Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 41, No. 7, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00085-8

Cardiac Imaging

Adenosine Myocardial Perfusion Single-Photon Emission Computed Tomography in Women Compared With Men

Impact of Diabetes Mellitus on Incremental Prognostic Value and Effect on Patient Management

Daniel S. Berman, MD, FACC,* Xingping Kang, MD,* Sean W. Hayes, MD,*
John D. Friedman, MD, FACC,* Ishac Cohen, PHD,* Aiden Abidov, MD,* Leslee J. Shaw, PHD,†
Aman M. Amanullah, MD,* Guido Germano, PHD, FACC,* Rory Hachamovitch, MD, MSC, FACC*
Los Angeles, California; and Atlanta, Georgia

OBJECTIVES This study was designed to assess the incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography (MPS) in women versus men, and to explore the prognostic impact of diabetes mellitus.

BACKGROUND Limited data are available regarding the incremental value of adenosine stress MPS for the prediction of cardiac death in women versus men and the impact of diabetes mellitus on post-adenosine MPS outcomes.

METHODS Of 6,173 consecutive patients who underwent rest thallium-201/adenosine technetium-99m sestamibi MPS, 254 (4.1%) were lost to follow-up, and 586 with early revascularization ≤60 days after MPS were censored, leaving 2,656 women and 2,677 men.

RESULTS Women had significantly smaller adenosine stress, rest, and reversible defects than men. During 27.0 ± 8.8 month follow-up, cardiac death rates were lower in women than men (2.0%/year vs. 2.7%/year, respectively, $p < 0.05$). Before and after risk adjustment, cardiac death risk increased significantly in both men and women as a function of MPS results. Multivariable models revealed that MPS results provided incremental prognostic value over pre-scan data for the prediction of cardiac death in both genders. Also, while comparative unadjusted rates of early (≤60 days post-test) coronary angiography (17% vs. 23%) and revascularization (8% vs. 12%) were significantly lower in women ($p < 0.05$), after adjusting for MPS, these rates were similar in men and women. Importantly, diabetic women had a significantly greater risk of cardiac death compared with other patients. Also, after risk adjustment, patients with insulin-dependent diabetes mellitus (IDDM) had higher risk of cardiac death for any MPS result than patients with non–insulin-dependent diabetes mellitus.

CONCLUSIONS The findings suggest that adenosine MPS has comparable incremental value for prediction of cardiac death in women and men and that MPS is appropriately influencing subsequent invasive management decisions in both genders. Diabetic women and patients with IDDM appear to have greater risk of cardiac death than other patients for any MPS result. (J Am Coll Cardiol 2003;41:1125–33) © 2003 by the American College of Cardiology Foundation

Although there is evidence that women with coronary artery disease (CAD) have a worse prognosis than men (1), it is unclear whether women are treated similarly to men for any given CAD amount (2–6). While stress myocardial perfusion single-photon emission computed tomography (MPS) is widely recognized as being useful for risk stratification in CAD (7), only a few studies have compared the prognostic value of MPS in men and women (6,8–10). Exercise MPS has been found to provide incremental prognostic value over clinical and exercise variables in both men and women. Although a gender bias has been reported in which women are less frequently catheterized than men (11,12), we previously reported that, with exercise MPS, apparent gender differences in outcome disappeared, or were minimized, after risk-adjusted analysis accounted for extent and severity of perfusion abnormalities (6). Recently, adenosine MPS has become the most common stress test in both men and women who are unable to exercise or have nondiagnostic stress electrocardiograms (ECGs). Yet, no study has investigated whether adenosine MPS provides comparable prognostic information or has a comparable effect on invasive management decisions in women and men. Additionally, while diabetes mellitus (DM) has been shown to be associated with increased risk for any degree of MPS abnormal-

From the *Departments of Imaging (Division of Nuclear Medicine), Department of Medicine (Division of Cardiology), and CSMC Burns and Allen Research Institute, Cedars-Sinai Medical Center, and the Department of Medicine, University of California Los Angeles, School of Medicine, Los Angeles, California; and the †Atlanta Cardiovascular Research Institute, Atlanta, Georgia. This work was supported, in part, by grants from Bristol-Myers Squibb Medical Imaging, Inc., Billerica, Massachusetts, and Fujisawa Healthcare, Inc., Deerfield, Illinois. Dr. Hachamovitch is a consultant to Bristol-Myers Squibb Medical Imaging and Fujisawa Healthcare. George A. Beller, MD, MACC, acted as the Guest Editor for this paper.

Manuscript received July 2, 2002; revised manuscript received August 30, 2002, accepted September 6, 2002.

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
DM	= diabetes mellitus
ECG	= electrocardiogram
IDDM	= insulin-dependent diabetes mellitus
MI	= myocardial infarction
MPS	= myocardial perfusion single-photon emission computed tomography
NIDDM	= non–insulin-dependent diabetes mellitus
PCI	= percutaneous coronary intervention
ROC	= receiver operating characteristic
SDS	= summed difference score
SRS	= summed rest score
SSS	= summed stress score
Tc	= technetium
Tl	= thallium

ity in both genders (13) and to have a greater prognostic impact in women (14), little is known about the relationship between DM and the prognostic implications of adenosine MPS in women compared with men. Thus, the present study sought to define whether adenosine MPS in women versus men provides similar incremental prognostic value or has comparable risk for any degree of perfusion abnormality, and to explore the relationship of diabetes and outcome as a function of adenosine MPS in both genders.

METHODS

Patients. The study population consisted of 6,173 consecutive patients with suspected or known CAD who had rest thallium (Tl)-201/adenosine technetium (Tc)-99m sestamibi dual-isotope MPS between 1991 and 1998 (each patient only considered once). Patients with known valvular heart disease or nonischemic cardiomyopathy were excluded. Of the initial population, 254 (4.1%) patients were lost to follow-up leaving 5,919 patients. For the purpose of prognostic assessment, 586 (9.9%) patients with early revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI] ≤60 days after index MPS) were censored as previously described (15). The final population consisted of 5,333 patients (2,656 women and 2,677 men).

Rest Tl imaging. Patients were requested to be free of the effects of nitrates, calcium blockers, and beta-blockers at the time of MPS. Thallium-201 (3.0 to 4.5 mCi) was injected intravenously at rest, and MPS acquisition was started 10 min later (16). Patients with resting defects usually returned for 24-h Tl-201 MPS to assess reversibility (17).

Adenosine MPS protocol. Adenosine MPS was performed as previously described (18). All patients were instructed not to consume caffeine-containing products for 24 h before testing. Adenosine was infused at 140 μg/kg/min for 5 to 6 min. At the end of the second or third minute of infusion (of the 5- and 6-min protocols, respectively), Tc-99m sestamibi (25 to 40 mCi) was injected, and MPS acquisition was started approximately 60 min later. During adenosine infusion, 1,138 of 5,919 patients (44% women) performed low-level treadmill exercise, walking at 0% to 10% grade and 1 to 1.7 mph.

MPS acquisition protocol. The MPS acquisitions were performed as previously described with a circular or elliptical 180° acquisition for 64 projections at 25 s/projection for Tc-99m or 35 s/projection for Tl-201 (16). All images were subject to quality-control measures. No attenuation or scatter correction was used. After filtered back projection, short-axis, vertical long-axis, and horizontal long-axis tomograms were generated.

Stress ECG. During adenosine infusion, 12-lead ECG was recorded each minute, with continuous monitoring of aVF, V_1, and V_5. Significant ST-segment depression during the adenosine stress test was defined as ≥1 mm of horizontal or downsloping or ≥1.5 mm of upsloping (slope of >0.25 mV per 0.04 s) occurring 80 ms after the J point.

Image interpretation. Semiquantitative visual interpretation of MPS images used short-axis and vertical long-axis tomograms divided into 20 segments for each patient (16). Each segment was scored by consensus of two expert observers using a five-point scoring system (0 = normal, 4 = absence of segmental uptake). Three global perfusion indexes previously defined by our group were employed to combine assessments of defect extent and severity (6). By adding the 20 segment scores, summed stress scores (SSS) and summed rest scores (SRS) were calculated, using the 24-h Tl-201 for SRS when available. The sum of the differences between the SSS and SRS was defined as the summed difference score (SDS), assessing defect reversibility. The SSS <4 was defined as a normal scan; SSS 4 to 8, 9 to 13, and >13 were defined as mildly, moderately, and severely abnormal scans, respectively (19). The SDS <2 was considered no ischemia, 2 to 7 mild to moderate, and >7 severe ischemia (20). The SRS <2 was considered normal, 2 to 7 mild to moderate, and >7 extensive resting defects.

Follow-up data. Follow-up was performed at 27.0 ± 8.8 months (all >1 year) by trained research personnel. The sole end point examined was cardiac death, confirmed by death certificate or medical records. Early revascularization was defined as performance of PCI or CABG ≤60 days after MPS.

Statistical analysis. All continuous variables are expressed as mean ± 1 standard deviation. Univariate analyses of continuous variables used unpaired *t* test. Univariate analyses of categorical variables were compared by chi-square. A threshold <0.05 was considered significant. The pre-scan likelihood of CAD was calculated by CADENZA (Advanced Heuristics Inc., Bainbridge Island, Washington) (21), which was based on clinical and historic information. For patients with known CAD, this likelihood is considered to represent the likelihood of ischemia.

The Kaplan-Meier method was used to depict survival curves. Cox proportional hazards model (S-PLUS 2000,

Table 1. Patient Characteristics

	Women (n = 2,656)	Men (n = 2,677)
Age	72 ± 11*	70 ± 11
Prior MI	561 (21%)*	933 (35%)
History of PCI	288 (11%)*	500 (19%)
History of CABG	266 (10%)*	755 (28%)
Hypertension	1,669 (63%)*	1,406 (53%)
Diabetes	608 (23%)	614 (23%)
Hypercholesterolemia	1,219 (46%)*	1,070 (40%)
Smoking	263 (10%)*	385 (14%)
Angina	1,407 (53%)*	1,146 (43%)
Shortness of breath	252 (9%)*	283 (11%)
Abnormal rest ECG	1,685 (63%)*	1,907 (71%)
Ischemic stress ECG	205 (8%)*	124 (5%)
Pre-scan Lk of CAD/ischemia	47 ± 30%*	43 ± 33%
With low-level exercise	447 (17%)*	538 (20%)

*$p < 0.02$ vs. men.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; ECG = electrocardiogram; Lk of CAD/ischemia = likelihood of CAD (in the suspected CAD patients) or ischemia (in the CAD patients); MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2. Adenosine MPS Variables in Women and Men

	Women (n = 2,656)	Men (n = 2,677)
SSS	4.8 ± 7.5*	9.7 ± 10.4
Normal (0–3)	1,649 (62%)*	1,004 (38%)
Mild abnormal (4–8)	476 (18%)	542 (20%)
Moderate abnormal (9–13)	199 (8%)*	325 (12%)
Severe abnormal (>13)	332 (13%)*	806 (30%)
SDS	3.1 ± 5.2*	5.1 ± 6.5
No ischemia (0–1)	1,551 (58%)*	1,126 (42%)
Mild-moderate ischemia (2–7)	697 (26%)*	808 (30%)
Severe ischemia (>7)	408 (15%)*	743 (28%)
SRS	1.6 ± 4.7*	4.4 ± 8.1
No defect (0–1)	2,156 (81%)*	1,635 (61%)
Mild-moderate defect (2–7)	293 (11%)*	499 (19%)
Extensive defect (>7)	207 (8%)*	543 (20%)

*$p < 0.002$ vs. men.

MPS = myocardial perfusion single phiton emission computed tomography; SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.

MathSoft, Inc., Seattle, Washington) identified univariable and multivariable predictors of cardiac events. Selection of variables for consideration for entry was based on both univariate statistical significance and clinical judgment. A stepwise multivariable Cox regression analysis was performed using: 1) pre-MPS data (clinical and historical information), and 2) the increment in prognostic value after "forcing in" the significant clinical variables and then adding the most predictive nuclear variable(s). A significant increase in the global chi-square of a model after addition of the nuclear variables indicated incremental prognostic value. Based upon these models, we derived risk-adjusted cumulative survival curves to compare women and men with normal and varying degrees of abnormal MPS. These models were performed in the overall cohort as well as in men and women separately.

Receiver operating characteristic (ROC) curve analysis was performed to compare the value of combined clinical and MPS results for predicting cardiac events in men versus women using the final Cox model. The differences between ROC curve areas (area ± SE) were compared (22).

RESULTS

Patient characteristics. Clinical characteristics by gender are shown in Table 1. Men and women differed with respect to all clinical characteristics except diabetes. The women were older, had higher pre-scan likelihood of CAD, more frequently had hypertension, hypercholesterolemia, anginal symptoms, and ischemic stress ECG; however, women less frequently had prior myocardial infarction (MI), PCI, CABG, shortness of breath, abnormal rest ECG, smoked, and underwent low-level treadmill exercise during adenosine stress compared with men ($p < 0.02$).

Adenosine MPS results. The MPS findings are shown in Table 2. Compared with men in the respective group, women had significantly lower SSS, SRS, and SDS, and a lower frequency of abnormalities of each of the subcategories of these perfusion findings.

Outcome events. During follow-up 117 cardiac deaths (4.4%) occurred in women and 164 (6.1%) in men ($p < 0.01$). Annual rates of cardiac death rose significantly as a function of SSS and are illustrated in Figure 1. Although the overall rates of cardiac death were lower in women than in men, after stratification by SSS, cardiac death rates in women and men were similar across scan categories (p = NS). This apparent discrepancy is explained by the greater frequency of normal scans in women than in men. Two-year unadjusted Kaplan-Meier survival estimates are shown in Figure 2 for men and women as a function of SSS. In both men and women, a significant decrease in survival is present with increasing SSS, with worsened observed survival in women compared with men (men vs. women, p = NS). Women tended to have worse survival in the setting of more severe and extensive perfusion defects, although this difference did not reach statistical significance (Figs. 1 and 2).

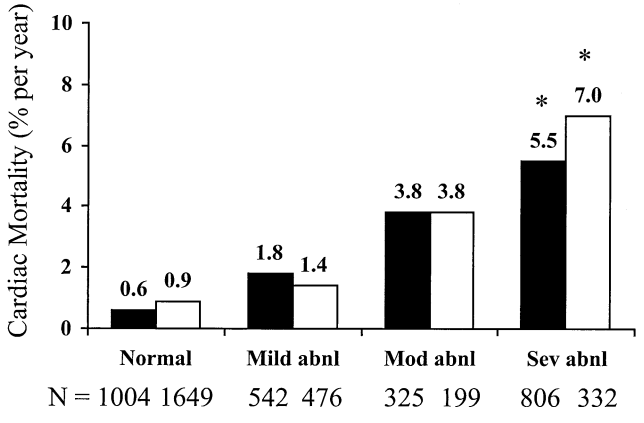

Figure 1. Annual rates of cardiac death in women **(open bars)** and men **(solid bars)** as a function of myocardial perfusion single-photon emission computed tomography results. *$p < 0.001$ across scan categories. abnl = abnormal; Mod = moderate; Sev = severe.

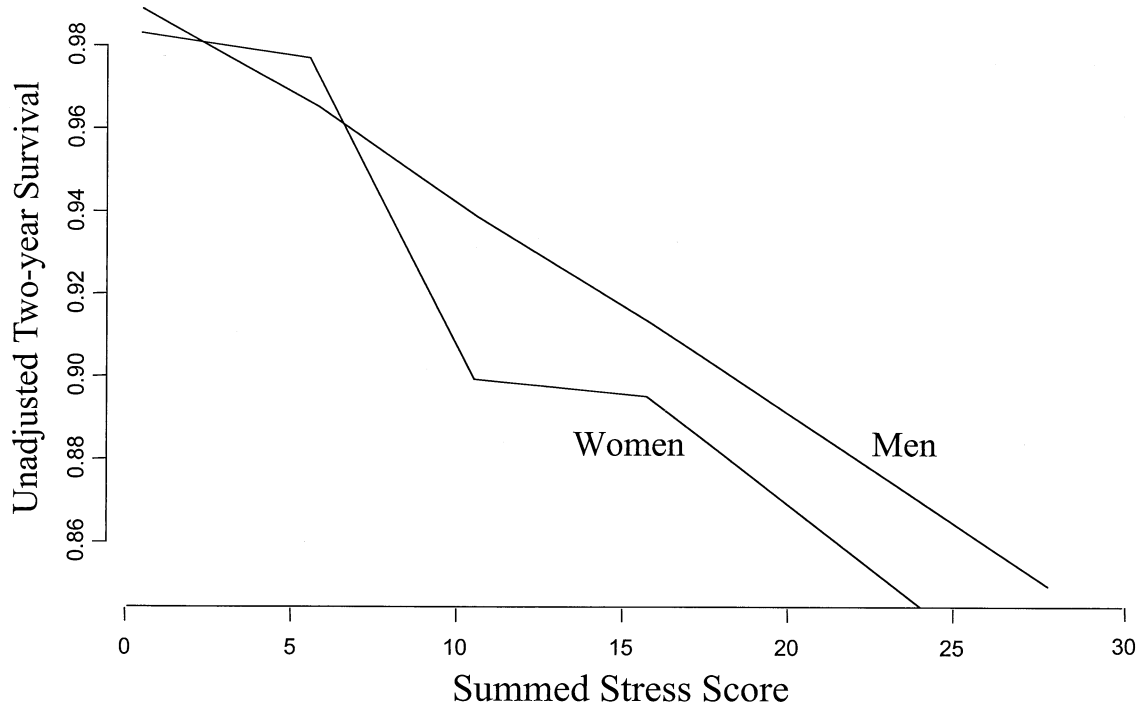

Figure 2. Unadjusted two-year Kaplan-Meier survival estimates in men and women as a function of summed stress score. No significant difference is present.

Early catheterization and revascularization. In the uncensored groups of 2,878 women and 3,041 men, overall referral rates to catheterization and revascularization within 60 days after MPS were lower in women than men (Table 3). However, after adjusting for the extent and severity of inducible ischemia or scan abnormality, no gender-related differences remained. Of interest, only 3% of women and men underwent early catheterization when SSS was <4, and those catheterized rarely underwent early revascularization. Patients with SSS 2 to 3 had low rates of early catheterization and revascularization, which were higher than in patients with SSS 0 to 1 (all, $p < 0.05$), but with no gender differences. In both genders, increases in referral rates as a function of worsening ischemia were noted ($p < 0.001$).

Multivariable survival analysis. The significant variables predictive of cardiac death by Cox models in the overall cohort, women, and men are shown in Table 4 (chi-square = 399, 202, and 199, respectively; all, $p < 0.0001$). In all three models, SSS and age were nonlinear and, thus, quadratic terms were added to the Cox model to satisfy its linearity assumptions (SSS^2, age^2). Further, a significant interaction was present between patient gender and diabetes, such that a greater risk of cardiac death was predicted for female diabetics over female nondiabetics or male diabetics. After adjustment for pre-MPS variables, addition of SSS provided a significant increase in chi-square (42% gain in chi-square), indicative of incremental prognostic value (Fig. 3) ($p < 0.0001$). In both men (gain in chi-square = 93) and women (gain in chi-square = 40), the addition of SSS yielded incremental information over prescan data alone for prediction of cardiac death (both, $p < 0.0001$).

Predicted mortality rates based on the overall model are

Table 3. Unadjusted Rates of Referral to Early Coronary Catheterization and Revascularization as a Function of Inducible Ischemia in Women and Men

	Catheterization		Revascularization	
	Women	Men	Women	Men
Total	17% (492/2,878)*	23% (705/3,041)	8% (222/2,878)*	12% (364/3,041)
Normal	3% (53/1,661)	3% (30/1,010)	0.7% (12/1,661)	0.6% (6/1,010)
SSS 0–1	2% (32/1,374)	2% (16/820)	0.5% (7/1,374)	0.1% (1/820)
SSS 2–3	7% (21/287)†	7% (14/190)†	2% (5/287)‡	3% (5/190)†
Abnormal	36% (439/1,217)	33% (675/2,031)	17% (210/1,217)	18% (358/2,031)
No ischemia	14% (20/139)	13% (36/278)	4% (5/139)	4% (10/278)
Mild-moderate ischemia	26% (134/521)	22% (159/735)	11% (56/521)	10% (73/735)
Severe ischemia	51% (285/557)§	47% (480/1,018)§	27% (149/557)§	27% (275/1,018)§

*$p < 0.001$ vs. men; †$p < 0.0001$ vs. SSS 0–1; ‡$p < 0.05$ vs. SSS 0–1; §$p < 0.001$ among groups.
SSS = summed stress score.

Table 4. Multivariable Predictors of Cardiac Death in the Overall Population, Women and Men

Model	Overall	Women	Men
Age*	+	+	+
Male gender	+	−	−
History of MI	−	+	−
History of CABG	+	−	−
History of revascularization	−	−	+
Digoxin use	+	+	+
Diabetes	+	+	−
Cholesterol ↑	+	+	+
Shortness of breath	+	+	+
Abnormal rest ECG	+	+	+
Left bundle branch block	+	−	−
Adenosine stress with walking	+	+	+
SSS*	+	+	+
Total chi-square	399	202	199
p Value	< 0.00001	< 0.0001	< 0.0001

*Modelled nonlinearly in all three models. + = significant in model; − = not significant in model.
Abbreviations as in Tables 1 and 2.

shown separately for nondiabetic men and women versus diabetic men and women (Figs. 4A and 4B). Among nondiabetics, predicted survival was nearly identical in men and women. However, among diabetics, women had a significantly higher predicted rate of cardiac death compared with men based on the Cox proportional hazards model.

The presence of prior CAD was of prognostic significance even after adjusting for other factors, but its value varied both as a function subset of prior CAD and patients examined. In the overall cohort, prior CABG was an incremental predictor of cardiac death in the overall cohort. In men, both prior CABG and prior PCI were predictive of cardiac death, while, in women, MI, but not revascularization, was an incremental predictor.

Comparison of prognostic value in women and men. The ROC curves showed excellent discrimination for predicting cardiac events in women and men using SSS (after adjusting for clinical variables). No gender-related differences in ROC areas were present (0.78 ± 0.02 vs. 0.83 ± 0.02, p = NS). These findings demonstrate that adenosine MPS is equally effective in identifying both men and women at high risk of cardiac mortality.

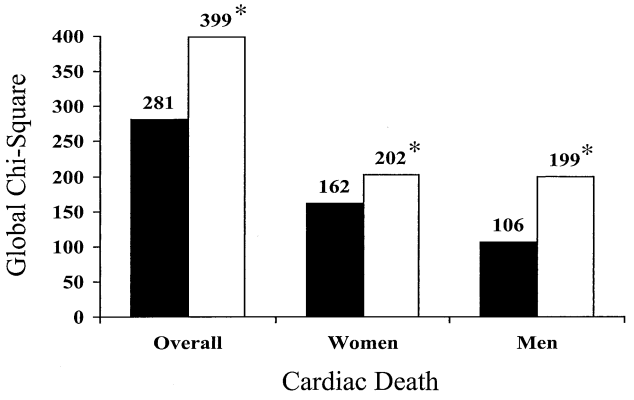

Figure 3. Chi-square values from the Cox proportional hazards models for the overall cohort, women, and men. Increase in chi-square is significant in all (*p < 0.0001). **Solid bar** = pre-MPS; **open bar** = pre-MPS + SSS.

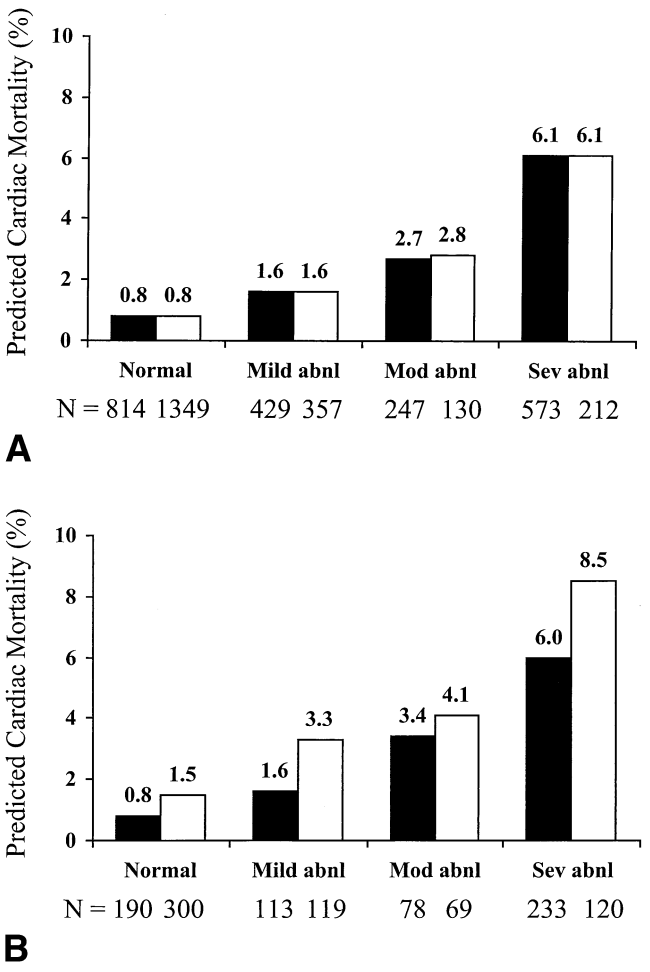

Figure 4. (A) Predicted cardiac mortality based on Cox proportional hazards model in nondiabetic men and women with normal, mildly, moderately, and severely abnormal scans. Significant difference in mortality as a function of increasing summed stress score (SSS) as based on the multivariable model (p < 0.0001). **(B)** Predicted cardiac mortality based on Cox proportional hazards model in diabetic men and women with normal, mildly, moderately, and severely abnormal scans. Significant difference in mortality as a function of increasing SSS as based on the multivariable model (p < 0.0001). abnl = abnormal; Mod = moderate; Sev = severe. **Solid bar** = men; **open bar** = women.

Comparison of insulin-dependent diabetes mellitus (IDDM) versus non–insulin-dependent diabetes mellitus (NIDDM). Subgroup analysis was performed in 2,826 patients from the overall cohort in whom information was available regarding the presence of IDDM or NIDDM. The characteristics of nondiabetics and two types of diabetics are shown in Table 5. The IDDM group was younger, more frequently had prior MI, PCI and CABG, hypertension, shortness of breath, and greater stress, rest, and reversible defects on MPS among the three groups (p < 0.05). However, they less frequently had angina, ischemic stress ECG, and had lower pre-scan likelihood of CAD (p

Table 5. Clinical and Adenosine MPS Data by Diabetic Status

	Nondiabetics (n = 2,237)	NIDDM (n = 354)	IDDM (n = 235)
Age	72 ± 11	71 ± 10	66 ± 12*
Female gender	1,108 (50%)	167 (47%)	125 (53%)
Prior MI	550 (25%)	102 (29%)	84 (36%)*
History of PCI	335 (15%)	54 (15%)	62 (26%)*
History of CABG	386 (17%)	86 (24%)	61 (26%)*
Hypertension	1,239 (55%)	238 (67%)	174 (74%)*
Hypercholesterolemia	1,000 (45%)	188 (53%)*	120 (51%)
Smoking	224 (10%)	29 (8%)	25 (11%)
Angina	1,162 (52%)	185 (52%)	106 (45%)*
Shortness of breath	241 (11%)	56 (16%)	41 (17%)*
Abnormal rest ECG	1,447 (65%)	234 (66%)	180 (77%)*
Ischemic stress ECG	176 (8%)	38 (11%)	10 (4%)*
Pre-scan Lk of CAD/ischemia	44 ± 31%	53 ± 32%	42 ± 35%*
With low-level exercise	794 (35%)	118 (33%)	71 (30%)
SSS	5.4 ± 8.3	7.7 ± 9.5	9.5 ± 10.6*
SRS	2.4 ± 6.3	3.2 ± 7.0	3.9 ± 7.5*
SDS	2.9 ± 5.0	4.4 ± 6.3	5.4 ± 7.0*

*$p < 0.05$ among groups.
IDDM = insulin-dependent diabetes mellitus; NIDDM = non–insulin-dependent diabetes mellitus. Other abbreviations as in Tables 1 and 2.

< 0.05). There was no difference in use of low-level exercise during adenosine stress (p = NS).

Observed cardiac mortality in these subgroups is shown in Figure 5. A significant difference in cardiac mortality was present between patients with IDDM, NIDDM, and nondiabetics in the setting of both normal and abnormal scans (both, $p < 0.05$). Further, a significant difference between normal and abnormal scans was present in nondiabetics as well as in patients with IDDM ($p < 0.05$). There was a very high rate of cardiac death in patients with IDDM and abnormal scans. Cox proportional hazards modeling of this subgroup using the same variables as the overall model revealed a greater cardiac death risk with IDDM than NIDDM patients, and nondiabetics having the lowest risk (Fig. 6) ($p < 0.001$).

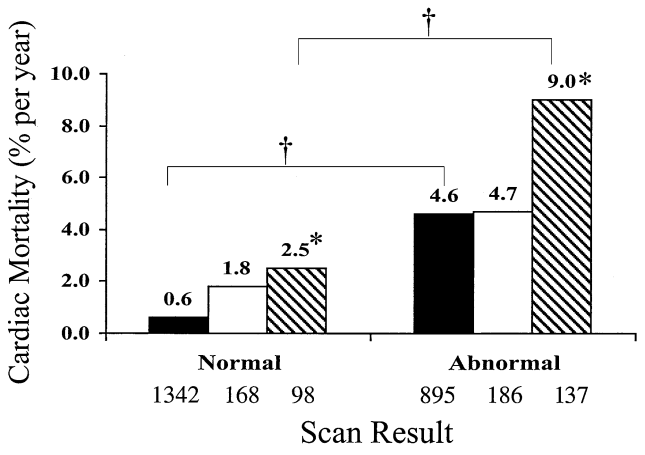

Figure 5. Cardiac mortality in patients without diabetes mellitus (DM) **(solid bar)**, with non–insulin-dependent diabetes mellitus (NIDDM) **(open bar)**, and with insulin-dependent diabetes mellitus (IDDM) **(hatched bar)** after normal versus abnormal myocardial perfusion single-photon emission computed tomography (MPS). *$p < 0.05$ among non–DM, NIDDM, and IDDM within MPS categories; †$p < 0.05$ between normal and abnormal MPS.

DISCUSSION

The present study demonstrates that adenosine Tc-99m sestamibi MPS provides significant incremental prognostic information over historical and clinical data in both women and men. Although women had smaller overall stress, rest, and reversible defects and lower overall cardiac mortality compared with men, they were at similar risk for adverse events as a function of adenosine MPS results according to both unadjusted and adjusted data. Multivariable modeling revealed that a significant interaction was present between gender and DM such that, although men and women without diabetes have similar risk, women with DM are at greater risk than either men with DM or women without DM. The ROC curve analysis showed no significant differences between the overall cohort of women and men for predicting cardiac death using MPS. Regarding impact on patient management of adenosine MPS, referral rates to early catheterization and revascularization paralleled the level of risk by MPS in both women and men. Overall, women had lower referral rates compared with men because of a large proportion of women with normal scans. An interesting finding emerging from assessment of the overall cohort was that, for any degree of SSS abnormality on adenosine MPS, patients with diabetes have a higher event rate than nondiabetics after risk adjustment for confounding variables. Subgroup analyses revealed that IDDM patients had an even higher risk compared with NIDDM patients, whose risk was higher than that of nondiabetic controls. Even in patients with normal scans, the presence of IDDM was associated

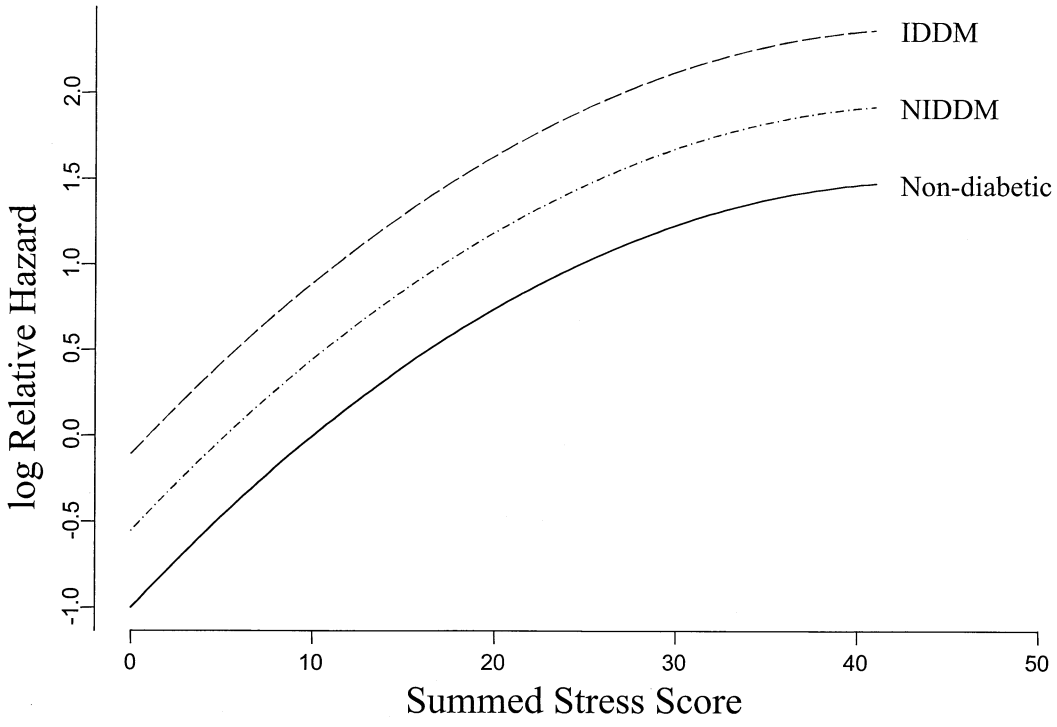

Figure 6. Relationship between log relative hazard for predicted cardiac mortality and summed stress score in insulin-dependent diabetes mellitus (IDDM), non–insulin-dependent diabetes mellitus (NIDDM), and nondiabetics. $p < 0.001$.

with a tendency to greater risk than NIDDM and nondiabetics.

Comparison with previous vasodilator MPS studies. While several studies have evaluated the incremental prognostic value of exercise MPS in women (6,8–10,23), only a few considered the prognostic implications of vasodilator stress MPS. Amanullah et al. (24) have shown that adenosine stress MPS added significant incremental prognostic value to clinical variables in women; however, there were no comparable data regarding men. In another study by Travin et al. (9), men and women with abnormal dipyridamole Tc-99m sestamibi MPS had similar event rates.

Our group previously reported the incremental value, role in risk stratification and post-MPS resource utilization of stress adenosine studies in a more limited cohort of 1,159 patients (25). We described that risk stratification was achieved by this test in men and women, and demonstrated the incremental prognostic value of this test in the overall cohort. Due to the limited size of the cohort, the detailed comparison of men and women contained in the present manuscript was not performed. Further, the impact of DM on the prognostic relationships was not addressed.

Comparison with previous exercise MPS studies. To our knowledge, this is the first study in a large population to compare the prognostic significance of adenosine stress MPS in women and men. Women less frequently had abnormal scan results, and only 21% of women but 42% of men had moderately to severely abnormal results on adenosine MPS. However, adenosine stress MPS provided comparable prognostic value for women and men in each category of perfusion defect abnormality. In the stepwise multivariable model, a similar increase in chi-square was seen in men and women by addition of adenosine MPS results to clinical data.

These findings are similar to what has been reported with exercise MPS; however, our findings revealed a greater mortality risk after adenosine stress than previously reported with exercise MPS in every category of scan abnormality. Pancholy et al. (23) examined 212 women who underwent coronary angiography and showed that exercise Tl201-MPS had independent and incremental prognostic value. Subsequently, Hachamovitch et al. (8) reported that exercise Tc-99m sestamibi MPS yielded incremental prognostic value in both women and men. In this study from our laboratory comprising 2,742 men and 1,934 women, we demonstrated that exercise MPS identifies low-risk women and men equally well, but relatively high-risk women more accurately than relatively high-risk men. Exercise MPS, therefore, was able to stratify women more effectively than men (8).

It has been generally appreciated that patients who undergo pharmacologic stress are "sicker" than patients who undergo exercise testing. In 1998, Hachamovitch et al. (19) reported that patients who underwent pharmacologic stress were older, more frequently had previous cardiac events or procedure, had a higher likelihood of CAD, more severe and extensive scan abnormalities, and greater subsequent rates of adverse outcomes. Others have found similar results (26,27). The use of pharmacologic stress rather than exercise has been shown to be an incremental predictor of poor

prognosis over clinical, historical, and single-photon emission computed tomography data (19,20,27).

Relationship between adenosine MPS findings and referral to catheterization. Overall, a larger proportion of men were referred to early catheterization and revascularization than women in the current study. However, after adjusting for the extent and severity of inducible ischemia or scan abnormality, catheterization and revascularization rates were similar in men and women. In 1995, Hachamovitch et al. (6) reported on apparent gender-related differences in clinical management in patients undergoing exercise sestamibi MPS. Although men were referred to catheterization more frequently than women early after nuclear testing, there were no differences in the rate of referral to catheterization or revascularization after stratification by the amount of abnormally perfused myocardium as determined by the SSS. In fact, in this previous study, women with extensive inducible ischemia had greater referral rates to catheterization than men. Despite generally similar referral rates to catheterization, the cardiac event rates were observed to be higher in women than in men. In the current study, despite the greater overall risk and associated catheterization and revascularization rates in men compared with women, gender-related differences were not generally present with respect to risk or resource utilization after adjusting for confounding factors, such as the MPS results.

Impact of DM on cardiovascular risk in women undergoing MPS. The current study shows that diabetic women have a significantly greater risk of cardiac death for any degree of scan abnormality compared with diabetic men or nondiabetic men or women. In studies not using MPS, younger women have been shown to be at a much lower risk of coronary disease mortality than men; however, multiple studies have shown that diabetes "erases" this female advantage, increasing the risk of heart disease much more in women than in men. Barrett-Connor et al. (14), in a 14-year follow-up of 207 men and 127 women with NIDDM compared with 2,137 adult controls, first showed the excess risk associated with DM in women compared with men. In their study, Cox proportional hazards modeling revealed the relative hazard of CAD in diabetics versus nondiabetics, after adjusting for age, was 3.3 in women and 1.8 in men, and remained the same even after adjusting for age, systolic blood pressure, cholesterol, body mass index, and cigarette smoking. Further, a recent meta-analysis of 16 prospective cohort studies containing both men and women with and without diabetes found that, after adjusting for other cardiac risk factors, the relative risk of coronary death from diabetes was 2.58 (95% confidence interval, 2.05 to 3.26) for women and 1.85 (1.47 to 2.33) for men (difference, $p < 0.05$) (28). Although the precise physiological mechanisms for the greater risk of diabetic women compared with men has not been elucidated, it is believed that they are at least partially related to greater lipid abnormalities as well as more insulin resistance resulting in premature, accelerated vascular disease (29).

Regarding diabetes and MPS, in a cohort of 1,271 patients with and 5,862 patients without diabetes undergoing either exercise or adenosine MPS, Kang et al. (13) previously demonstrated that risk-adjusted event rates were higher in patients with diabetes than in those without diabetes in all SSS categories. These results were supported by a subsequent multisite data registry reporting a smaller group of diabetics (30). Our results are consistent with previous studies examining the impact of DM on cardiovascular risk in women and extend them to the extrapolation of risk in diabetic women from MPS results.

IDDM versus NIDDM. In the overall cohort, men and women combined, we found that there was an increased risk in the IDDM beyond that observed in NIDDM. After risk adjustment we found that the increased risk extended across the entire spectrum of MPS results. To our knowledge this increased risk for any MPS finding in patients with IDDM has not been previously reported.

Study limitations. This is a retrospective study in nature, although all data were collected and entered prospectively. The patients in this study were referred to a university-affiliated community hospital in a major urban area limiting the generalizability of the findings. Assessments of global and regional ventricular function with gated MPS were not performed in this study, as gated MPS was not routinely performed in our laboratory until 1995.

In this study, patients were not formally tested for the presence of DM. Hence, the "nondiabetic" group may have contained undiagnosed diabetics that may have diluted the study results. Although all patients were questioned regarding the type of diabetes they had, insulin use was not routinely recorded in the database until 1995.

Conclusions. The results of this study indicate that adenosine stress MPS has comparable strong incremental prognostic value over clinical variables and has a similar effect on catheterization and revascularization referrals in both men and women. Women with DM are at greater risk of adverse outcomes for any level of stress perfusion defects compared with nondiabetic women or diabetic men. Patients with IDDM have a greater risk than patients with NIDDM.

Reprint requests and correspondence: Dr. Daniel S. Berman, Department of Imaging, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room A042, Los Angeles, California 90048. E-mail: bermand@cshs.org.

REFERENCES

1. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. N Engl J Med 1993;329:247–56.
2. Steingart RM, Packer M, Hamm P, et al. Sex differences in the management of coronary artery disease. N Engl J Med 1991;325:226–30.
3. Shaw LJ, Miller DD, Romeis JC, Kargl D, Younis LT, Chaitman BR. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994;120:559–66.
4. Bergelson BA, Tommaso CL. Gender differences in clinical evaluation and triage in coronary artery disease. Chest 1995;108:1510–3.

5. Wenger NK. Clinical characteristics of coronary heart disease in women: emphasis on gender differences. Cardiovasc Res 2002;53:558–67.
6. Hachamovitch R, Berman DS, Kiat H, et al. Gender-related differences in clinical management after exercise nuclear testing. J Am Coll Cardiol 1995;26:1457–64.
7. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). Circulation 1999; 99:2829–48.
8. Hachamovitch R, Berman DS, Kiat H, et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. J Am Coll Cardiol 1996;28:34–44.
9. Travin MI, Duca MD, Kline GM, Herman SD, Demus DD, Heller GV. Relation of gender to physician use of test results and to the prognostic value of stress technetium 99m sestamibi myocardial single-photon emission computed tomography scintigraphy. Am Heart J 1997;134:73–82.
10. Marwick TM, Shaw LJ, Lauer MS, et al., on behalf of END Study Group. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. Am J Med 1999;106:172–8.
11. Tobin JN, Wassertheil-Smoller S, Wexler JP, et al. Sex bias in considering coronary bypass surgery. Ann Intern Med 1987;107:19–25.
12. Shaw LJ, Miller DD, Romeis JC, et al. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann Intern Med 1994;120:559–66.
13. Kang X, Berman DS, Lewin HC, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. Am Heart J 1999;138:1025–32.
14. Barrett-Connor EL, Cohen BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo study. JAMA 1991; 265:627–31.
15. Staniloff HM, Forrester JS, Berman DS, Swan HJC. Prediction of death, myocardial infarction, and worsening chest pain using thallium scintigraphy and exercise electrocardiography. J Nucl Med 1986;27: 1842–8.
16. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. J Am Coll Cardiol 1993;22:1455–64.
17. Sharir T, Berman DS, Lewin HC, et al. Incremental prognostic value of rest-redistribution Tl-201 single-photon emission computed tomography. Circulation 1999;100:1964–70.
18. Amanullah A, Kiat H, Friedman JD, Berman DS. Adenosine technetium-99m sestamibi myocardial perfusion SPECT in women: diagnostic efficacy in detection of coronary artery disease. J Am Coll Cardiol 1996;27:803–9.
19. Hachamovitch R, Berman DS, Shaw LJ, et al. 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. Circulation 1998;97:535–43.
20. Sharir T, Germano G, Kang X, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the post-stress ejection fraction. J Nucl Med 2001;42:831–7.
21. Diamond GA, Staniloff HM, Forrester JS, Pollock BH, Swan HJC. Computer assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. J Am Coll Cardiol 1983;1:444–55.
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143: 29–36.
23. Pancholy SB, Fattah AA, Kamal AM, Ghods M, Heo J, Iskandrian AS. Independent and incremental prognostic value of exercise thallium single-photon emission computed tomographic imaging in women. J Nucl Cardiol 1995;2:110–6.
24. Amanullah AM, Berman DS, Erel J, et al. Incremental prognostic value of adenosine myocardial perfusion single-photon emission computed tomography in women with suspected coronary artery disease. Am J Cardiol 1998;82:725–30.
25. Hachamovitch R, Berman DS, Kiat H, et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. Am J Cardiol 1997;80:426–33.
26. Heller GV, Herman SD, Travin MI, Baron JI, Santos-Ocampo C, McClellan JR. Independent prognostic value of intravenous dipyridamole with technetium-99m sestamibi tomographic imaging in predicting cardiac events and cardiac-related hospital admissions. J Am Coll Cardiol 1995;26:1202–8.
27. Ho K, Miller TD, Christian TF, Hodge DO, Gibbons RJ. Prediction of severe coronary artery disease and long-term outcome in patients undergoing vasodilator SPECT. J Nucl Cardiol 2001;8:438–44.
28. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care 2000;23:962–8.
29. Charney P. Women and coronary disease. In: Fuster V, Alexander RW, O'Rourke RA, editors. The Heart. 10th ed. New York, NY: McGraw-Hill, 2001:2357–71.
30. Giri S, Shaw LJ, Murthy DR, et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging inpatients with symptoms suggestive of coronary artery disease. Circulation 2002;105:32–40.