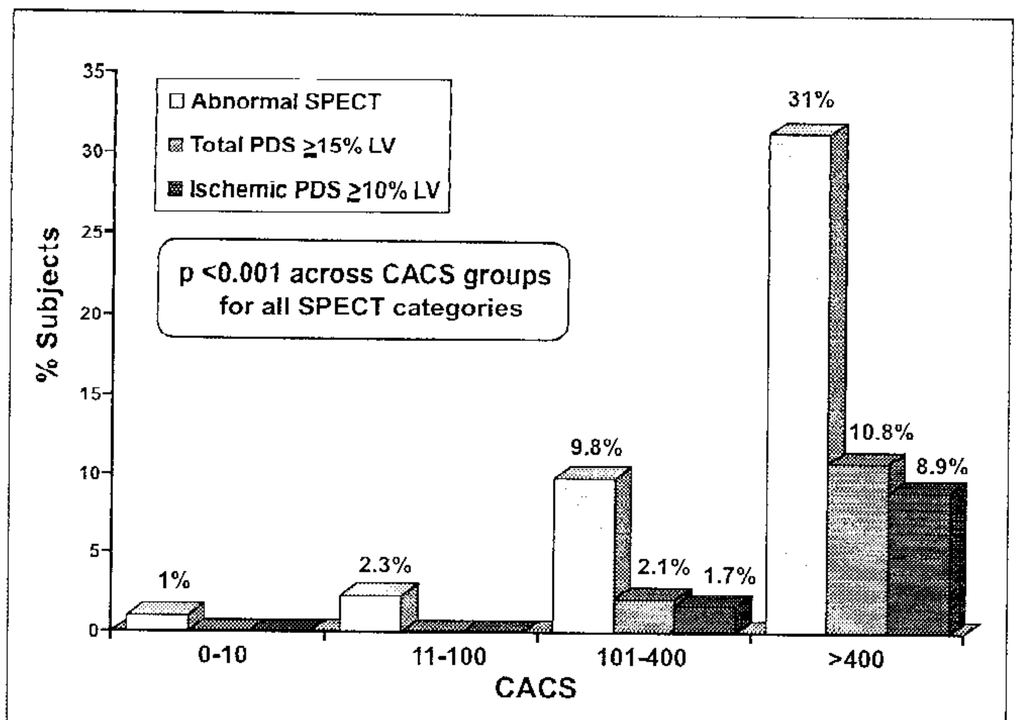

Figure 1 **Relation Between CACS and SPECT Results**

Relation between coronary artery calcium score (CACS) severity and stress single-photon emission computed tomography (SPECT) results in 717 subjects who underwent both tests within 6 months. The percentage of subjects with an abnormal SPECT result ($p < 0.001$) and those with a large stress-induced total (≥15%) and ischemic (≥10%) left ventricular (LV) perfusion defect size (PDS) ($p < 0.001$) significantly increased with increasing CACS severity.

400 and >400, respectively ($p < 0.001$). No one with a CACS ≤100 had a high-risk SPECT profile based on the stress-induced total or ischemic LV PDS, but this significantly increased as the CACS increased from moderate (2.1% and 1.7%) to severe (10.8% and 8.9%), respectively ($p < 0.001$) (Fig. 1).

Cardiac events. Over a median follow-up of 6.9 years, there were 145 primary events (33 cardiac deaths, 22 nonfatal MIs, and 90 revascularization procedures) and 109 secondary events (87 deaths and 22 nonfatal MIs). Most coronary revascularization procedures (n = 77 or 86%) were performed late (>60 days) after electron beam tomography or SPECT imaging. Only 2 of 977 subjects (0.20%) with a normal SPECT result versus 11 of 149 (7.4%) with an abnormal SPECT result underwent early revascularization ($p < 0.001$). The prevalence of early revascularization procedures in each CACS group is as follows: 0 to 10: 0%; 11 to 100: 0%; 101 to 400: 1.3%; and >400: 3.0%.

Predictors of events. Univariate predictors of total cardiac events were age, the presence of hypertension and diabetes mellitus, increasing CACS, inability to exercise, an intermediate- or high-risk Duke treadmill score, and an abnormal SPECT result (all $p < 0.05$). Univariate predictors of all-cause death/MI were age, inability to exercise, an intermediate- or high-risk Duke treadmill score, an increasing CACS, and an abnormal SPECT result (all $p < 0.05$). Independent predictors of total cardiac events by multivariate analysis were increasing CACS severity and a high-risk SPECT result (LV PDS ≥15%). Independent predictors of all-cause death/MI were age, female sex, inability to exercise, increasing CACS, and a high-risk SPECT result (Table 4). An ischemic PDS ≥10% was also an important predictor of total cardiac events (hazard ratio [HR]: 4.36; 95% confidence interval [CI]: 2.44 to 7.77; $p < 0.01$) and death/MI (HR: 2.67; 95% CI: 1.31 to 5.44; $p = 0.007$) when substituted for PDS ≥15% in the original model. A separate analysis limited to the 946 subjects who had treadmill exercise showed that an intermediate- or high-risk Duke treadmill score was also an independent predictor of total cardiac events (HR: 1.82; 95% CI: 1.12 to 2.94; $p = 0.02$).

Cardiac events based on CACS and SPECT results. The risk for total cardiac events and all-cause death/MI increased significantly with increasing CACS severity (Fig. 2) and the presence and extent of SPECT abnormalcy (Figs. 3 and 4). In subjects with a normal SPECT result, the total and all-cause death/MI event rates remained low at <1%/year and <0.5%/year over the first 4 years of follow-up, respectively (Figs. 3 and 4). However, subjects with a large (≥15%) stress-induced LV PDS had a significantly higher annualized total (9.6% vs. 3.8%, $p < 0.001$) and all-cause death/MI (6.1% vs. 2.3%; $p < 0.001$) event rate than those with smaller defects, respectively, and this was observed throughout the follow-up period (Fig. 3). Similarly, subjects with a large (≥10%) ischemic LV PDS had significantly higher annualized total (11.4% vs. 4.0%; $p < 0.001$) and all-cause death/MI (7.6% vs. 3.4%; $p < 0.001$) event rates than those with smaller ischemic defects, respectively (Fig. 4).

The integration of CACS and SPECT results further improved risk stratification (Fig. 5). Subjects with a moderate or severe CACS had significantly higher annualized overall and all-cause death/MI event rates when SPECT was abnormal (5.9% and 3.5%) versus normal (2.0% and 1.6%), respectively (both $p < 0.001$) (Fig. 5). This was particularly true in those who had a large (≥15%) stress-induced PDS in which the annualized overall total cardiac

Table 4 **Multivariable Predictors of Events**

	Total Cardiac Events			All-Cause Death/Myocardial Infarction		
	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Age (per yr)	0.99	0.98–1.01	0.62	1.05	1.03–1.08	0.0001
Female sex	1.35	0.88–2.08	0.17	1.80	1.15–2.81	0.01
Inability to exercise	1.11	0.72–1.71	0.64	1.76	1.14–2.74	0.01
CACS (per group increment)	1.65	1.34–2.0	<0.001	1.37	1.10–1.69	0.004
SPECT PDS ≥15% LV	4.16	2.55–7.10	<0.001	2.21	1.15–4.26	0.02

CI = confidence interval; other abbreviations as in Tables 1 and 2.

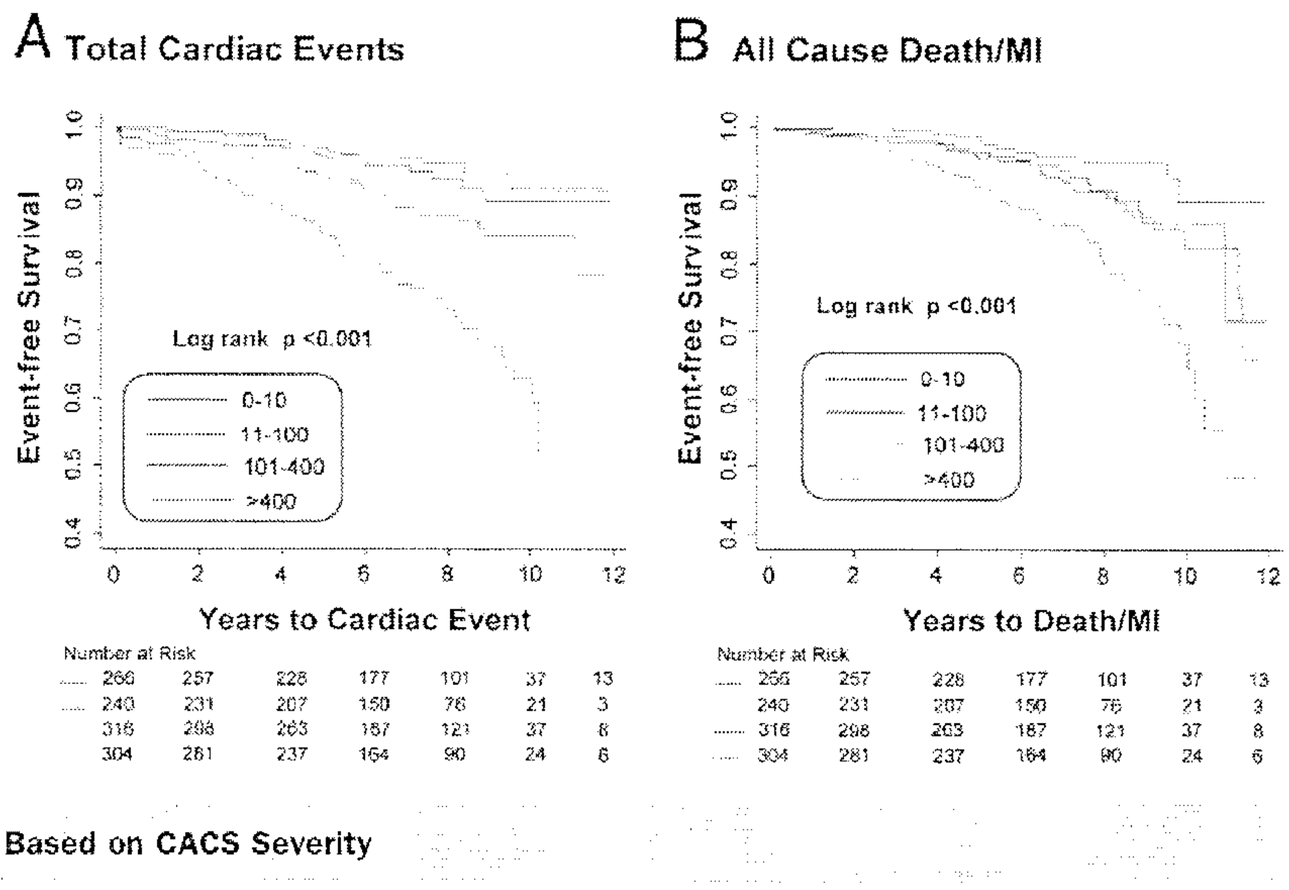

Figure 2 **Event Rates Based on CACS Severity**

Total cardiac death, myocardial infarction (MI), and coronary revascularization **(A)** and all-cause death/MI **(B)** event rates based on CACS severity. Abbreviations as in Figure 1.

and all-cause death/MI event rates increased to 10.3% and 6.1%, as compared with 4.3% and 2.6% in those with an LV PDS <15% (both $p < 0.001$). In subjects who had a large (≥10%) stress-induced ischemic PDS, the annualized overall total cardiac and all-cause death/MI event rates also increased to 12% and 7.8%, as compared with 4.6% and 2.6% in those with an ischemic PDS <10% (both $p < 0.001$). Conversely, in subjects with a normal SPECT result, the total cardiac and all-cause death/MI event rates significantly increased with increasing CACS severity (Fig. 5).

The improvement in predicting risk by combining CACS and SPECT results was also analyzed relative to the lowest-risk cohort (i.e., subjects with a normal SPECT result and CACS ≤10). By Cox proportional hazard modeling, the relative risk for total cardiac and all-cause death/MI events significantly increased in subjects with a normal SPECT result when CACS exceeded 400 (Table 5). Time point analysis showed separation of the survival curves between the minimal (0 to 10) and severe (>400) CACS groups at 3 years after initial testing for total cardiac events ($p = 0.02$) and at 5 years for death/MI ($p = 0.02$) (Fig. 6).

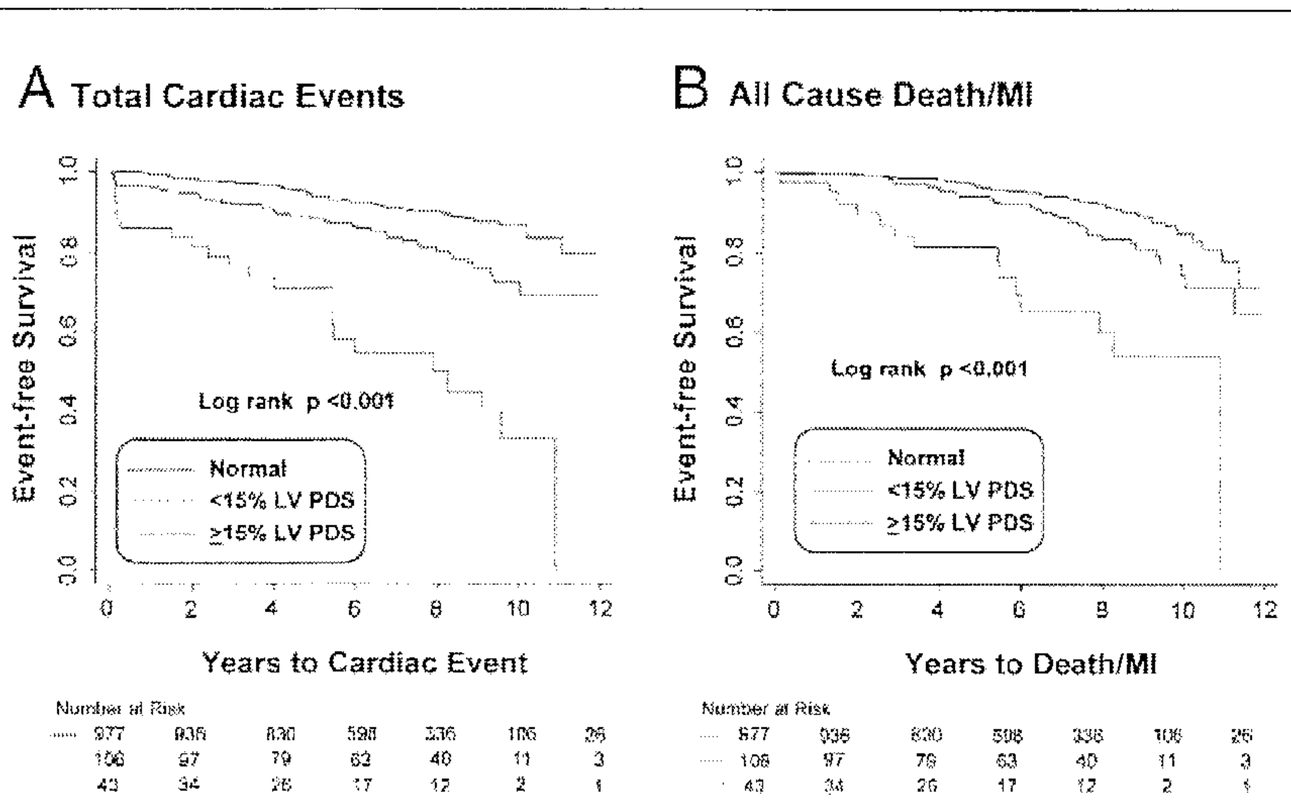

Figure 3 **Event Rates Based on SPECT Results: Total Perfusion Defect Size**

Total cardiac death, MI, and coronary revascularization **(A)** and all cause death/MI **(B)** event rates based on stress SPECT results of normal, abnormal with an LV PDS <15%, and abnormal with an LV PDS ≥15%. Abbreviations as in Figures 1 and 2.

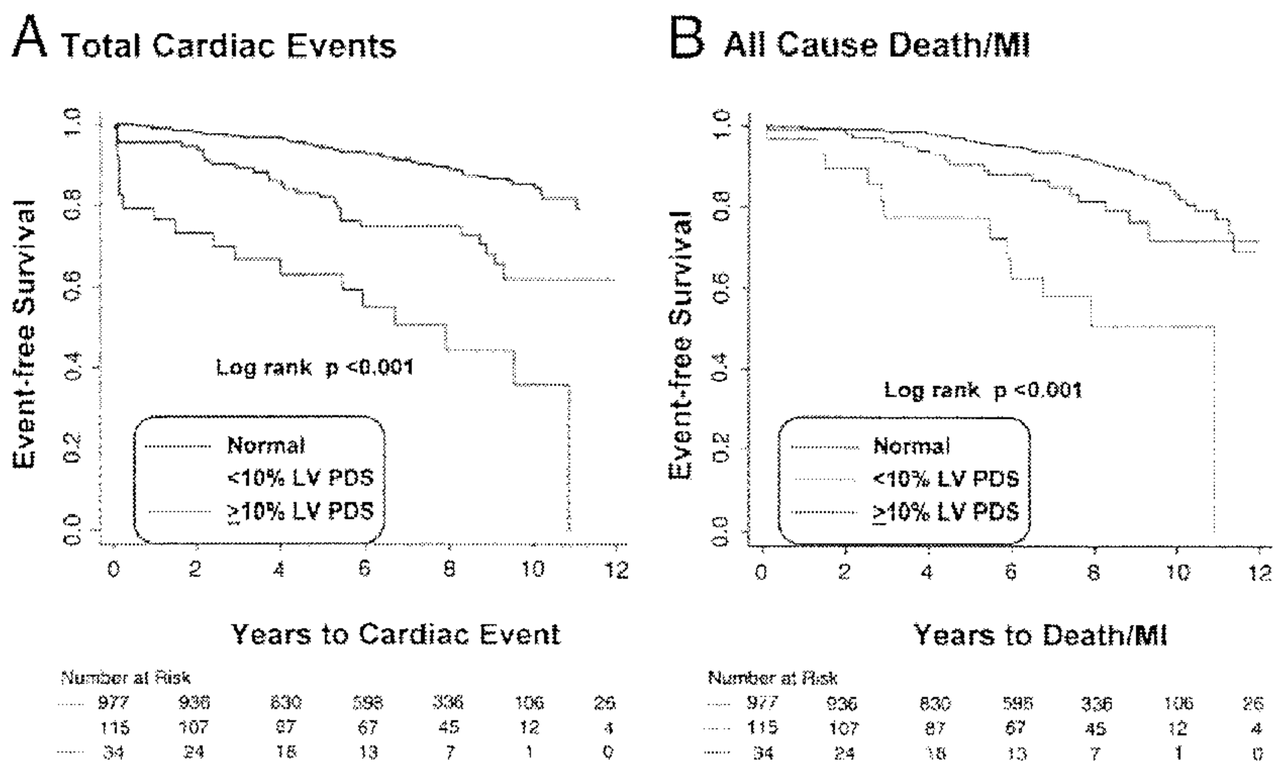

Figure 4 **Event Rates Based on SPECT Results: Ischemic Perfusion Defect Size**

Total cardiac death, MI, and coronary revascularization **(A)** and all-cause death/MI **(B)** event rates based on stress SPECT results of normal, abnormal with a <10% ischemic PDS, and abnormal with a ≥10% ischemic PDS. Abbreviations as in Figures 1 and 2.

This indicates that when the CACS is severe, the "warranty period," for a normal SPECT result expires within several years.

Incremental prognostic value of CACS and SPECT results over clinical information. The addition of high risk SPECT variables (i.e., total PDS ≥15%, ischemic PDS ≥10%) significantly increased the predictive power of the clinical model alone (Fig. 7). The global chi-square statistic (likelihood ratio) increased from 40.8 to 78.2 ($p < 0.001$, total cardiac events) and from 82.6 to 90.9 ($p = 0.02$, all-cause death/MI) with the addition of total PDS. Likewise, addition of ischemic PDS to the clinical model increased the global chi square value from 40.8 to 76.3 ($p < 0.001$, total cardiac events) and from 82.6 to 91.6 ($p = 0.01$, all-cause death/MI). Adding CACS results to the combined SPECT and clinical information further increased the global chi-square statistic for predicting both total cardiac events and death/MI irrespective of whether total or ischemic PDS was used as the SPECT variable.

Impact of symptoms and testing intervals on outcomes. The annual event rates in different CACS and SPECT groups among subjects who did or did not have chest pain were not statistically significant. The testing interval between SPECT and electron beam tomography did not significantly modify the effect of CACS and perfusion results on outcome (interaction $p = 0.23$ for cardiac events and 0.42 for death/MI).

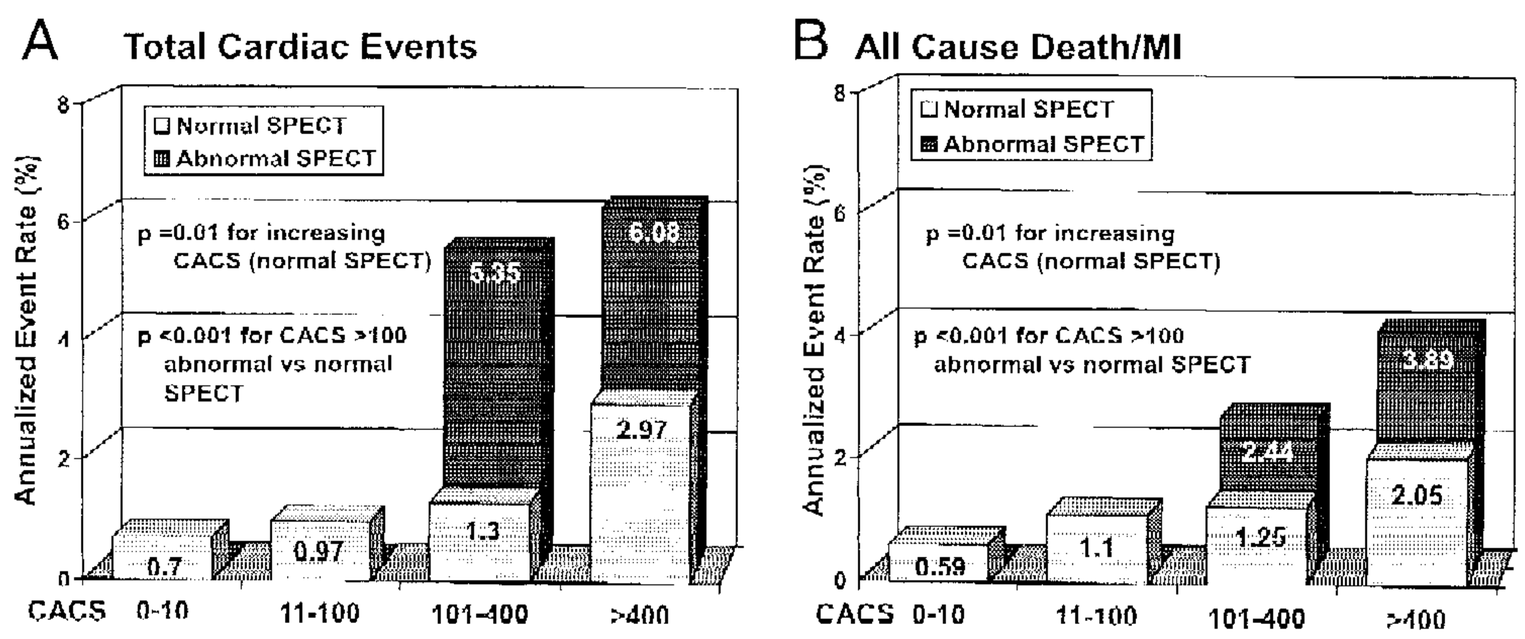

Figure 5 **Adjusted Annualized Event Rates Based on CACS and SPECT Results**

Adjusted annualized total cardiac death, MI, and coronary revascularization **(A)** and all-cause death/MI **(B)** event rates based on CACS and SPECT results. Abbreviations as in Figures 1 and 2.

Table 5 Subjects With a Normal Stress SPECT: Relative Risk of Events Based on CACS Severity

	Total Cardiac Events			All-Cause Death/Myocardial Infarction		
Normal SPECT	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
CACS 0–10	1			1		
CACS 11–100	1.28	0.60–2.74	0.52	1.96	0.89–4.3	0.09
CACS 101–400	1.53	0.75–3.12	0.24	1.72	0.81–3.63	0.15
CACS >400	3.55	1.78–7.09	<0.001	2.75	1.29–5.85	0.008

Abbreviations as in Tables 1 and 4.

Discussion

Precisely defining short- and long-term cardiac risk is pivotal for guiding therapy in individual patients. The current study followed up a large cohort of generally asymptomatic subjects for nearly a decade and shows that CACS and SPECT results provide both independent and complementary prognostic information. The most provocative finding we report is that although a normal SPECT result predicts excellent short-term event-free survival, long-term outcome is significantly worse if the CACS is severe. This is not altogether surprising because the CACS is directly related to the extent of coronary atherosclerotic plaque burden (13), which cannot be measured by functional SPECT imaging. Based on results from several clinical trials (14–16), current American College of Cardiology Foundation/American Society of Nuclear Cardiology guidelines recommend SPECT imaging to assess for ischemia in asymptomatic subjects with a severe (≥400) CACS (17). Our results support a more important role for CACS testing among patients with a normal SPECT result within current guideline recommendations. Doing so would help to identify those at high long-term risk for cardiac events, in whom an earlier focus on aggressive risk factor modification and other medical therapeutic measures may be beneficial.

SPECT for assessing risk. Over 2 decades of clinical trials in over 100,000 patients have established the central role of stress SPECT in the routine clinical management of subjects with suspected or known CAD (3). A normal SPECT result generally defines a group with a <1% annual risk of cardiac death and/or nonfatal MI, which increases to approximately 6% if the study result is abnormal (3,4). In patients with a clearly abnormal SPECT, total PDS and the presence and extent of residual ischemia further define high risk (18). Consistent with these prior observations, our subjects with a normal SPECT result also had a very low annual all-cause death/MI rate (<1%), which increased significantly among those with large total (6.1%) or ischemic (7.6%) perfusion defects, respectively.

Despite the well recognized role of SPECT imaging in risk stratification, there are certain patient populations in whom a normal study result may not necessarily confer the same low risk (3,19,20). In addition, the "warranty period" of a normal SPECT result decreases significantly in patients with diabetes or known CAD and in those unable to

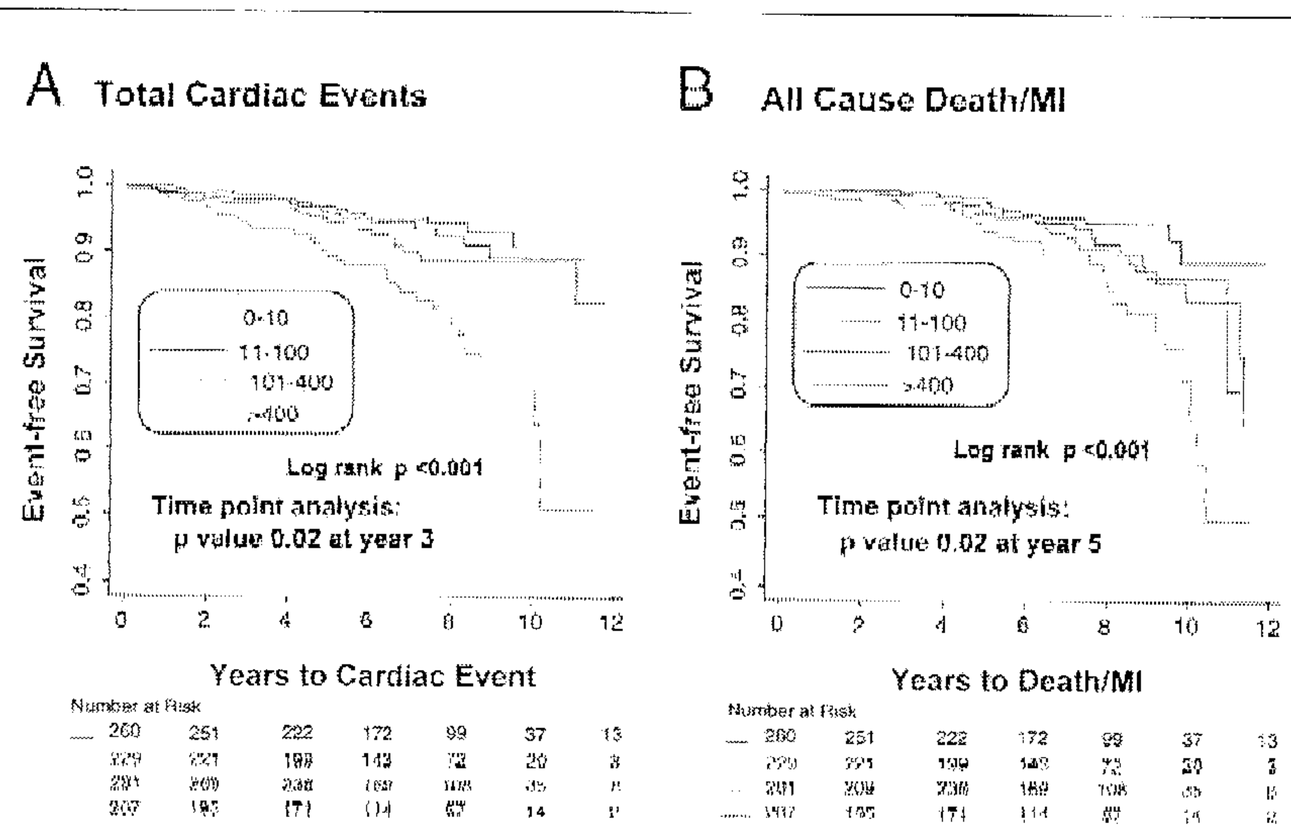

Figure 5 Event Rates in Subjects With a Normal SPECT Result Based on CACS Severity

Total cardiac death, MI, and coronary revascularization (**A**) and all-cause death/MI (**B**) event rates based on CACS severity in subjects with a normal stress SPECT result. Abbreviations as in Figures 1 and 2.

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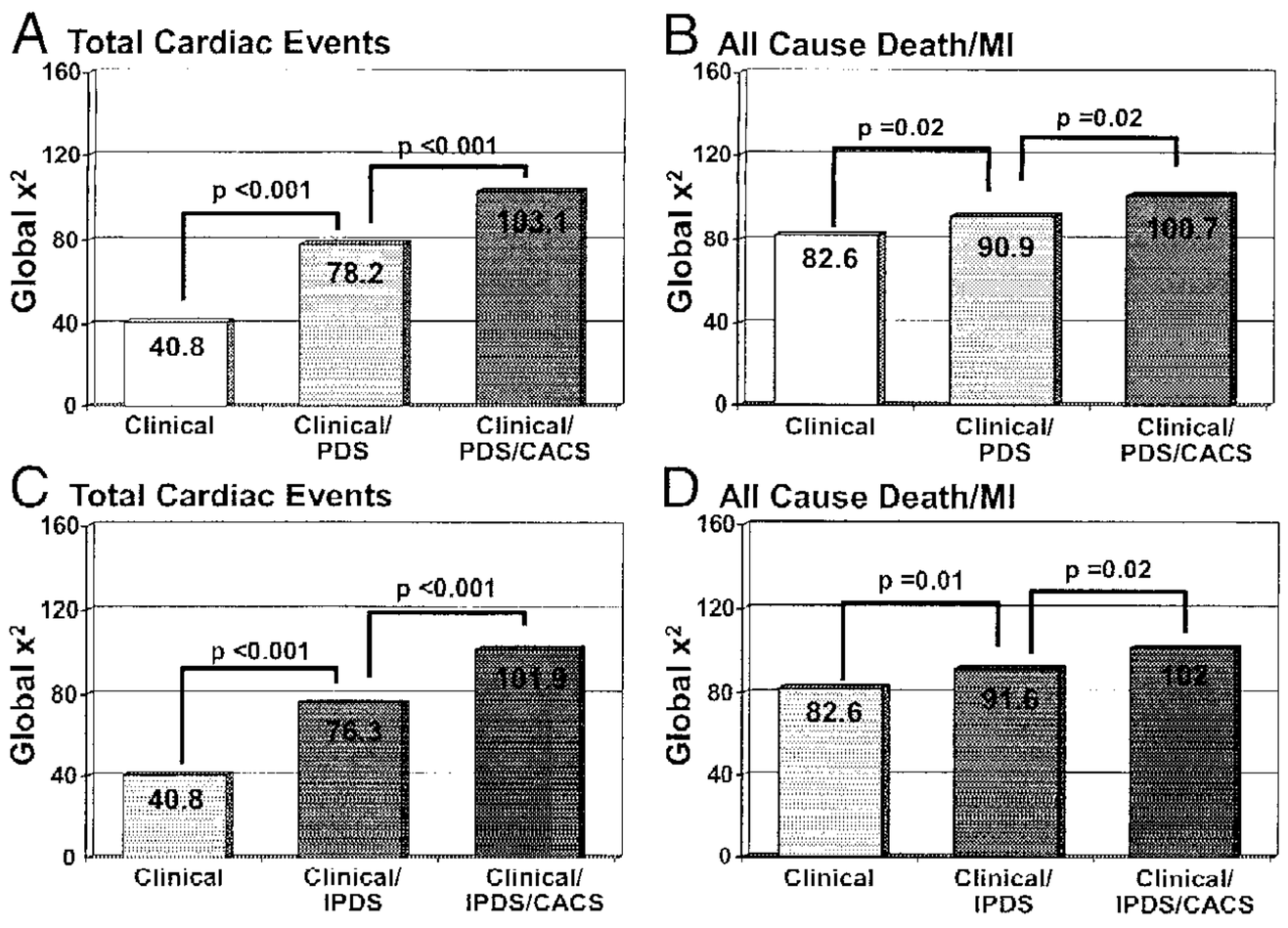

Figure 7 **Incremental Prognostic Value of Clinical, SPECT, and CACS Results**

Incremental predictive value of CACS and stress SPECT results over clinical information by global chi-square analysis. **(A and B)** Total PDS was used as the SPECT variable. **(C and D)** Ischemic perfusion defect size (IPDS) was used as the SPECT variable. Clinical model: age, sex, diabetes, hypertension, hyperlipidemia, smoking history, family history of coronary artery disease, chest pain, abnormal resting electrocardiogram, and inability to exercise. Abbreviations as in Figures 1 and 2.

exercise (21). Our results show that the addition of CACS more precisely defines this "warranty period," because cardiac event rates significantly increase beginning 3 years after a normal SPECT result when the CACS is severe. More vigilant risk factor modification in such high-risk individuals would, therefore, seem warranted.

CACS for assessing risk. Calcium scoring has been studied extensively over the past decade for predicting outcome in generally asymptomatic subjects at intermediate clinical risk for CAD (1,2). A CACS of 0 consistently identifies a very low risk cohort, even among clinically high-risk groups such as diabetic patients (22). In our study, only 1 cardiac death and 2 nonfatal MIs occurred over 7 years in the 266 subjects (1.2%) with a CACS ≤10. This finding is very similar to those reported from other large prospective observational population-based studies (23). Conversely, cardiac events significantly increase with increasing CACS, and this occurs across all ethnic groups (2). Interestingly, our study showed that the CACS was a stronger predictor of cardiac events than diabetes mellitus, which has been considered a coronary heart disease risk equivalent (24).

Why integrate CACS with SPECT results? Combining an anatomic assessment of coronary atherosclerotic plaque burden with a functional assessment of myocardial ischemia may temporally refine risk stratification among subjects at varying clinical risk. One could envision SPECT providing a better short-term risk assessment because it identifies the functional significance of more advanced stages of CAD. However, the CACS may better estimate longer-term prognosis because of its ability to detect varying degrees of coronary atherosclerosis before the development of stress-induced myocardial ischemia.

Our results and those of others (25,26) support this concept. In a recent study following up asymptomatic diabetic subjects for more than 2 years, CACS and the extent of ischemic myocardium by SPECT both predicted patient outcome (25). However, combining CACS and SPECT results significantly improved risk stratification, with no events in patients with a normal SPECT result and a low CACS (<100) but a 10% event rate in those with a CACS >1,000 (25). Conversely, in patients with a CACS >100, the extent of stress-induced ischemia further predicted outcome. We report similar observations, with the total cardiac event rate increasing from 2.0% to 5.9% ($p < 0.001$) in our subjects with a CACS >100 based on whether the SPECT result was normal or abnormal. In another study of predominantly symptomatic patients with a high pre-test likelihood of CAD, CACS added prognostic value to rubidium-82 perfusion results (26). In contrast, another study reported no additional risk information from CACS when the SPECT result was normal (27). However, this seeming discrepancy with our study results is probably related to the relatively short follow-up period of only 2 years.

In addition to the size of our patient cohort, the 7-year follow-up is longer than performed in any previous study, allowing us to better clarify the temporal interrelationship between CACS and SPECT findings for defining risk. Our

data indicate that a severe CACS even among scintigraphically normal patients defines a group at considerable risk for events if followed up for a long enough period of time. Although patients with a normal SPECT result and low (≤10) CACS have an excellent overall prognosis, a normal SPECT result may lead to a false sense of long-term security among those with an underlying severe CACS in whom the annual overall cardiac event rate approached 3%.

Our results support performing a CACS in patients at intermediate or high clinical risk for CAD who have a normal SPECT result because approximately 20% will have a CACS of at least moderate severity that cannot be predicted from the patient's clinical profile (28). In this regard, calcium scoring allows identification of high-risk individuals among the heterogeneous group of relatively low-risk patients with a normal SPECT result. The value of CACS as a high-risk marker may extend beyond its prognostic implications. Although not specifically addressed in this study, identification of early atherosclerosis, defined by CACS, may improve patient outcome through earlier and more intensive risk factor modification and treatment of hyperlipidemia. For example, preliminary data suggest that intensive treatment of hyperlipidemia may reduce CACS progression (29) and thereby decrease cardiac event rates (30). In a similar fashion, initiating statin therapy in patients with a surrogate marker of high risk (i.e., C-reactive protein) was recently shown to reduce cardiac events despite a relatively normal low-density lipoprotein cholesterol level (31). The hypothesis that selectively targeting therapy based on CACS and SPECT results may reduce downstream medical and overall health care costs is one that warrants further study.

Study limitations. First, this was not an epidemiologic study, so it comes with unavoidable patient selection bias. After an abnormal screening CACS, SPECT was variably recommended, which probably explains why a relatively large proportion of our cohort had a CACS >100. However, many of our subjects even with a CACS ≤10 also underwent SPECT because they had chest pain symptoms that required further clarification. Second, CACS and SPECT results were available to subjects and referring physicians, who could then initiate lifestyle changes and/or pharmacological interventions and potentially reduce cardiac event rates. However, this should have biased our study against observing a relationship between CACS and cardiac events. Rather, our data are consistent with previous reports showing the independent prognostic value of SPECT (3) and CACS (1,2). Third, not all studies were performed in close temporal relationship to each other. However, the duration of the interval between performing CACS and SPECT imaging did not affect our results.

Conclusions

The CACS and stress SPECT results are independent and complementary for predicting events. A severe CACS identifies a subgroup of subjects at high long-term risk even in the presence of a normal stress SPECT study. Our results support a strategy of adding CACS testing in patients with a normal SPECT result to identify those at high long-term risk for cardiac events. In these patients, earlier aggressive risk factor modification may deter further progression of coronary atherosclerosis and improve outcome. The cost effectiveness of such an approach will require further study.

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