

# Incremental Prognostic Value of Myocardial Perfusion Single Photon Emission Computed Tomography for the Prediction of Cardiac Death

## Differential Stratification for Risk of Cardiac Death and Myocardial Infarction

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**Background**—The incremental prognostic value of stress single photon emission computed tomography (SPECT) for the prediction of cardiac death as an individual end point and the implications for risk stratification are undefined.

**Methods and Results**—We identified 5183 consecutive patients who underwent stress/rest SPECT and were followed up for the occurrence of cardiac death or myocardial infarction. Over a mean follow up of  $642 \pm 226$  days, 119 cardiac deaths and 158 myocardial infarctions occurred (3.0% cardiac death rate, 2.3% myocardial infarction rate). Patients with normal scans were at low risk ( $\leq 0.5\%/y$ ), and rates of both outcomes increased significantly with worsening scan abnormalities. Patients who underwent exercise stress and had mildly abnormal scans had low rates of cardiac death but higher rates of myocardial infarction (0.7%/y versus 2.6%/y;  $P < .05$ ). After adjustment for prescan information, scan results provided incremental prognostic value toward the prediction of cardiac death. The identification of patients at intermediate risk of nonfatal myocardial infarction and low risk for cardiac death by SPECT may result in significant cost savings when applied to a clinical testing strategy.

**Conclusions**—Myocardial perfusion SPECT yields incremental prognostic information toward the identification of cardiac death. Patients with mildly abnormal scans after exercise stress are at low risk for cardiac death but intermediate risk for nonfatal myocardial infarction and thus may benefit from a noninvasive strategy and may not require invasive management. (*Circulation*. 1998;97:535-543.)

**Key Words:** prognosis ■ tomography ■ perfusion

The application of prognostic testing is based on the premise that patients identified as being at high risk for adverse outcomes can be intervened on and the natural history of their disease altered so that their subsequent risk is reduced. Ideally, the prognostic utility of a test is defined with respect to a particular outcome whose occurrence can be prevented by a specific treatment, rather than being defined with respect to a combination of end points that are treated dissimilarly. To date, studies evaluating the prognostic value of myocardial perfusion single photon emission computed tomography (SPECT) have used the combination of myocardial infarction and cardiac death (“hard events”) or hard events and late revascularization as study end points because of the relatively low frequency of serious adverse outcomes and relatively small study cohorts.<sup>1</sup> Because the treatment of patients for prevention of each of these outcomes may differ, the application of prognostic nuclear testing to patient management is potentially difficult.

Prospective, randomized clinical trials have shown several treatment modalities to reduce cardiac mortality in selected patient subsets.<sup>2-4</sup> Recent trials of medical therapy have demonstrated reductions in both fatal and nonfatal myocardial infarction rates and cardiac death.<sup>5-8</sup> Hence, patients at risk for nonfatal myocardial infarction but not cardiac death may benefit from aggressive medical management and not require revascularization. If nuclear testing could identify these patients, significant cost savings could be realized by the potential reduction in referral to catheterization and revascularization.

To this end, the goals of the present study were threefold: (1) to define the incremental prognostic value of myocardial perfusion SPECT for the prediction of future cardiac death; (2) to define the ability of nuclear testing to risk stratify patients into three groups (low risk for both myocardial infarction and cardiac death, intermediate to high risk for myocardial infarction but low risk for cardiac death, and at intermediate to high risk for both outcomes); and (3) to determine the impact on

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the cost of testing if patients at low risk for cardiac death but intermediate risk for nonfatal myocardial infarction were treated medically and not referred to catheterization as initial therapy.

## Methods

### Study Population

We prospectively identified 5807 consecutive patients who underwent dual isotope SPECT with either exercise or pharmacological stress between January 1, 1991, and December 30, 1993, at Cedars-Sinai Medical Center, excluding patients with significant valvular heart disease or nonischemic cardiomyopathies. Of this initial population, 269 patients were lost to follow-up, and 4 had missing data. The remaining 5534 patients with successful follow-up (95%) were included in this study. The 351 patients revascularized in the first 60 days after nuclear testing were excluded from the prognostic portion of the analyses.<sup>9,10</sup> Thus, the prognostic data presented here are based on a subset of 5183 patients.

### Rest Thallium Imaging

All patients underwent stress dual isotope myocardial perfusion SPECT as previously described.<sup>11</sup> Initially, thallium-201 (2.5 to 3.5 mCi) was injected intravenously at rest, with dose variation based on patient weight. Rest thallium imaging was initiated 10 minutes after injection of the isotope.

### Exercise Myocardial Perfusion Protocol

Patients performed a symptom-limited treadmill exercise test using standard protocols with a 12-lead ECG recording each minute of exercise and continuous monitoring of leads aVF, V<sub>1</sub>, and V<sub>5</sub>. At near-maximal exercise, a 20- to 30-mCi dose of technetium-99m sestamibi was injected (actual patient dose varied with patient weight), and exercise continued for 1 minute after injection. SPECT was begun 30 minutes after isotope injection. Whenever possible,  $\beta$ -blockers and calcium channel antagonists were discontinued 48 hours before testing, and nitrate compounds were discontinued at least 6 hours before testing.

### Adenosine Myocardial Perfusion Protocol

Patients were instructed not to consume caffeine-containing products for 24 hours before the test. After rest thallium SPECT, pharmacological stress was performed by use of adenosine infusion (140  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 6 minutes). Sestamibi was injected at the end of the third minute of infusion, and SPECT was initiated  $\approx$ 60 minutes after the end of the adenosine infusion.<sup>12</sup>

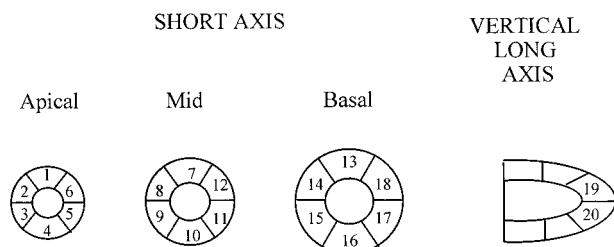
During both types of stress, blood pressure was measured and recorded at rest, at the end of each stress stage, and at peak stress. Maximal degree of ST-segment change at 80 milliseconds after the J point of the ECG was measured and assessed as horizontal, upsloping, or downsloping.

### SPECT Acquisition Protocol

SPECT studies were performed as previously described with a circular 180° acquisition for 64 projections at 20 seconds per projection.<sup>11</sup> During imaging, two energy windows were used for thallium-201, and a 15% window centered on the 140 keV peak was used for technetium-99m sestamibi.

### Image Interpretation

Semiquantitative visual interpretation was performed with short-axis and vertical long-axis myocardial tomograms divided into 20 segments for each study (Fig 1). These segments were assigned on six evenly spaced regions in the apical, midventricular, and basal slices of the short-axis views and two apical segments on the midventricular long-axis slice.<sup>12</sup> The scoring system used is described in the legend to Fig 1. A summed stress score was obtained by adding the scores of the 20 segments of the stress sestamibi images.<sup>13,14</sup> Summed stress scores <4 were considered normal; between 4 to 8, mildly abnormal; 9 to 13,



**Figure 1.** Assignment of myocardial regions for scoring of SPECT images.

moderately abnormal; and >13, severely abnormal. A summed rest score was obtained by similarly adding the scores of the 20 segments of the rest thallium images. The sum of the differences between each of the 20 segments on the stress and rest images was defined as the summed difference score. Each of these variables incorporate the extent and severity of perfusion defects, both of which independently add prognostic information.<sup>10</sup>

### Patient Follow-up

Patient follow-up was performed by scripted telephone interview by individuals blinded to the patients' test results. Events were defined as either cardiac death as noted and confirmed by review of death certificate and hospital chart or physician's records or nonfatal myocardial infarction as evidenced by the appropriate combination of symptoms, ECG, and enzyme changes. All patients included in this report were followed for at least 1 year. The mean follow-up interval was  $642 \pm 226$  days.

### Likelihood of Coronary Artery Disease

We used analysis of the prescan likelihood of coronary artery disease as an aggregate descriptor of proven prognostic importance based on Bayesian analysis of patient data and calculated with CADENZA.<sup>15</sup> For patients undergoing pharmacological stress, only clinical and historical information was considered, whereas for patients undergo-

**TABLE 1. Patient Characteristics**

	Exercise Stress (n=4104)	Adenosine (n=1079)	P
Sex, M	2723	541	<.001
Age	62.6 $\pm$ 12.1	70.4 $\pm$ 11.3	<.001
Hx myocardial infarction, n (%)	850 (21)	346 (32)	<.001
Hx coronary artery bypass surgery, n (%)	544 (13)	219 (20)	<.001
Hx PTCA, n (%)	473 (11)	143 (13)	
Anginal symptoms, n (%)	1452 (35)	500 (46)	<.001
Cardiac risk factors	1.4 $\pm$ 1.0	1.6 $\pm$ 1.1	<.001
Pre-ETT likelihood of CAD	0.36 $\pm$ 0.24	0.46 $\pm$ 0.22	<.001
Post-ETT likelihood of CAD	0.34 $\pm$ 0.34	NA	
Abnormal rest ECG, n (%)	1059 (26)	452 (42)	<.001
Exercise duration	7.2 $\pm$ 2.9	NA	
%Max HR	92.7 $\pm$ 9.7	NA	
Cardiac death, n (%)	47 (1)	72 (7)	<.001
Myocardial infarction	100 (2)	58 (5)	<.001
Follow-up, d	591 $\pm$ 177	839 $\pm$ 278	<.001
Summed stress score	5.4 $\pm$ 8.4	8.8 $\pm$ 10.0	<.001
Summed difference in scores	3.5 $\pm$ 5.6	5.0 $\pm$ 6.0	<.001

Hx indicates history; PTCA, percutaneous transluminal coronary angioplasty; ETT, exercise tolerance test; CAD, coronary artery disease; and %Max HR, percent of maximum predicted heart rate achieved.

ing exercise stress, the prescan likelihood of coronary disease included clinical, historical, and exercise test information.

### Statistical Analysis

Comparisons between patient groups were performed by use of a one-way ANOVA (with a Bonferroni correction where appropriate) for continuous variables and a  $\chi^2$  test for categorical variables. Continuous variables were described as a mean  $\pm$  SD. A value of  $P < .05$  was considered statistically significant.

The Cox proportional hazards model (BMDP version 7, program 2L<sup>16</sup>) was applied in a stepwise fashion to define three models with cardiac death and hard events as separate end points: (1) a prescan model (prescan likelihood of coronary artery disease, history of coronary disease, type of stress performed), (2) a nuclear scan model (in the absence of generally accepted nuclear aggregate variables, we used the derived nuclear variables shown in Table 2), and (3) a combined model evaluating the increase in prognostic information (model 2 adjusted for model 1). The threshold for entry of variables into all models was  $P < .05$ . A statistically significant increase in the global  $\chi^2$  of the model after the addition of the nuclear variables defined incremental prognostic value.

Cumulative event-free survival rates as a function of time after the index nuclear exercise test were calculated by use of the Kaplan-Meier method and compared by use of the Mantel-Cox test (BMDP version 7, 1L<sup>16,17</sup>). Patients were first stratified by the combination of prescan likelihood of coronary artery disease (for patients with known coronary artery disease, a value of 1 was assigned) into low, intermediate, and high clinical risk subgroups (prescan likelihood of coronary artery disease  $< 0.15$ ,  $0.15$  to  $0.85$ , and  $> 0.85$ , respectively). These subgroups were then further stratified by the results of the nuclear scan. Incremental value was defined as a statistically significant difference in the survival rates of the subgroups after inclusion of nuclear information ( $P < .05$  by Mantel-Cox test).

### Cost and Decision Analysis

Cost was calculated on the basis of Medicare hospital charges (adjusted by cost-charge ratios) and physician billing data.<sup>18</sup> Median cost estimates and probability values from the multivariable model were

used in a decision model to compare the cost savings (ie, marginal cost) provided by use of two comparative strategies: catheterization of all patients with an abnormal scan and catheterization of patients with summed stress score  $> 8$ . Cost-effectiveness was defined as change in cost of strategy divided by change in hard event rate. Marginal cost was calculated by comparing the difference in cost to the change in the number of cardiac events identified between the two comparative strategies. This decision model was performed with TREEAGE software and included a threshold analysis, rollback, and a one-way sensitivity analysis. Cost estimates were included in the model and were varied by 30% to simulate the complexity of patient presentation and to examine the probable input of bias in the assumptions made in the model.<sup>19</sup> Sensitivity analysis was also performed by varying the cardiac death rates.

## Results

### Initial Patient Population

The 4104 patients in this study who underwent exercise stress and the 1079 who underwent pharmacological stress are characterized in Table 1. Comparison of the patients who underwent exercise versus pharmacologic stress shows that the patients who underwent the latter were older, more frequently had previous cardiac events or procedures, had greater likelihoods of coronary artery disease, had more severe and extensive scan abnormalities, and had greater subsequent rates of adverse outcomes.

### Outcome Events

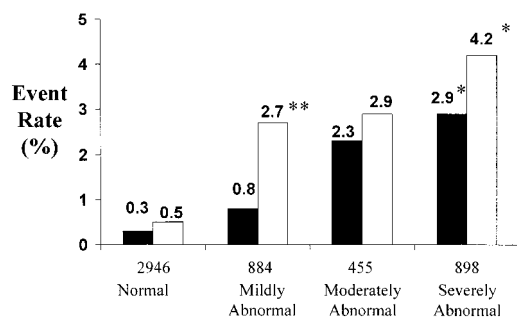
Among the 5183 patients included in this study, 119 cardiac deaths and 158 myocardial infarctions occurred (3.0% cardiac death rate, 2.3% myocardial infarction rate). Revascularization within the first 60 days after nuclear testing numbered 351 (181 coronary artery bypass graft surgery [CABG] and 170 percu-

**TABLE 2. Patient Characteristics**

	Cardiac Death (n=119)	Myocardial Infarction (n=158)	No Events (n=4922)
Male sex, %	60	59	63
Age, y	73.6 $\pm$ 12.2	67.7 $\pm$ 11.3*	63.9 $\pm$ 12.3†‡
Number of cardiac risk factors	1.6 $\pm$ 1.1	1.8 $\pm$ 1.1	1.4 $\pm$ 1.0†‡
Hx myocardial infarction, n (%)	57 (48)	76 (48)	1071 (22)†‡
Hx angioplasty, n (%)	19 (16)	31 (20)	569 (12)†‡
Hx bypass surgery, n (%)	26 (22)	39 (25)	705 (14)†‡
Symptoms, n (%)			
Asymptomatic	34 (29)	34 (21)	1820 (37)‡
Nonanginal	21 (18)	25 (16)	1117 (23)
Atypical angina	30 (25)	46 (29)	1203 (24)
Angina	20 (17)	38 (24)	623 (13)‡
Dyspnea	14 (12)	15 (9)	157 (3)†‡
Pre-scan Lk CAD	0.50 $\pm$ 0.26	0.43 $\pm$ 0.32	0.36 $\pm$ 0.32†‡
Abnormal rest ECG, n (%)	82 (69)	71 (45)*	1366 (28)†‡
Summed stress score	17.6 $\pm$ 12.0	13.1 $\pm$ 10.9*	5.7 $\pm$ 8.4†‡
Summed rest score	8.6 $\pm$ 10.7	5.1 $\pm$ 8.9*	2.0 $\pm$ 5.4†‡
Summed difference score	8.5 $\pm$ 7.4	7.8 $\pm$ 7.1	3.6 $\pm$ 5.6†‡

Hx indicates history; Lk, likelihood; and CAD, coronary artery disease.

\*Statistically significant difference between cardiac death and myocardial infarction groups ( $P < .05$ ); †Statistically significant difference between cardiac death and no event groups ( $P < .05$ ); ‡Statistically significant difference between myocardial infarction and no event groups ( $P < .05$ ).



**Figure 2.** Rates of cardiac death (open bars) and myocardial infarction (solid bars) per year as a function of scan result. The numbers are shown underneath the columns. \*Statistically significant increase as a function of scan result. \*\*Statistically significant increase in rate of myocardial infarction vs cardiac death within scan category.

taneous transluminal coronary angioplasty [PTCA]; 6.7% early revascularization rate).

### Univariable Analysis

Descriptive patient characteristics and exercise and nuclear variables in patients with or without events on follow-up are presented in Table 2. Comparison of patients with cardiac death or myocardial infarction on follow-up with those without shows that the former were older, had more cardiac risk factors, more frequently had an abnormal rest ECG, had a greater prescan likelihood of coronary disease, had more frequent histories of previous myocardial infarction or revascularization, and more frequently experienced dyspnea as their presenting symptom (Table 2). In addition, patients who had myocardial infarction on follow-up more frequently had angina and less frequently were asymptomatic at the time of testing relative to patients with no event on follow-up. Of note, 59% of patients who experienced cardiac death and 46% of patients who experienced myocardial infarction did not experience anginal symptoms at the time of their nuclear test. Compared with patients who had myocardial infarction on follow-up, those who had cardiac death were older and more frequently had an abnormal rest ECG.

With respect to nuclear variables (Table 2), patients with events on follow-up had more extensive and severe scan abnormalities with respect to both fixed and reversible defects. Compared with patients who had myocardial infarction on follow-up, those who had cardiac death had more severe and extensive stress perfusion scan abnormalities caused by more nonreversible defects but similar amounts of ischemia.

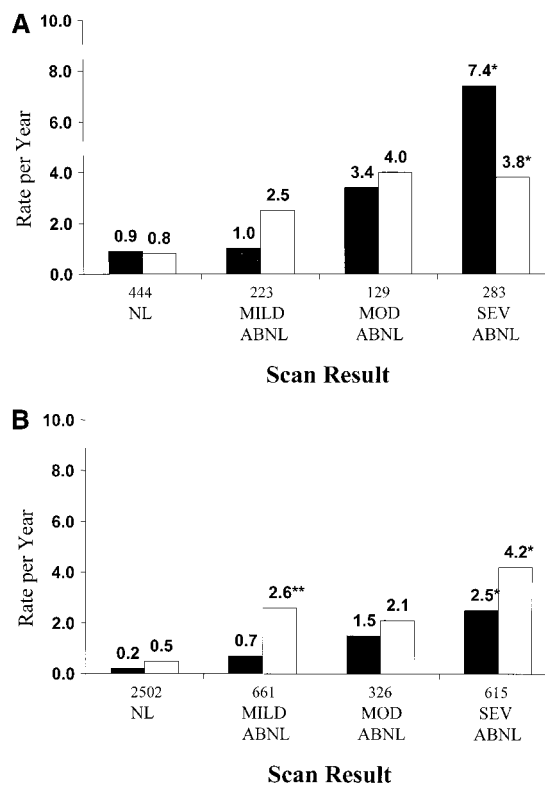
### Perfusion Scan Abnormalities and Outcomes

The frequency of events per year of follow-up as a function of the scan result is illustrated in Fig 2. The rates of both cardiac death and myocardial infarction increased as a function of scan result (both  $P < .001$ ). In the mildly abnormal scan category, a greater rate of myocardial infarction than cardiac death was present (0.8%/y versus 2.7%/y, respectively;  $P < .05$ ). When examined by the type of stress performed (Fig 3A and 3B), a significant increase in the rates of myocardial infarction and cardiac death occurred as a function of scan result (both  $P < .001$ ). In the mildly abnormal scan category, a significantly greater rate of myocardial infarction than cardiac death oc-

curred in the exercise stress group. No such difference was found in the pharmacological stress group, possibly because of the small number of patients ( $n=223$ ). The rate of cardiac death per year in patients with severely abnormal scans was significantly greater in patients who underwent adenosine stress compared with exercise stress ( $P < .01$ ).

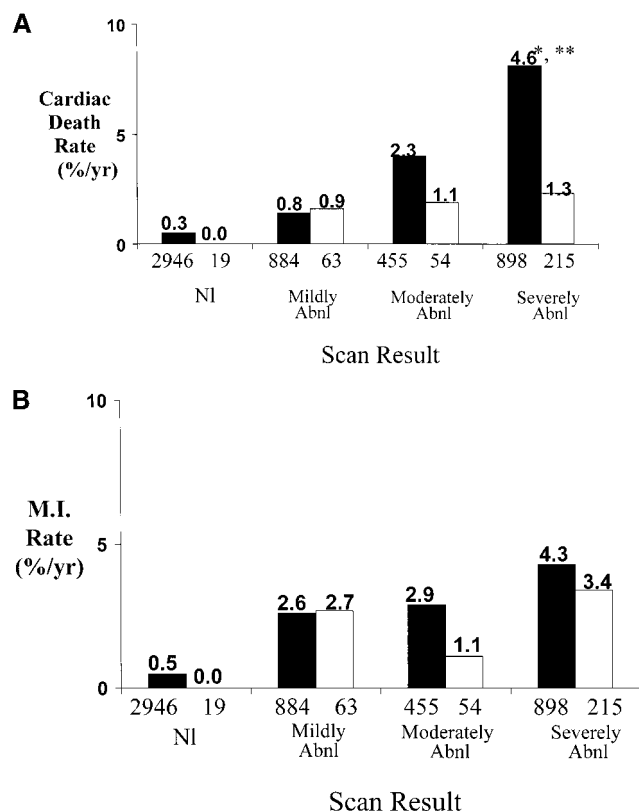
The distribution of events as a function of scan result also differed with respect to the two end points. Of the cardiac deaths, 13% were in normal scans and 10%, 15%, and 62% occurred in mildly, moderately, and severely abnormal scans, respectively. With respect to myocardial infarctions, 17% occurred in normal scans and 26%, 15%, and 42% occurred in mildly, moderately, and severely abnormal scans, respectively.

The rates of cardiac death in patients who underwent revascularization early after testing compared with those patients who were treated with medical therapy (Fig 4A) was significantly lower in patients with severely abnormal scans (summed stress score  $> 13$ ). There was a significant increase in the rate of cardiac death as a function of scan abnormality in patients undergoing medical therapy that was not present in patients undergoing early revascularization. The rates of myocardial infarction were similar in all abnormal scan categories; the exception to this was the moderately abnormal scan group in which there were an inadequate number of patients for adequate comparison (Fig 4B).



**Figure 3.** Rates of cardiac death (open bars) and myocardial infarction (solid bars) per year as a function of scan result in patients undergoing (A) adenosine and (B) exercise stress. The numbers for each subgroup are shown underneath the columns. \*Statistically significant increase as a function of scan result. \*\*Statistically significant increase in rate of myocardial infarction vs cardiac death within scan category ( $P < .05$ ). NL indicates normal; ABNL, abnormal; MOD, moderately; and SEV, severely.





**Figure 4.** Rates of (A) cardiac death and (B) myocardial infarction per year as a function of scan result. Solid bars represent patients undergoing initial medical therapy after nuclear testing; open bars represent patients undergoing revascularization early after nuclear testing. \*  $P < .01$  vs patients undergoing revascularization early after nuclear testing; \*\*  $P < .001$  within patients treated with medical therapy after nuclear testing. Abbreviations as in Fig 3.

### Incremental Value

Significant information was contained in the model containing clinical, historical, and exercise data and the model containing nuclear variables alone (Fig 5). Significant increases in global  $\chi^2$  ( $P < .00001$ ) occurred after adjustment for the nuclear data for prescan information, including the type of stress performed.

The cardiac death and myocardial infarction rates in each prescan likelihood of coronary artery disease category were further stratified with respect to their risk of both cardiac death and myocardial infarction by the nuclear scan result (Fig 6). Patients with both normal and mildly abnormal scans had low cardiac death rates ( $< 1\%$  per year of follow-up), whereas moderately to severely abnormal scans had intermediate to high rates in all clinical risk categories. Patients with normal scans had low rates of myocardial infarction per year of follow-up in all clinical risk categories (Table 4). The rates of myocardial infarction in the mildly abnormal scan group were  $> 1\%/y$  and increased in the moderately to severely abnormal scan groups in all clinical risk categories. Risk-adjusted survival also revealed low risk for cardiac death in normal and mildly abnormal scan groups but low risk for combined events only in the normal scan group (Fig 7).

### Risk Adjusted Models: Role of Early Revascularization

After adjustment for clinical, exercise, and nuclear results, the presence of early revascularization yielded further significant increases in global  $\chi^2$  ( $P < .005$ ) for the prediction of cardiac death. The risk-adjusted survival curves for patients who underwent early revascularization versus medical therapy based on this analysis (Fig 8) reveal an improved survival rate in patients who underwent revascularization early after nuclear testing.

### Major Subgroup Analysis

As shown in Table 3, the pattern of outcomes described above—low mortality rates in normal and mildly abnormal scans, low myocardial infarction rates in normal scans, and intermediate to high rates in abnormal scans—was present in a number of subgroups examined.

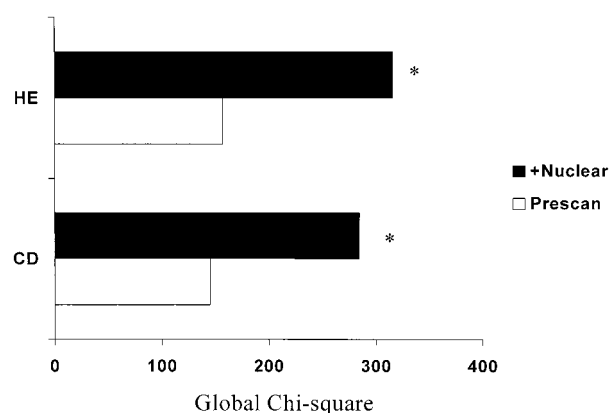
### Integrative Clinical History and Nuclear Decision Making

Compared with a strategy in which all patients undergoing exercise stress with abnormal scans are referred to catheterization, a strategy referring only those patients with moderately to severely abnormal scans to catheterization resulted in a 33.5% total cost savings ( $P < .001$ ) with similar outcome rates (Table 4). Total cost savings of 34.7%, 35.1%, and 26.8% could be accrued for low-, intermediate-, and high-risk patients ( $P < .001$ ). The marginal cost for the identification of hard events using a strategy of catheterization in all abnormal scans was \$157 412 per hard event in patients with intermediate clinical risk. The marginal cost was far greater for identifying hard events in patients at low and high clinical risk.

The superiority of the latter strategy was not altered in a sensitivity analysis when cost and outcome rates were varied. Further, no threshold was elucidated in which catheterization of all abnormal studies would be equally as effective or more effective than the moderate to severely abnormal catheterization strategy.

### Discussion

We found that after consideration of all prescan patient information, nuclear information provided statistical incre-



**Figure 5.** Results of Cox proportional hazards analysis. Prescan variables include the prescan likelihood of coronary artery disease, history of coronary artery disease, and type of stress used. \*  $P < .00001$  for gain in  $\chi^2$ .

## Kaplan-Meier Analysis: Stratification by Nuclear Testing

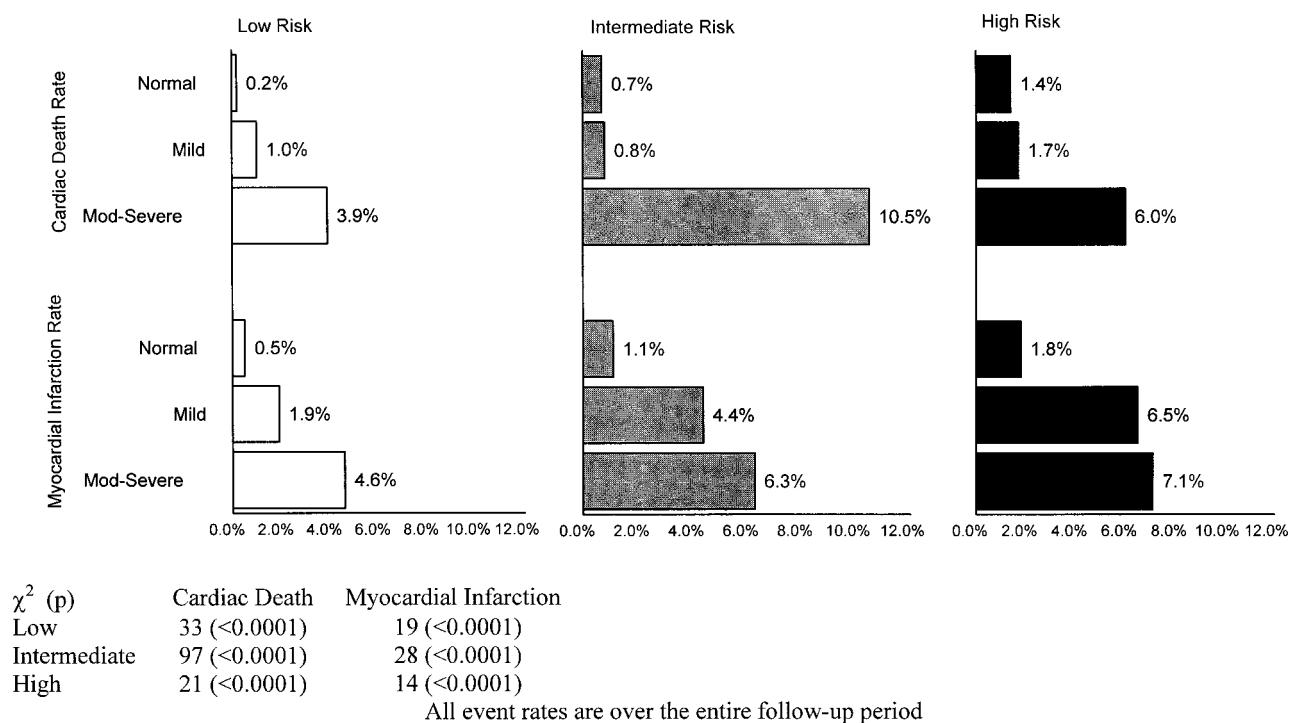


Figure 6. Nuclear stratification by Kaplan-Meier analysis.

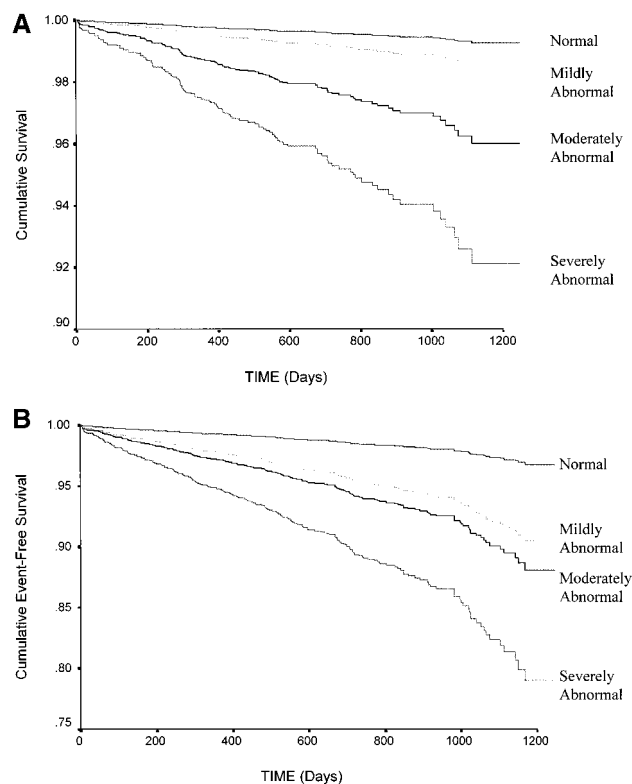
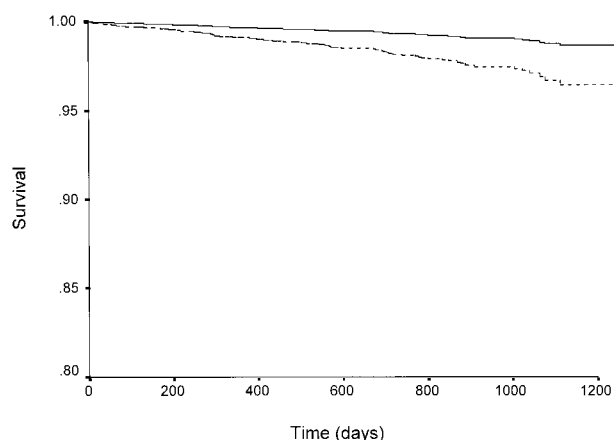


Figure 7. Risk-adjusted survival as a function of scan result using (A) cardiac death and (B) hard events as an end point.  $P < .00001$  across scan results for both end points.

mental prognostic value toward the prediction of both myocardial infarction and cardiac death. Statistically significant and clinically relevant risk stratification was achieved by the nuclear test even after initial stratification by prescan information. Patients with normal scans had low rates of both outcomes, whereas patients with mildly abnormal scans who underwent exercise stress were at intermediate risk for myocardial infarction but low risk of cardiac death, and patients with moderately or severely abnormal scans were at intermediate to high risk of both myocardial infarction and cardiac death. A risk-adjusted comparison of post-nuclear testing referral to early revascularization versus medical therapy suggested a survival advantage to the former, predominantly in patients with severely abnormal scans. Finally, cost analysis reveals that referral to catheterization only in those patients with moderately to severely abnormal scans rather than all abnormal scans after exercise stress would result in a 33.5% cost savings.

### Comparison With Previous Studies

The current study is the first to be sufficiently powered to examine differences in the rates of myocardial infarction and cardiac death after stress perfusion testing. Although a number of previous studies have demonstrated the incremental prognostic value of myocardial perfusion SPECT over clinical and exercise data,<sup>1,13,14,20-23</sup> they all used either combined hard events or total events (hard events or late revascularization) as end points. Although the results of radionuclide angiography have been assessed toward the end point of cardiac death,<sup>24</sup> no previous study has assessed myocardial perfusion imaging toward this end point. Harris and colleagues<sup>25</sup> compared the rates of cardiac death and myocardial infarction in 1214



**Figure 8.** Risk-adjusted survival in patients who underwent revascularization early after nuclear testing (solid line) versus medical therapy (dashed line). Mantel-Cox  $P < .005$ .

catheterized patients treated medically. In this study, patients with single-vessel disease experienced predominantly nonfatal myocardial infarction as their events, whereas patients with more extensive anatomic disease had cardiac death as a larger proportions of their events.

### Prevention of Myocardial Infarction Versus Prevention of Cardiac Death

Several large trials have demonstrated the superiority of CABG over medical treatment for lowering cardiovascular mortality in select subsets of patients with chronic coronary artery disease.<sup>2-4,26</sup> Recently, multivessel PTCA and CABG have been shown to have similar short-term survival rates.<sup>27-29</sup> It should be emphasized, however, that these randomized trials of PTCA and CABG dealt with a highly selective group of patients in whom the Duke databank experience and previous randomized trials would suggest very little benefit from revas-

**TABLE 3. Rates of Cardiac Death and Myocardial Infarction by Scan Result**

			Scan Result			
			Normal	Mildly Abnormal	Moderately-Severely Abnormal	
No known CAD	Anginal Sx	CD	0.2%	0.4%	3.2%	
		MI	0.3%	2.2%	6.3%	
		n	677	154	144	
	No anginal Sx	CD	0.1%	0.8%	5.6%	
		MI	0.2%	2.2%	2.2%	
		n	1639	282	183	
History of CAD	History of myocardial infarction	CD	1.0%	1.4%	3.7%	
		MI	1.3%	4.1%	4.1%	
		n	218	251	727	
		History of revascularization	CD	0.5%	0.2%	3.3%
			MI	2.1%	3.0%	3.0%
			n	324	262	602
	Anginal Sx	CD	0.8%	0.8%	3.7%	
		MI	1.6%	3.7%	4.4%	
		n	289	202	486	
	No anginal Sx	CD	1.2%	0.9%	3.5%	
		MI	1.7%	2.5%	3.1%	
		n	341	246	540	
Normal	Anginal Sx	CD	0.1%	0.2%	2.3%	
		MI	0.5%	3.4%	4.5%	
		n	729	249	375	
Rest ECG	No anginal Sx	CD	0.1%	0.8%	1.7%	
		MI	0.3%	1.9%	2.1%	
		n	1545	351	423	
Abnormal	Anginal Sx	CD	1.2%	1.6%	5.6%	
		MI	1.2%	2.1%	5.3%	
		n	237	107	255	
Rest ECG	No anginal Sx	CD	1.0%	1.0%	7.2%	
		MI	1.0%	3.2%	3.8%	
		n	435	177	300	

Sx indicates symptoms; CD, cardiac death; MI, myocardial infarction; and CAD, history of coronary artery disease. All rates are expressed per year of follow-up.  $P < .01$  in all groups as a function of scan result.

**TABLE 4. Comparative Costs of Clinical Strategies in Patients Undergoing Exercise Stress**

Strategy	Lk CAD	pCATH	pCD	Total Cost, \$	Cost per $\Delta$ HE, \$/ $\Delta$ HE
Catheterization of all abnormal scans	Low	.15	.0033	1 084 950	568 037
	Int	.23	.0108	1 785 150	419 049
	High	.45	.0144	1 201 350	702 544
Catheterization of scans with SSS >8	Low	.09	.0028	708 050*	266 184*
	Int	.15	.0072	1 159 050*	261 637*
	High	.32	.0288	879 650*	339 633*

Lk CAD indicates prescan likelihood of coronary artery disease; pCATH, probability of catheterization; pCD, probability of cardiac death; Total Cost, cost of overall strategy; Cost per  $\Delta$ HE, cost of testing relative to difference in hard event rate; and summed stress score (SSS) >8 defined moderately and severely abnormal scans.

\* $P < .001$  vs strategy of referring all abnormal scans to catheterization.

cularization over medical therapy with respect to survival would exist, although the impact on symptom relief would be significant.

Although the large, multicenter randomized clinical trials failed to show a reduction in infarction rates with surgical treatment, these studies were not powered to detect this difference, nor was myocardial infarction a primary end point. Furthermore, comparisons of infarction rates between the surgical and medical arms of these studies are obfuscated by the relatively high frequency of perioperative myocardial infarctions. A number of medical therapies have been shown to lower the frequency of both cardiac death and myocardial infarction in specific patient groups and to reduce the frequency of myocardial infarction in a general population.<sup>5-8</sup> If it would be possible to identify patients at intermediate to high risk for myocardial infarction but with a low risk of cardiac death (as shown previously<sup>25</sup>), a unique window of opportunity for treatment would exist.

### Implications for the Use of Nuclear Testing

In this study, all patients with a low prescan likelihood of coronary disease were at very low risk (<1% risk of either outcome). Because of the excessive cost to identify the few events that occurred (Table 4), these patients probably did not require nuclear testing unless quality of life was an issue. Of note, one third of our cohort fell into this low-risk category, as previously described.<sup>13,14</sup> The results of the present study were unchanged when this low-risk group was excluded, as shown by the results in patients with intermediate and high clinical risk that paralleled the overall study results.

In the present study, patients with mildly abnormal scans after exercise stress had a low risk of cardiac death but an intermediate risk of nonfatal myocardial infarction. Because these patients are unlikely to benefit from revascularization procedures (particularly because both PTCA and CABG are associated with mortality risks of  $\geq 1\%$ ) but would experience lowering of their risk for myocardial infarction by medical treatment, referral to catheterization and its accompanying costs may not be needed if these patients' symptoms could be controlled by medical therapy. Conversely, patients with severe and/or extensive scan abnormalities are at significant risk of cardiac death and should undergo further evaluation of their coronary anatomy. Unfortunately, the rate of referral to catheterization after nuclear testing has not been found to exceed 50% to 60% even in those patients with the greatest underlying risk.<sup>14,30,31</sup>

### Study Limitations

#### Technical

The SPECT studies used were interpreted by experienced observers using a standardized, validated semiquantitative visual method,<sup>11-14</sup> a method that served as the basis for the quantitative computer program developed in our center<sup>32</sup>; thus, our results should be similar to those obtained with quantification. Because the expertise of the observers in this study limits the extrapolation of our results to visual results from other centers, further studies using objective quantitative methods for analysis of SPECT studies would be of interest.

#### Clinical and Statistical

The patients in this study were typical of those referred to a university-affiliated community hospital in a major urban area, and the results of this study should be applicable to this setting. Because of the expertise of our laboratory, it is possible that our findings may not be applicable to all laboratories nationally.

Although myocardial infarction and cardiac death are related in many cases, it is virtually impossible to accurately determine the exact cause of cardiac death in each patient. The separation of these two events may be problematic. However, numerous major, well-accepted, prospective, randomized clinical trials have included these end points as separate outcomes.<sup>2-8</sup> With respect to the identification of differential risk for myocardial infarction compared with cardiac death, the pattern of risk we describe for particular patient subgroups is not dissimilar to that previously described with other modalities.<sup>25</sup> Although the prediction of cardiac death versus myocardial infarction in a particular patient is difficult, it appears to be possible to identify distinct populations in which one event is significantly more likely to occur than the other. Finally, the analysis comparing medical and early revascularization treatments after nuclear testing is limited in that it is a nonrandomized analysis; risk-adjusting these models in no way overcomes the nonrandomized nature of this analysis.

### Conclusions

Even after all clinical, historical and exercise information is considered, myocardial perfusion SPECT yields incremental prognostic information for prediction of both cardiac death and hard events. Clinically relevant stratification was present with both exercise and adenosine stress in intermediate- and high-clinical-risk subgroups. This stratification revealed that patients with mildly abnormal scans after exercise stress are at



low risk for cardiac death but intermediate risk for nonfatal myocardial infarction and thus may benefit from medical management and may not require invasive intervention.

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## **Incremental Prognostic Value of Myocardial Perfusion Single Photon Emission Computed Tomography for the Prediction of Cardiac Death: Differential Stratification for Risk of Cardiac Death and Myocardial Infarction**

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