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Effective Risk Stratification Using Exercise Myocardial Perfusion SPECT in Women: Gender-Related Differences in Prognostic Nuclear Testing

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Objectives. **This study was designed to evaluate the incremental prognostic value over clinical and exercise variables of rest thallium-201/exercise technetium-99m sestamibi single-photon emission computed tomography (SPECT) in women compared with men and to determine whether this test can be used to effectively risk stratify patients of both genders.**

Background. **To minimize the previously described gender-related bias in the evaluation of coronary artery disease in women, there is a need to identify a noninvasive testing strategy that is able to accurately and effectively risk stratify women.**

Methods. **We identified 4,136 consecutive patients (2,742 men, 1,394 women) who underwent dual-isotope SPECT. The incremental value of nuclear testing was determined using both a stepwise Cox proportional hazards model and Kaplan-Meier survival analysis. Receiver operating characteristic curve analysis was performed to determine test discrimination for high risk patients in men and women.**

Results. **The patient population was followed up for 20 ± 5 months for events (cardiac death or nonfatal myocardial infarction). During this time, 63 myocardial infarctions and 32 cardiac deaths occurred in the men, and 31 myocardial infarctions and 14 cardiac deaths occurred in the women. Nuclear testing significantly stratified both men and women irrespective of their rest electrocardiogram. Cox proportional hazards analysis revealed that nuclear testing added incremental prognostic value in both men and women after inclusion of the most predictive clinical and exercise variables (overall chi-square 89 in men vs. 120 in women, $p < 0.005$). Kaplan-Meier survival analysis demonstrated that nuclear testing further stratified men and women with both intermediate to high and low prescan likelihoods of coronary artery disease ($p < 0.005$ for all). Receiver operating characteristic curve analysis demonstrated superior discrimination for the nuclear scan results in identifying high risk women than men (area under the curve: 0.84 ± 0.03 vs. 0.71 ± 0.03 in men, $p < 0.0005$). The odds ratio comparing event rates in patients with abnormal versus those with normal scan results was greater in women than in men, suggesting superior stratification using nuclear testing in women.**

Conclusions. **Dual-isotope myocardial perfusion imaging yields incremental prognostic value in both men and women. This modality identifies low risk women and men equally well but relatively high risk women more accurately than relatively high risk men and, thus, is able to stratify women more effectively than men.**

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Ischemic heart disease is the leading cause of death in both men and women in the United States (1). Although the incidence of nonfatal coronary artery disease has doubled among women in the past decade (2), and the rate of referral of women to interventional testing and revascularization has also increased (2), a number of studies have found that coronary artery disease in women is identified less often (3), at a later stage (4) and treated less aggressively than in men (5–10).

Some investigators suggest that these differences are appropriate when corrected for baseline group differences (9–11), but others consider them illustrative of a gender-related bias in the diagnosis and management of coronary artery disease (6–9). To minimize this bias in the evaluation of women, there is a need for a noninvasive test strategy that is able to accurately and economically risk stratify women, thus identifying a subset of patients in need of further, invasive testing and possible revascularization. In this context, although previous studies have contrasted the diagnostic efficacy of electro-

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cardiographic (ECG) and nuclear stress testing in women and men, prognostic efficacy has not been similarly compared.

We undertook the present study to determine whether nuclear exercise testing adds similar incremental prognostic information over that provided by clinical and exercise data in women compared with men and whether this modality, incorporated in a clinical strategy, can be used to effectively risk stratify both men and women.

Methods

Study population. This study was a retrospective analysis of data from 4,620 consecutive patients (3,100 men, 1,520 women) who underwent rest thallium-201/exercise technetium-99m sestamibi separate-acquisition dual-isotope single-photon emission computed tomography (SPECT) between January 1, 1991 and December 1, 1993 at Cedars-Sinai Medical Center. Patients who were known to have valvular heart disease or primary cardiomyopathy were excluded. Of the initial population, 139 men and 59 women were lost to follow-up, and 12 men and 4 women were excluded because of missing data, resulting in a study population of 4,406 (2,949 men, 1,457 women).

Patients who underwent revascularization within 60 days of the index dual-isotope SPECT exercise test were censored from all analysis and were not considered in the analysis of patient outcomes after 60 days. Of the 4,406 patients (2,949 men, 1,457 women [95% of the initial population]), 207 men and 63 women were thus censored. This temporal threshold was utilized to provide discrimination between patients with and without clinical deterioration that may have resulted in late referral to revascularization. We have previously reported (12,13) that patients who are referred to revascularization within the first 60 days after nuclear testing do so, in large part, on the basis of their scan results, whereas patients who are referred to revascularization >60 days after nuclear testing tend to be referred because of worsening of clinical status. Thus, the data presented here are based on a subset of 4,136 patients (2,742 men, 1,394 women).

Exercise myocardial perfusion protocol. All patients underwent exercise dual-isotope myocardial perfusion imaging as previously described (13). Whenever possible, beta-adrenergic blocking agents and calcium channel antagonists were discontinued 48 h before testing, and nitrate compounds were discontinued for 6 h before testing. Before exercise, thallium-201 (2.5 to 3.0 mCi) was injected intravenously at rest, with dose variation based on patient weight. Rest thallium-201 SPECT imaging was initiated 10 min after injection of the isotope. In a minority of patients, thallium redistribution images (24-h images) were obtained, and the results were considered in our analysis in place of the rest thallium scores. After thallium imaging, all patients performed a symptom-limited exercise treadmill test (ETT) using standard protocols with 12-lead ECG recording of each minute of exercise. Blood pressure was recorded at rest, at the end of each exercise stage and at peak exercise. Maximal degree of ST segment change at 80 ms after the J point of the ECG was measured and assessed as horizontal, upsloping or downsloping.

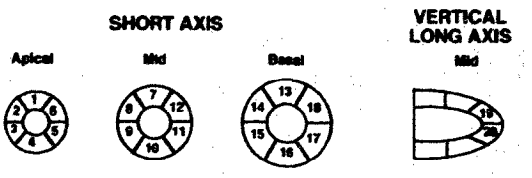


Figure 1. Assignment of myocardial regions for scoring of SPECT images. Usually, scans with multiple segments scored as having stress/rest scores of 1 to 0 or a single segment with a stress score of 2 were classified as equivocal. Scans with two segments assigned stress scores of 2 were classified as probably abnormal, and scans containing two or more stress segments assigned scores of 2 or scans with one or more segments assigned scores of 3 were classified as definitely abnormal. Assignment of segmental scores took into account knowledge of normal segment variation. Reversibility of segmental scores influenced the interpretation toward abnormal. When fixed defects on the stress study were considered to be secondary to attenuation, their score was decreased to 1. If apparent apical defects were considered likely to represent normal apical thinning, or if defects were considered to be secondary to breast attenuation, they were assigned a score of 1. On the basis of these scoring guidelines, the observers judged each patient's study results as normal, probably normal, equivocal, probably abnormal or definitely abnormal in a reading blinded to the patients clinical historical and exercise treadmill information. The observers were then made aware of the patient's other relevant, nonnuclear information and formed a final interpretation of the study (scan result), which by agreement among observers could not vary by more than one grade from the initial (blinded) interpretation.

The *ECG response* to testing was categorized as either *nonischemic* (no significant ECG changes), *ischemic* (>1-mm horizontal or downsloping ST segment elevation or depression except in leads without significant Q waves or in lead aVR), *equivocal* (borderline ECG changes) or *nondiagnostic* (exercise-induced ECG changes uninterpretable because of digoxin use, paced rhythm, bundle branch block). The *clinical response* to exercise was also assessed as either *nonischemic, ischemic* (anginal symptoms during exercise), *equivocal* or *abnormal* (exertional hypotension or inappropriate shortness of breath).

At near-maximal exercise, a 20- to 30-mCi dose of Tc-99m sestamibi was injected (actual patient dose varied with patient weight), and exercise continued for one additional minute after injection. The SPECT imaging was begun 30 min after isotope injection and was performed as previously described (14). All images were subject to quality control measures (15).

Image interpretation. Semiquantitative visual interpretation was performed using short-axis, vertical long-axis and horizontal long-axis tomograms (15). The short-axis and vertical long-axis myocardial tomograms were divided into 20 segments and were scored by consensus of two experienced observers (Fig. 1).

Scintigraphic indexes. A summed stress score was obtained by adding the score of the 20 segments of the stress images. A summed rest thallium defect score was obtained by similarly adding 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* and represents the amount of ischemia present. All three of these derived nuclear variables measure both the extent and severity of perfusion abnormalities (13,14). Whenever available, scores of late redistribution rather than rest thallium images were used. Fewer women than men had late imaging (43 [3.1%] of 1,394 women, 155 [5.6%] of 2,742 men, $p < 0.001$).

Patient follow-up. Patient follow-up was performed by scripted telephone interview by interviewers who had knowledge of the patient's test results. *Events* were defined as either cardiac death (confirmed by review of death certificate and hospital chart or physician's records) or nonfatal myocardial infarction (documented by appropriate ECG and cardiac enzyme level changes). If a patient was found to have had both more than one event after nuclear testing, the more serious event (e.g., cardiac death) was considered; if two myocardial infarctions occurred, the temporally proximal event to the index test was considered. When *interventions* (cardiac catheterization, coronary artery bypass surgery or percutaneous translumina! coronary angioplasty) were identified, these outcomes were confirmed by hospital records or physician's office records. All patients included in this report were followed up for at least 1 year (mean 20 ± 5 months).

Likelihood of coronary artery disease. For purposes of analyzing patients in different risk subsets, we used analysis of the preexercise and prescan likelihood of coronary artery disease as aggregate descriptors of proven prognostic importance based on Bayesian analysis of age, gender, symptom classification, rest ECG, cardiac risk factors and (for prescan likelihood) the results of ECG stress testing but not the nuclear scan information (exercise heart rate, blood pressure, duration, magnitude and slope of ST segment changes, exertional hypotension and rest ECG characteristics) and calculated using CADENZA (16). In patients with a prior history of myocardial infarction, the likelihood of coronary artery disease was assumed to be 1, and in patients with previously documented coronary artery disease without prior myocardial infarction, the value represents the likelihood of exercise-induced ischemia rather than likelihood of anatomic disease (17).

Statistical analysis. Comparisons between patient groups were performed using a one-way analysis of variance for continuous variables and a chi-square test for categoric variables. All continuous variables are described as mean value ± SD. Receiver operating characteristic curves are described as mean value ± SEM. A p value < 0.05 was considered statistically significant.

Incremental value. To determine the additive prognostic value of a test it is necessary to include all other information known regarding the patient before that time. With this in mind, incremental prognostic value was determined in three different ways:

MULTIVARIATE ANALYSIS. The Cox proportional hazards model (BMDP version 7) (18,19) was developed in a stepwise fashion to determine four distinct statistical models each determining the best predictor of events on the basis of 1) clinical information, 2) exercise information, 3) nuclear information, and 4) the increase in prognostic information after adding the most predictive clinical and exercise variables (model 2) to a model that "forces in" the best clinical variables (model 1), and 5) a model to determine the increase in prognostic information after adding the most predictive nuclear variables (model 3) to a model that "forces in" the best clinical and exercise variables (model 4). Entry significance threshold into the model was $p < 0.05$. A statistically significant increase in the global chi-square of the model after the addition of the nuclear variables would indicate incremental prognostic value. Details of this analysis are described in the Appendix.

SURVIVAL ANALYSIS. Cumulative survival rates as a function of time after the index nuclear exercise test were calculated using the Kaplan-Meier method and compared using the Mantel-Cox test (19,20). Patients were first stratified in this analysis by prescan likelihood of coronary artery disease (thus incorporating information derived from patient historical data and risk factors as well as the results of exercise ECG testing) into low and high clinical risk subgroups. 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 ($p < 0.05$ by Mantel-Cox test).

Test discrimination. The areas under the receiver operating characteristic (ROC) curves (expressed as the area ± SEM) were compared to assess the relative ability of nuclear testing to discriminate between low and high risk patients in both men and women. Differences between ROC curve areas were expressed relative to a baseline area of 0.5, a value reflecting absence of discrimination (20–25).

Effectiveness of stratification. Effectiveness of stratification, that is, the assignment of patients to high and low risk groups, was expressed as an odds ratio of an event given an abnormal versus a normal scan. These odds ratios in men and women were compared using the Mantel-Haenszel statistic and test of homogeneity of odds ratios (19).

Results

Initial patient population. The 2,742 men and 1,394 women included in the prognosis analysis are characterized in Table 1. The women were significantly older and presented with nonanginal symptoms or atypical angina and multiple cardiac risk factors more frequently than did the men, who more commonly presented without symptoms at the time of nuclear testing. The men had a more frequent history of previous myocardial infarction or cardiovascular intervention (cardiac catheterization, bypass surgery or percutaneous translumina! coronary angioplasty) and had a higher pre-ETT and prescan likelihood of coronary artery disease.

Outcome events. Among the 2,742 men and 1,394 women, a total of 95 events occurred during the follow-up period in men and 45 events in women. These included 63 myocardial infarctions and 32 cardiac deaths in the men and 31 myocardial

Table 1. Patient Characteristics

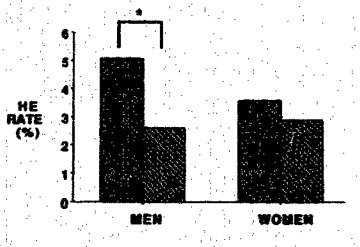
	Men (n = 2,742)	Women (n = 1,394)	p Value
Age (yr)	61.7 ± 12.2	64.5 ± 11.8	<0.001
Cardiac risk factors			
0	23% (635)	19% (259)	<0.004
1	37% (1,016)	34% (477)	NS
2	26% (719)	31% (431)	<0.001
>2	14% (372)	16% (227)	NS
Symptoms			
Asymptomatic	43% (1,193)	28% (387)	<0.001
Nonanginal	21% (592)	27% (374)	<0.001
Atypical angina	20% (554)	28% (386)	<0.002
Typical angina	12% (341)	14% (191)	NS
SOB	2% (62)	4% (56)	NS
Hx MI	24% (666)	14% (198)	<0.001
Hx cath	39% (1,070)	19% (271)	<0.001
Hx PTCA	14% (398)	6% (91)	<0.001
Hx CABG	17% (466)	6% (86)	<0.001
Hx CAD	46% (1,267)	25% (353)	<0.001
Pre-ETT Lk CAD	0.49 ± 0.36	0.42 ± 0.34	<0.001
Postscan Lk CAD	0.49 ± 0.42	0.41 ± 0.38	<0.001

Data presented are mean value ± SD or percent (number) of patients. CABG = coronary artery bypass surgery; CAD = coronary artery disease; cath = cardiac catheterization; ETT = exercise test; Hx = history of; Lk = likelihood of; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SOB = shortness of breath.

infarctions and 14 cardiac deaths in the women. The overall event rate was 3.5% in the men and 3.2% in the women (p = NS). The censored revascularization rate (revascularization within the first 60 days after nuclear testing) was 7.5% in men (207 patients) and 4.5% in women (63 patients, p = 0.04).

The frequency of events as a function of presenting symptoms is illustrated in Figure 2. Although a difference in the event rate between anginal and nonanginal presentations was present in men (anginal 5.1%, nonanginal 2.6%, p < 0.001), there was no such difference in women (anginal 3.6%, nonanginal 2.9%, p = NS). The frequency of events as a function of scan result is illustrated in Figure 3. The event rate increased as a function of scan result in both men and women (both p < 0.001). This rate increased more rapidly in women than in men

Figure 2. Event rates in men and women as a function of presenting symptoms (anginal [**solid bars**] vs. nonanginal [**hatched bars**]). The event rate in men with anginal symptoms was significantly greater than that in men with nonanginal symptoms (*p < 0.0001). HE rate = hard event rate over the follow-up period. No such difference was present in the women.



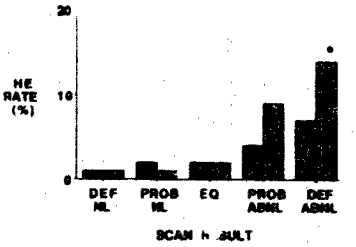


Figure 3. Event rates in men (**solid bars**) and women (**hatched bars**) as a function of scan result. The event rate in women with definitely abnormal (DEF ABNL) scan results was significantly greater than that in men (*p < 0.001). EQ = equivalent; DEF NL = definitely normal; HE rate = hard event rate over the follow-up period; PROB ABNL = probably abnormal; PROB NL = probably normal.

as the scan result worsened; women with a definitely abnormal scan response had greater than twofold higher event rate than men (13.9% vs. 6.6%, p = 0.001).

Incremental value and the rest ECG: univariate analysis. The frequency of events as a function of summed stress score after subgrouping by rest ECG results is shown in Figure 4. In both men (Fig. 4A) and women (Fig. 4B), significant stratification occurred as a function of summed stress score in patients with both interpretable and uninterpretable rest ECGs. After elimination of patients at low risk (prescan likelihood of coronary artery disease < 0.15), the remaining women and men with interpretable rest ECGs were significantly stratified by the nuclear test result (Fig. 4).

Univariate analysis. Clinical patient characteristics, exercise and nuclear variables in patients with and without subsequent events after nuclear testing in men and women are presented in Tables 2 to 4, respectively. In general, the patients with events were older and more symptomatic, had a higher pre-ETT and post-ETT likelihood of coronary artery disease as well as greater abnormalities on their exercise and nuclear tests.

Multivariate analysis. In men, the likelihood of coronary artery disease before exercise testing, an ECG uninterpretable for exercise testing, a history of known coronary artery disease and number of cardiac risk factors were found to be the clinical predictors of events (global chi-square 56), whereas likelihood of coronary artery disease before exercise testing, an ECG uninterpretable for exercise testing and number of cardiac risk factors were included in the most predictive Cox clinical model in the women (global chi-square 48). In the Cox model for combined clinical and exercise variables, likelihood of coronary artery disease before exercise testing, peak rate-pressure product and exercise duration were the clinical and exercise model predictors in men (global chi-square 75). In women, the clinical and exercise Cox model consisted of prescan likelihood of coronary artery disease, peak rate-pressure product and exercise duration (global chi-square 75). The Cox model for nuclear variables consisted of the summed stress score in men (global chi-square 61) and the summed difference score and multivessel disease by perfusion scan in the women (global chi-square 114).

JACC Vol. 28, No. 1
July 1996:34–44

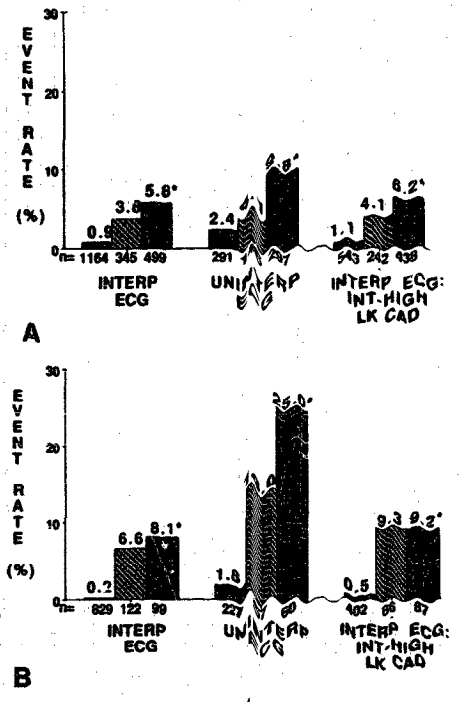


Figure 4. Event rates in men (A) and women (B) subgrouped by rest electrocardiogram interpretable for treadmill testing (INTERP ECG), uninterpretable for treadmill testing (UNINTERP ECG) and interpretable for treadmill testing but excluding patients with a prescan likelihood of coronary artery disease <0.15 (INTERP ECG: INT-HIGH LK CAD). Within each of the three subgroups, in both men and women, there was a significant difference found in the hard event rate over the follow-up period as a function of the summed stress score. **Solid bars** = summed stress score <4 (normal); **hatched bars** = summed stress score 4 to 8 (mildly abnormal); **gray bars** = summed stress score >8 (severely abnormal). *p < 0.05.

Incremental value. *Cox proportional hazards.* As shown in Figure 5, when added to the clinical and exercise model in the Cox proportional hazards analysis, nuclear data provided 17% additional prognostic information in the men and 37% in the women compared with clinical and exercise variables alone (both $p < 0.001$). The gain in total chi-square was 15 in the men (global chi-square 90) and 45 in the women (global chi-square 120).

Kaplan-Meier analysis. In the men, stratification of the study cohort into low clinical risk (prescan likelihood of coronary artery disease <0.15, n = 977) and high clinical risk (prescan likelihood of coronary artery disease ≥ 0.15, n = 1,765) resulted in populations with significantly different event rates (low risk 1.0% vs. high risk 4.4%, p = 0.0002, chi-square 14) (Fig. 6A). The use of nuclear testing stratified the high clinical risk group into a subgroup with normal scan results and a low event rate (1.9% [1.1%/year of follow-up]) and subgroups with significantly higher event rates with abnormal scan results (event rate 6.2%, $p < 0.0001$, chi-square 19 vs. normal scan results) (Fig. 6C). The low clinical risk group was also further stratified into a low event rate subgroup with normal scan results (0.2% event rate) and a higher risk group with abnormal scan results (event rate 4.6%, p = 0.00001, chi-square 20 vs. normal scan results and low clinical risk) (Fig. 6B). In both low and high risk subgroups, the use of scan findings resulted in a fivefold difference in event rates between normal and abnormal scan results.

In the women, a qualitatively similar but quantitatively more impressive stratification was present. Prescan likelihood of coronary artery disease separated the cohort into low clinical risk (n = 556, event rate 0.7%) and high clinical risk (n = 838, event rate 4.4%) subgroups, $p < 0.001$, chi-square 11) (Fig. 7A). The high clinical risk group was stratified into a subgroup with normal scan results and a low (0.8%) event rate and a high risk group with abnormal scan results (event rate 12.7%, $p < 0.0001$, chi-square 58 vs. normal scan results) (Fig. 7C). Significant stratification was noted in the low clinical risk women; a normal scan result identified a low risk subgroup (event rate 0.2%), whereas an abnormal scan result identified a subgroup with a higher event rate (4.3% [2 events in 46 patients], $p < 0.0002$, chi-square 14 vs. normal scan results) (Fig. 7B). These analyses demonstrate a more clinically relevant incremental prognostic value of nuclear testing in men and women.

Comparison of discrimination of nuclear testing in men and women. To directly compare the relative discrimination of nuclear testing in men versus women with respect to identifying high risk subjects, we compared the areas under the ROC curves to compare the discrimination for predicting events using the summed stress score. The area under the curve in women (0.84 ± 0.03) was significantly greater than that for men (0.71 ± 0.03, $p < 0.0005$ vs. women). This finding demonstrates that nuclear testing is better able to identify women at high risk of future events than men independently of baseline event rates, diagnostic thresholds or selection bias.

Test effectiveness. Nuclear testing also risk stratified women more effectively than men (odds ratio [OR] for an event with abnormal vs. normal scan results: men 4.4, women 22.8, Mantel-Haenszel OR 6.8, 95% confidence interval ([CI] 4.7 to 9.7, chi-square 109, $p < 0.0001$). This significant difference in stratification effectiveness was present between men and women in all prescan likelihood categories, demonstrating that this effectiveness was independent of underlying patient characteristics and ECG exercise test results (Mantel-Haenszel OR 5.1, 95% CI 2.2 to 11.9 for low [<0.15] prescan likelihood of coronary artery disease; OR 8.0, (95% CI 4.2 to 15.4 for intermediate [0.15 to 0.85] prescan likelihood of coronary artery disease; OR 3.6, (95% CI 1.9 to 6.9 for high [>0.85] prescan likelihood of coronary artery disease). Thus, although the results of nuclear testing risk stratified both men and women, the resultant stratification was more effective in women—similar low event rates in both male and female patients with normal scan results but significantly higher event

Table 2. Clinical Patient Characteristics After Nuclear Testing

	Women			Men		
	Events (n = 45)	No Events (n = 1,349)	p Value	Events (n = 95)	No Events (n = 2,647)	p Value
Age (yr)	69.4 ± 11.6	64.4 ± 11.8	<0.005	66.2 ± 13.1	61.5 ± 12.1	<0.004
Symptoms						
No angina	40% (18)	55% (743)	NS	44% (42)	66% (1,743)	<0.001
Angina	47% (21)	41% (556)	NS	48% (46)	32% (849)	<0.001
SOB	13% (6)	4% (50)	<0.01	7% (7)	2% (55)	<0.003
Pre-ETT Lk CAD	0.68 ± 0.33	0.42 ± 0.31	<0.009			
ECG uninterp for ETT	60% (27)	23% (317)	<0.001	44% (42)	26% (692)	<0.001
Hx CAD	58% (26)	24% (327)	<0.001	76% (72)	43% (1,135)	<0.001
Cardiac risk factors*						
0 or 1	31% (14)	60% (722)	<0.006	49% (46)	69% (1,821)	<0.04
>1	69% (31)	40% (627)	<0.006	51% (47)	31% (984)	<0.04

*Hypertension, diabetes, elevated cholesterol levels, family history of coronary artery disease. Data presented are mean value ± SD or percent (number) of patients. ECG = electrocardiogram; uninterp = uninterpretable; other abbreviations as in Table 1.

rates in women with abnormal scan results than their male counterparts (11.5% for women, 5.8% for men, $p < 0.0001$).

Discussion

To our knowledge, this is the first study to compare the prognostic significance of exercise myocardial perfusion scintigraphy in men and women. This study demonstrates that exercise dual-isotope myocardial perfusion scintigraphy yields additional prognostic information over that obtained from clinical and treadmill exercise variables alone in both women and men followed up over a 20-month mean period after testing. This incremental value was demonstrated in the setting of rest ECGs that were interpretable and uninterpretable for treadmill testing both in men and in women. After stratification by clinical criteria, high risk groups could be further stratified by nuclear testing into subgroups with low (<1% event rate/year) and relatively high event rates (>5% event rate/year) in both men and women, thus demonstrating clinically relevant incremental prognostic information. Prognostic nuclear testing had superior discrimination for identifying high risk patients in women compared with men in this study. Finally, stratification was more effective in women than men, as measured by the odds ratio of events in abnormal versus normal scan results, a function of the greater event rate associated with abnormal scan results in women.

Coronary artery disease in women. Numerous studies have demonstrated differences in coronary artery disease characteristics, management and related outcomes in men and women (2–9,11,26–32). There is conflicting information regarding the

Table 3. Exercise Characteristics After Nuclear Testing

	Women			Men		
	Events	No Events	p Value	Events	No Events	p Value
Ex duration (min)	4.1 ± 2.0	5.8 ± 2.3	<0.001	6.6 ± 2.7	8.0 ± 2.9	<0.001
Peak heart rate (beats/min)	135 ± 14	144 ± 18	<0.001	135 ± 18	147 ± 20	<0.001
Peak BP (mm Hg)	163 ± 28	172 ± 26	<0.001	167 ± 26	177 ± 26	<0.001
RPP (beats/min × mm Hg)	22,085 ± 4,653	24,782 ± 4,814		22,629 ± 5,016	26,271 ± 5,478	
Post-ETT Lk CAD	0.76 ± 0.32	0.39 ± 0.36				
MPHR (%)	90.5 ± 9.4	92.3 ± 10.3	NS	86.0 ± 10.1	92.9 ± 9.8	NS
ECG response						
Nonischemic	24% (11)	46% (618)	<0.004	36% (34)	45% (1,187)	NS
Ischemic	27% (12)	22% (304)	NS	25% (24)	27% (706)	NS
Abnormal	42% (19)	20% (277)	<0.001	35% (33)	20% (531)	NS
Equivocal	7% (3)	11% (150)	NS	4% (4)	8% (223)	NS
Ex-induced angina						
None	55% (25)	81% (1,098)	<0.07	65% (62)	83% (2,194)	0.001
Present	29% (13)	9% (128)	<0.04	20% (19)	9% (249)	0.001
Equivocal	9% (4)	6% (82)	<0.04	4% (4)	3% (94)	NS
Abnormal response but nonischemic	7% (3)	3% (42)	NS	10% (10)	4% (110)	NS

Data presented are mean value ± SD or percent (number) of patients. BP = blood pressure; ECG = electrocardiographic; Ex = exercise; HR = heart rate; MPHR = maximal predicted heart rate, achieved; RPP = rate-pressure product.

JACC Vol. 28, No. 1
July 1996:34–44

Table 4. Nuclear Variables After Nuclear Testing*

	Women		Men	
	Events	No Events	Events	No Events
SSS	11.2 ± 8.4	2.7 ± 5.5	14.1 ± 11.1	6.5 ± 8.9
SDS	8.9 ± 8.1	1.9 ± 3.4	7.9 ± 7.9	4.2 ± 6.0
SRS	2.2 ± 4.0	0.8 ± 3.1	6.0 ± 8.3	2.2 ± 5.7
Nonreversible defects	0.9 ± 0.7	0.3 ± 1.2	2.2 ± 2.9	0.8 ± 2.0
Reversible defects	3.5 ± 3.0	0.6 ± 1.6	3.2 ± 3.2	1.6 ± 2.5
Multivessel disease	82% (37)	5% (68)	39% (37)	14% (384)
Normal scan results	13% (6)	78% (1,050)	21% (20)	54% (1,437)

*$p < 0.001$ for all comparisons. Data presented are mean value ± SD or percent (number of patients). SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.

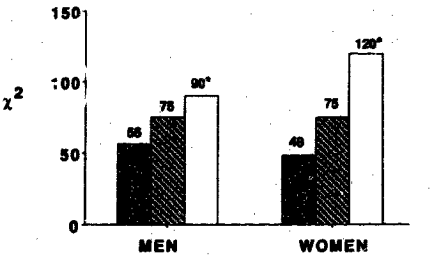


Figure 5. Results of determination of incremental prognostic value using the Cox proportional hazards model in men and women for the three models tested (clinical variables **[solid bars]**, clinical plus exercise variables **[hatched bars]**, clinical plus exercise plus nuclear variables **[open bars]**). The chi-square of the model including all variables was significantly greater than that for clinical plus exercise variables in both men and women. *$p < 0.0001$.

accuracy of noninvasive methods in identifying coronary artery disease in women. Although we previously showed (33) that the diagnostic accuracy of perfusion scintigraphy is similar in women and men, technical difficulties in the interpretation of scans in women has led to a perception of reduced diagnostic accuracy in this group.

Risk stratification in women by noninvasive testing. Studies assessing the prognostic value of noninvasive testing in women have been limited. Data from the Coronary Artery Surgery Study indicate that exercise ECG testing was able to risk stratify both men and women (34). Recently, Pancholy et al. (35) found that nuclear testing was prognostically predictive in women and added incremental prognostic information over clinical and exercise variables in a catheterized population but did not compare their prognosis with a male group. The present study also demonstrates the incremental prognostic value of nuclear testing in women and extends these findings by demonstrating that nuclear testing has superior effectiveness and greater discrimination for the identification of high risk patients in women than in men.

Greater cardiac risk in women. In our current study, although men and women had similar low event rates after a normal scan, women had a higher event rate than men after an abnormal nuclear scan, explaining, in part, the statistically superior prognostic performance of nuclear testing in women. Previous reports have also shown that women with known coronary artery disease, myocardial infarction or coronary artery bypass surgery are at higher risk of an adverse outcome than their male counterparts (28–32). Shaw et al. (6) also found that women referred for noninvasive testing had a markedly greater rate of myocardial infarction or death than men (6.9% vs. 2.4%, $p < 0.002$). Several hypotheses have been advanced to account for these gender-related mortality differences. Surgical mortality increases with decreased patient height and lower coronary artery lumen diameter, both characteristics associated with women (36), possibly predisposing women to lowered thresholds for coronary occlusion by acute thrombus. Potentially, delayed referral or underreferral of women to intervention may also play a role in mortality and morbidity differences. However, we previously demonstrated (11) that after consideration of the extent and severity of stress perfusion abnormalities, no referral bias to catheterization or revascularization was present between men and women after nuclear testing. In fact, a greater rate of referral to catheterization was present in women with severe ischemia than in their male counterparts (11). The greater risk of adverse outcome in women with coronary artery disease and the difficulties associated with identification of high risk women on clinical grounds emphasize the need to identify a noninvasive testing modality to identify women at high risk of future events. The results of the current study suggest that this need can be met by nuclear testing in appropriate patient subsets.

Clinical implications for risk stratification. Although the Cox proportional hazards analysis documented the incremental value of nuclear testing in the overall patient population, the Kaplan-Meier analysis extended these findings by demonstrating the ability of nuclear testing to further stratify the patients in both low and high clinical risk groups. The use of nuclear testing in patients with a low prescan likelihood of coronary artery disease is questionable because of their low overall risk (37). However, the results of this analysis in the population of patients with an intermediate to high prescan likelihood of coronary artery disease is of clear importance because of their overall intermediate risk, indicating the need for further risk stratification.

When the two genders were compared directly, women were stratified significantly more effectively than men in the current study. Because proportionally fewer women than men had abnormal scan results and were thus categorized as high risk after nuclear testing, fewer women would require referral to further testing (e.g., catheterization). Thus, a clinical strategy incorporating nuclear testing may be less costly in women than men. However, this possibility requires further investigation and should be evaluated in future trials.

Incremental value as a function of rest ECG. Two recent studies have demonstrated that the incremental diagnostic value of nuclear testing for identifying severe coronary artery disease in patients with normal rest ECG findings is too small

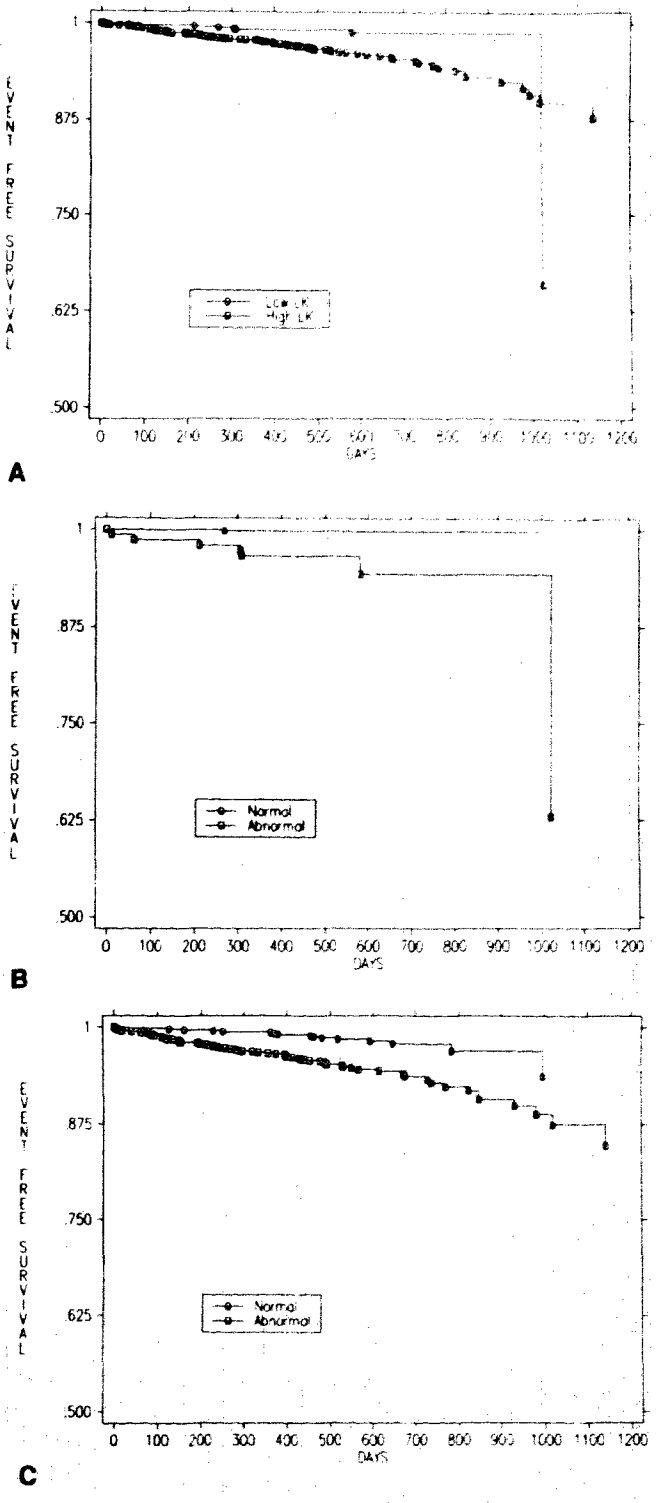


Figure 6. Survival curves for occurrence of events (cardiac death or nonfatal myocardial infarction) in men with **(A)** low and intermediate to high prescan likelihood **(LK)** of coronary artery disease, **(B)** low prescan likelihood of coronary artery with normal or abnormal scan results and **(C)** intermediate to high prescan likelihood of coronary artery disease with normal or abnormal scan results. Event-free survival was significantly lower for a high than a low prescan likelihood of coronary artery disease in **(A)** ($p < 0.001$) and for abnormal versus normal scan results **(B)** and **(C)** ($p < 0.005$ for both).

JACC Vol. 28, No. 1
July 1996:34–44

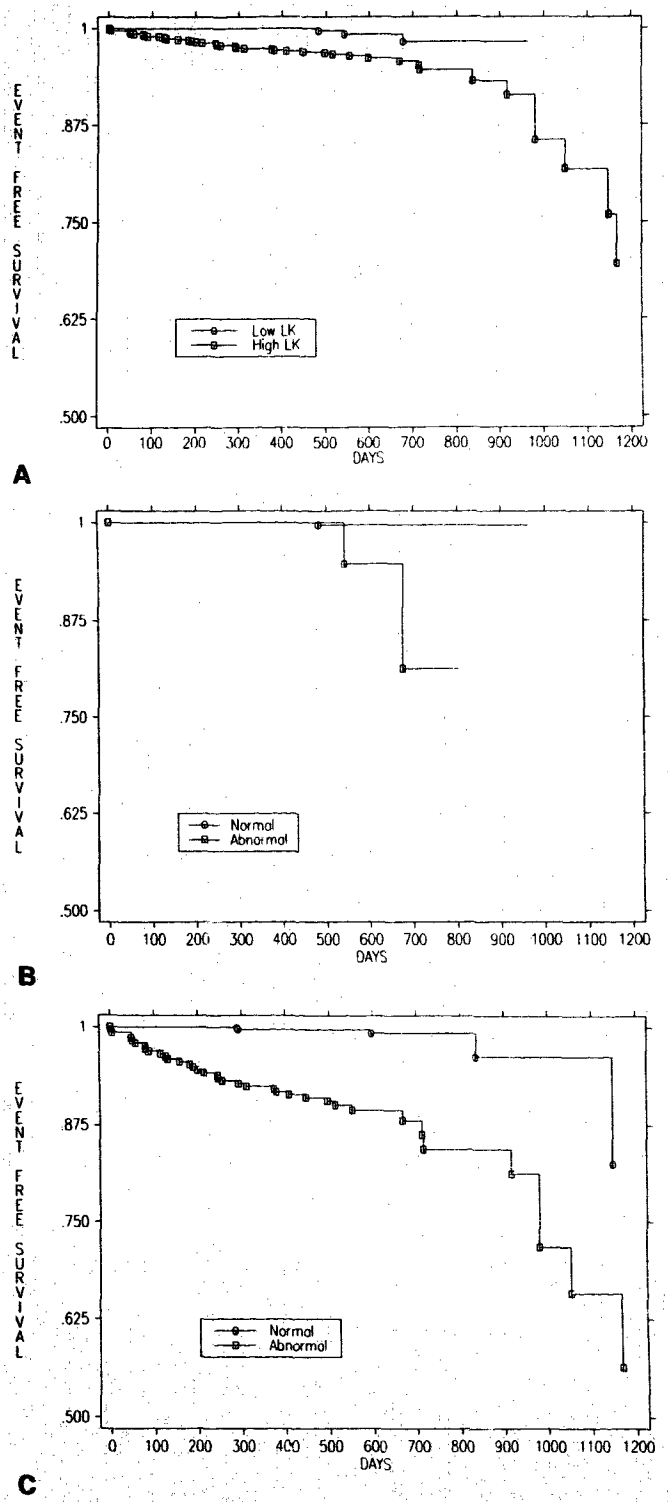


Figure 7. Survival curves for occurrence of events (cardiac death or nonfatal myocardial infarction) in women with **(A)** low and intermediate to high prescan likelihood (LK) of coronary artery disease, **(B)** low prescan likelihood of coronary artery disease with normal or abnormal scan results and **(C)** intermediate to high prescan likelihood of coronary artery disease with normal or abnormal scan results. Event-free survival was significantly lower for a high than a low prescan likelihood of coronary artery disease in **(A)** ($p < 0.002$) and for abnormal versus normal scan results in **(B)** and **(C)** ($p < 0.0001$ for both).

to justify its use (38,39). We previously demonstrated (37) that when an optimized noninvasive strategy is used in selecting patients for testing, sestamibi imaging significantly enhances both risk stratification and reduces the cost of the testing strategy in patients with normal rest ECG findings. The current study demonstrates that significant risk stratification is achieved by nuclear testing in both men and women with rest ECGs that are interpretable for exercise testing. This finding was present even after exclusion of patients with a low prescan likelihood of coronary artery disease who may not have required nuclear testing (Fig. 4).

Study limitations. *Technical.* Scintigraphic studies in the present study were assessed by experienced observers using a standardized, semiquantitative approach to visual interpretation that we previously developed (14) and documented to be highly reproducible (15). Nonetheless, the subjective nature of this analysis and its dependence on the expertise of the observer present a limitation with respect to the extrapolation of our results to those of other centers that would have been avoided by the use of quantitative methods for analysis of technetium-99m myocardial perfusion SPECT studies (40). These programs correlate highly with both visual scan assessment and coronary angiography (41). At the time of collection of the SPECT studies in this patient population, we did not have a quantitative analysis technique in operation on all of our camera/computer systems. Prognostic studies using quantitative analysis would be of interest.

The results of the present study may not be generalizable to myocardial perfusion imaging performed in women with stress–rest thallium protocols because the ability to assess stress-induced lung uptake of thallium, a powerful prognostic variable, is not possible with stress sestamibi protocols. However, the use of sestamibi in women may be advantageous because of its improved image quality and potentially reduced attenuation artifacts frequently found in women (42).

Patient cohort. Our patient population is taken from a group referred to exercise myocardial perfusion imaging for both prognostic and diagnostic testing, and we cannot exclude the possibility of bias introduced by way of this referral. The patients are nevertheless typical of those referred to a community hospital (university affiliated) in a major urban area, and the results of the present study should be applicable to this setting.

Statistical. The use of the Cox proportional hazards model is limited by the number of events accumulated during the follow-up period. The low loss to follow-up rate, the large patient group used and the adequate number of events favor the accuracy of our multivariate results (20).

Conclusions. The results of the present study demonstrate that nuclear stress perfusion imaging is an effective noninvasive means to risk stratify women into patient subgroups who are at low or relatively high risk of future cardiac events irrespective of rest ECG findings. In light of previous work demonstrating a gender-related referral bias in the diagnosis and treatment of cardiac disease, as well as gender-related differences in cardiac risk, this modality can play an important role in the assessment, and perhaps guide clinical management, of coronary artery of ischemic heart disease in women.

Appendix

Cox Proportional Hazards Model

In performing Cox proportional hazards analysis, we limited the number of variables entered into any model to 1 per 10 events of interest to avoid overfitting (20). The variables initially considered for analysis included clinical (all those listed in Table 1 as well as the rest ECG and the presence of individual cardiac risk factors); exercise (all those listed in Table 3 as well as blood pressure response to exercise and prescan likelihood of coronary disease); and nuclear (all those listed in Table 4 as well as the presence of transient ischemic dilation of the left ventricle) variables.

The selection of the variables for entry into the multivariate models detailed here was based on the results of univariate analysis. Variables were examined for colinearity, and the proportional hazards assumption was tested. For men the particular variables entered into the models included 1) *clinical*—pre-exercise treadmill testing (ETT) likelihood of coronary artery disease, age, number of cardiac risk factors and presenting symptoms; 2) *exercise*—prescan likelihood of coronary artery disease, clinical response to exercise, exercise duration, rate-pressure product and ECG response to exercise; 3) *clinical plus exercise*—pre-ETT likelihood of coronary artery disease, uninterpretable rest ECG, coronary artery disease, number of cardiac risk factors, prescan likelihood of coronary artery disease, rate-pressure product and exercise duration; 4) *nuclear*—multivessel disease by scan, summed stress score and summed difference score; and 5) *clinical plus exercise variables forced in, with nuclear variables added*—uninterpretable rest ECG, coronary artery disease and number of cardiac risk factors, exercise duration, rate-pressure product forced in and the summed stress score added. Those for women included 1) *clinical*—pre-ETT likelihood of coronary artery disease, history of coronary artery disease, number of cardiac risk factors, age, uninterpretable rest ECG for exercise testing; 2) *exercise*—prescan likelihood of coronary artery disease, rate-pressure product, exercise duration, clinical response to exercise and ECG response to exercise; 3) *clinical plus exercise*—pre-ETT likelihood of coronary artery disease, uninterpretable rest ECG, number of cardiac risk factors, exercise duration and rate-pressure product; 4) *nuclear*—multivessel disease by scan, summed stress score and summed difference score; 5) *clinical plus exercise variables forced in, with nuclear variables added*—exercise duration, prescan likelihood of coronary artery disease, rate-pressure product forced in and the summed difference score and multivessel disease by scan added.

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