Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: What is the warranty period of a normal scan?

Rory Hachamovitch, Sean Hayes, John D. Friedman, Ishac Cohen, Leslee J. Shaw, Guido Germano and Daniel S. Berman

J. Am. Coll. Cardiol. 2003;41;1329-1340
doi:10.1016/S0735-1097(03)00125-6

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

Vol. 41, No. 8, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00125-6

Cardiac Imaging

Determinants of Risk and its Temporal Variation in Patients With Normal Stress Myocardial Perfusion Scans

What Is the Warranty Period of a Normal Scan?

Rory Hachamovitch, MD, MSc, FACC,* Sean Hayes, MD,† John D. Friedman, MD, FACC,† Ishac Cohen, PhD,† Leslee J. Shaw, PhD,‡ Guido Germano, PhD, MBA, FACC,† Daniel S. Berman, MD, FACC†

Los Angeles, California; and Atlanta, Georgia

OBJECTIVES The aim of this study was to determine the predictors of risk and the temporal characteristics of risk associated with normal myocardial perfusion single photon emission computed tomography (MPS).

BACKGROUND No empiric data exist regarding predictors of risk after normal MPS and their temporal characteristics.

METHODS Follow-up (mean: 665 ± 200 days, 96% complete) of 7,376 consecutive patients with normal exercise or adenosine MPS identified 78 hard events (HE) (45 cardiac deaths, 33 non-fatal myocardial infarction; 1.1% cumulative HE rate, 0.6%/year). Cox proportional hazards analysis was used to identify predictors of HE. Parametric survival analysis was used to model predicted time to HE.

RESULTS The HE rates were greater in patients with versus without previous coronary artery disease (CAD). The Cox proportional hazards model identified pharmacologic stress, known CAD, diabetes mellitus (DM), male gender, and increasing age, with interactions between stress type and previous CAD (lower risk in patients without previous CAD undergoing exercise stress vs. all others) and between DM and gender (higher risk in DM females vs. all others) as the model most predictive of HE. The highest risk subgroups had a maximal event rate of 1.4% to 1.8%/year. Parametric survival models revealed that in patients without previous CAD the level of risk was uniform with time, but in patients with known CAD, risk increased with time (e.g., risk in the first year was less than in the second year, hence, a dynamic temporal component of risk was present).

CONCLUSIONS Multiple clinical factors add incremental prognostic value in patients with normal MPS, affecting their risk and its temporal pattern, and may alter the appropriate timing of repeat testing, hence establishing the existence of a "warranty" period for normal MPS studies. (J Am Coll Cardiol 2003;41:1329–40) © 2003 by the American College of Cardiology Foundation

Stress myocardial perfusion single photon emission computed tomography (MPS) plays an important role in risk assessment of patients with known or suspected coronary artery disease (CAD). It has been shown to risk stratify a variety of patient populations and, when incorporated in an overall testing strategy, lower the overall cost and enhance the effectiveness of testing (1–3). The low risk associated with normal MPS is an important component of these findings—by identifying patients at sufficiently low risk for subsequent events, they can be safely managed medically, and additional, costly testing and interventions can be avoided (1–4).

To date, most studies examining risk after a normal MPS have reported rates of hard events (HE) (cardiac death or nonfatal myocardial infarction [MI]) of <1% per year of follow-up. Many have claimed that this low risk is independent of imaging type (single photon emission computed tomography [SPECT] vs. planar), stress performed (exercise vs. pharmacologic), isotope used, clinical characteristics, or previous history of CAD (1–3,5–13). However, studies of patients undergoing pharmacologic stress, a population at higher risk, and more comorbidities than patients undergoing exercise have reported HE rates of 1.3% to 2.7% per year (14–18), suggesting that underlying clinical risk and previous CAD may influence event rates after a normal MPS. Thus, although MPS provides incremental prognostic information over clinical information alone, it appears that clinical information also yields incremental prognostic value over MPS data after normal MPS. Further, if these clinical and historical factors also affect the temporal characteristics

From the *Division of Cardiovascular Medicine, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; †Departments of Imaging (Division of Nuclear Medicine) and Medicine (Division of Cardiology), Cedars-Sinai Medical Center Burns and Allen Research Institute, Department of Medicine, UCLA School of Medicine, Los Angeles, California; and the ‡Atlanta Cardiovascular Research Institute, Atlanta, Georgia. Presented in part at the 68th Annual Scientific Sessions of the American Heart Association, in Anaheim, California, in November 1995. Supported in part by a grant from Bristol-Myers Squibb Medical Imaging and from Fujisawa Healthcare. Barry Zaret, MD, acted as the Guest Editor for this article.

Manuscript received July 5, 2002; revised manuscript received October 22, 2002, accepted November 11, 2002.

JACC Vol. 41, No. 8, 2003
April 16, 2003:1329–40

Abbreviations and Acronyms

CAD	= coronary artery disease
ECG	= electrocardiogram
ETT	= exercise tolerance test
HE	= hard event
MI	= myocardial infarction
MPHR	= maximal predicted heart rate
MPS	= myocardial perfusion single photon emission computed tomography
PTCA	= percutaneous transluminal coronary angioplasty
SPECT	= single photon emission computed tomography
Tc	= technetium
Tl	= thallium

of this risk, how long risk remains low after a normal MPS may be dictated by clinical and historical characteristics.

To date, MPS prognosis studies have expressed results as cumulative event rates, and normal MPS are considered to indicate low risk if the event rate is below 1% per year. Knowledge of this event rate alone, however, is potentially misleading. For example, while an event rate of >1% per year after a normal MPS may be the result of a constant >1% per year event rate over the follow-up interval, it may also result from an event rate of <1% during the first year and a markedly increased event rate later in the follow-up period. Similarly, even an event rate of <1% per year over more than one year does not exclude the possibility that risk was exceedingly low initially, but increased with time, and risk was not <1% later. These temporal characteristics of risk (how risk changes with time) are as yet undefined but may be important in determining MPS test performance.

The goals of the current study were to: 1) determine whether clinical factors alter risk for HE after normal MPS; 2) identify the predictors of increased risk and shortened survival time in patients with normal MPS; and 3) determine the impact of these predictors on the length of time that patients remain at low risk after the index normal MPS, hence defining whether a "warranty" period exists.

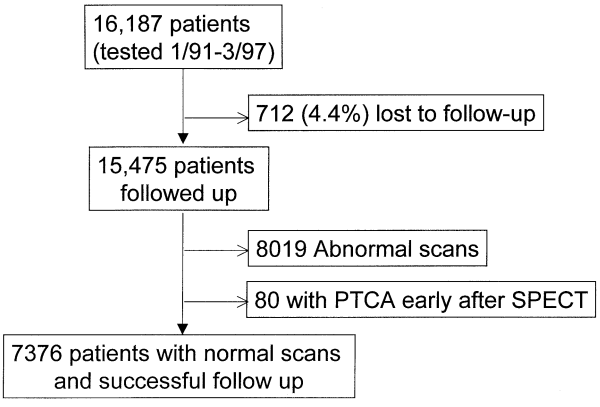

Figure 1. Outline of patient selection. PTCA = percutaneous transluminal coronary angioplasty; SPECT = single photon emission computed tomography.

METHODS

Study population. We identified 16,187 consecutive patients who underwent dual-isotope MPS between January 1, 1991 and March 27, 1997 (Fig. 1). Patients with valvular heart disease or primary cardiomyopathy were excluded from this study. Of the initial population, 712 patients (4.4%) were lost to follow-up. Of the remaining patients, 8,019 were excluded because of abnormal scans, leaving a study population of 7,456 patients with normal MPS. Of these, 80 patients who underwent SPECT within 90 days after percutaneous transluminal coronary angioplasty (PTCA) were excluded owing to the relative instability of their disease, thus leaving 7,376 patients in this study (48% of the follow-up population). Patients with previous MI or revascularization were considered to have known CAD.

Rest thallium (Tl)-201 imaging. All patients underwent stress dual-isotope SPECT as previously described (19,20). Whenever possible, beta-blockers and calcium channel antagonists were terminated 48 h before testing. Initially, Tl-201 (2.5 to 3.5 mCi) was injected intravenously at rest, with dose variation based on patient weight, and rest Tl-201 imaging was initiated 10 min afterward.

Exercise stress protocol. All patients performed a symptom-limited treadmill exercise test using standard protocols. At near maximal exercise, a 20- to 30-mCi dose of technetium (Tc)-99m sestamibi was injected (actual patient dose varied with patient weight) and exercise continued for 1 min after injection. The Tc-99m sestamibi SPECT imaging was begun 15 to 30 min after isotope injection (19).

Adenosine stress protocol. Patients were instructed not to consume coffee or other products containing caffeine for 24 h before MPS. After rest Tl-201 SPECT, infusion (140 μg/kg/min for 6 min) was performed, and Tc-99m sestamibi was injected at the end of the third minute of infusion. Single photon emission computed tomography was initiated approximately 60 min after adenosine infusion (19).

During both types of stress, 12-lead electrocardiographic recording was performed each minute of stress with continuous monitoring of leads aVF, V_1, and V_5. Blood pressure was measured and 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 electrocardiogram (ECG) was measured and assessed as horizontal, upsloping, or downsloping.

SPECT acquisition protocol. Myocardial perfusion single photon emission computed tomography was performed as previously described (19,20) using a circular or elliptical 180° acquisition for 64 projections at 20 s per projection. Images were subject to quality control measures as previously described (20). No attenuation or scatter correction was used. After filtered back-projection, short-axis, vertical, and horizontal long-axis tomograms were generated.

Image interpretation. Semiquantitative visual interpretation used short-axis and vertical long-axis tomograms di-

Table 1. Characteristics of Patients With No History of Previous CAD

	Measure	Observed Risk		Attributable Risk		Relative Risk		CoxPH
	End Point	CD	HE	CD	HE	CD	HE	HR
Male gender	51% (3,070)	0.3%	0.5%	−0.4%	−0.4%	0.43	0.55	0.59
Age (yrs)	61 ± 13 (51–71)	1.3%	1.6%	1.1%	1.3%	6.50	5.30	1.09
Exercise stress	77% (4,667)	0.1	0.3	−1.4%	−1.7%	0.07	0.15	0.18
Cardiac risk factors								
Hypertension	41% (2,475)	0.6%	0.9%	0.2%	0.4%	1.50	1.80	1.61
DM	9.6% (578)	1.6%	2.2%	1.3%	1.7%	5.33	4.40	4.20
Family history	41% (1,349)	0.1%	0.3%	−0.5%	−0.5%	0.17	0.37	0.39
Smoking	13% (814)	0.2%	0.7%	−0.3%	0%	0.40	0.10	1.12
Increased cholesterol symptoms	41% (2,486)	0.4%	0.6%	−0.1%	−0.2%	0.80	0.75	0.76
Asymptomatic	33% (1,989)	0.4%	0.4%		—	—	—	0.5
NACP	29% (1,757)	0.2%	0.5%	−0.2%	0.1%	0.50	1.25	0.65
Atypical angina	26% (1,595)	0.6%	0.9%	0.2%	0.5%	1.50	2.25	1.52
Typical angina	8% (490)	0.4%	0.8%	0	0.4%	1.00	2.00	1.17
Dyspnea	4% (215)	2.8%	2.8%	2.4%	2.4%	7.00	7.00	4.97
Likelihood of CAD	0.22 ± 0.41 (0.03–0.42)	1.0%	1.5%	0.7%	1.1%	3.33	3.75	7.76
Medications								
Beta-blockers	6% (366)	0.5%	0.8%	0%	0.1%	1.00	1.14	1.18
CCB	7.4% (450)	0.7%	2.0%	0.3%	1.4%	1.75	3.33	3.43
NTG	3.0% (179)	0%	0.6%	−0.5%	−0.1%	0	0.86	0.80
Abnormal rest ECG	51% (3,117)	0.7%	1.0%	0.5%	0.7%	3.50	3.33	2.93

Categorical variables are described as % (n), continuous variables as mean ± SD (25th, 75th percentiles). Risk is expressed as event rate over follow-up period. Continuous variables are dichotomized at the level of the 75th percentile, except for determination of hazard ratio based on the Cox proportional hazards model.

CAD = coronary artery disease; CCB = calcium channel blocker; CD = cardiac death; CoxPH = Cox proportional hazards model (univariable); DM = diabetes mellitus; ECG = electrocardiogram; HE = hard event; HR = hazard ratio; NACP = nonanginal chest discomfort; NTG = nitroglycerin.

vided into 20 segments (2,4). Each segment was scored by consensus of two experienced observers using a five-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of uptake, and 4 = absence of detectable tracer uptake). A summed stress score (SSS) was obtained by adding the scores of the 20 segments of the stress sestamibi images; SSS <4 was considered normal (2,4).

Patient follow-up. Patient follow-up was performed by scripted telephone interview by individuals blinded to the patient's test results, as previously described (1,2,4). Events were defined as either cardiac death (confirmed by review of death certificate, hospital chart, or physician's records) or non-fatal MI (documented by appropriate cardiac enzyme and electrocardiographic changes). The mean follow-up interval was 665 ± 200 days.

Likelihood of CAD. The pre- and post-exercise tolerance test (ETT) likelihood of CAD were calculated using CADENZA (Advanced Heuristics Inc., Bainbridge Island, Washington), a software package utilizing Bayesian analysis of clinical data (21). The pre-scan likelihood of CAD was defined as the pre-ETT likelihood of CAD in patients who underwent adenosine stress and the post-ETT likelihood in patients who underwent exercise. In patients with known CAD, this calculated likelihood is modified to be a likelihood of ischemia.

Statistical analysis. Comparisons between patient groups were performed using a chi-square test for categorical variables and a one-way analysis of variance, with a Bonferroni correction where appropriate. Categorical variables were described as a frequency, and continuous variables were described as a mean ± SD (25th and 75th percentiles). Observed, attributable, and relative risks were calculated. Attributable risk is defined as the risk in exposed individuals that can be attributed to the exposure. This measure is derived by subtracting the event rate in nonexposed persons from the corresponding rate among exposed individuals. Relative risk is defined as the ratio of the risk among those exposed to the risk among those not exposed. A p value of <0.05 was considered significant.

Cox proportional hazards analysis was used to determine the predictors of adverse outcomes, and parametric survival models (accelerated failure time models) were used to identify which variables influenced time to event and to estimate risk-adjusted event rates at specific time intervals and the length of time to specific risk thresholds. First, models were developed to identify variables most predictive of events, using a stepwise approach employing the most significant univariable predictors from Tables 1 and 2. Variables were first categorized into the following groups: 1) cardiac risk factors (age, hypertension, diabetes, pre-scan likelihood); 2) abnormal rest ECG, stress type, medications, symptoms; and 3) in patients with known CAD, historical variables. The most predictive variables from each of these were entered into a final model. For parametric survival analyses, separate models were developed for patients with versus without previous CAD. Based on the distribution of survival times in our cohort, a Weibull distribution was selected for the parametric models (22,23). All multivariable modeling was performed using S plus 2000 (Insightful

Table 2. Characteristics of Patients With History of Known CAD

	Measure	Observed Risk		Attributable Risk		Relative Risk		CoxPH
	End Point	CD	HE	CD	HE	CD	HE	HR
Male gender	56% (739)	0.9%	3.1%	−0.7%	0.7%	0.56	1.31	1.37
Age (yrs)	66 ± 12 (59–75)	3.6%	4.3%	3.0%	1.9%	6.19	1.83	1.04
Exercise stress	65% (866)	1.0%	2.9%	−0.7%	0.3%	0.60	1.12	1.68
Cardiac risk factors								
Hypertension	52% (692)	1.6%	3.0%	0.6%	0.5%	1.69	1.21	1.23
DM	15% (197)	1.5%	3.6%	0.3%	0.9%	1.23	1.34	1.29
Family history	26% (348)	1.4%	3.4%	0.2%	0.9%	1.18	1.35	1.42
Smoking	11% (141)	0.7%	2.8%	−0.6%	0.1%	0.53	1.02	0.99
Increased cholesterol	50% (670)	1.0%	2.5%	−0.5%	−0.5%	0.69	0.84	0.89
Symptoms								
Asymptomatic	28% (371)	0.8%	2.4%	0.7%	−0.5%	0.55	0.83	0.85
NACP	33% (434)	2.1%	3.8%	1.0%	1.4%	1.99	1.54	1.53
Atypical angina	21% (286)	1.2%	2.3%	−0.2%	−0.7%	0.86	0.76	0.75
Typical angina	15% (198)	0.5%	2.5%	−0.9%	−0.3%	0.36	0.89	0.88
Dyspnea	3% (41)	4.9%	4.9%	3.7%	2.2%	4.19	1.80	2.01
Likelihood of ischemia	0.38 ± 0.35 (0.08–0.68)	1.2%	2.1%	−0.1%	−1.0%	0.90	0.68	0.72
Medications								
Beta-blockers	11% (146)	2.1%	3.4%	0.9%	0.7%	1.74	1.27	1.32
CCB	18% (234)	0.9%	3.0%	−0.5%	0.3%	0.62	1.09	1.00
NTG	8% (112)	3.6%	3.6%	2.5%	0.9%	3.35	1.32	1.07
Abnormal rest ECG	64% (846)	1.8%	3.4%	1.4%	1.8%	4.29	2.07	2.00
History of angiography	85% (1,127)	1.4%	3.2%	0.9%	2.7%	2.88	6.48	6.81
History of PTCA	26% (350)	1.1%	4.0%	−0.2%	1.7%	0.86	1.70	1.70
History of CABG	21% (278)	1.1%	4.3%	−0.3%	1.9%	0.81	1.82	1.67
History of MI	34% (455)	1.3%	2.2%	0.1%	−0.9%	1.05	0.71	0.67

Categorical variables are described as % (n), continuous variables as mean ± SD (25th, 75th percentiles). Risk is expressed as event rate over follow-up period. Continuous variables are dichotomized at the level of the 75th percentile, except for determination of hazard ratio based on the Cox proportional hazards model.

CABG = coronary artery bypass surgery; MI = myocardial infarction; NACP = nonanginal chest discomfort; PTCA = percutaneous transluminal coronary angioplasty; Other abbreviations as in Table 1.

Corp., Seattle, Washington). When appropriate, assumptions of linearity, proportional hazards, and multiplicity were tested (22–24). Patients undergoing revascularization early after nuclear testing were not censored, because the revascularization was not related to the result of MPS. Although the parametric modeling was used to estimate predicted time to risk and levels of risk at specific time intervals, the limited number of events in this study compromises the accuracy of these estimates, and their purpose is to illustrate the impact of confounders on time and risk. The threshold for entry of variables into models was $p < 0.10$.

RESULTS

Outcome events. A total of 78 HE (45 cardiac deaths and 33 non-fatal MI) occurred, representing a 1.1% cumulative HE rate (0.6%/year). The 8,019 patients with abnormal MPS who underwent testing during this time interval experienced 530 HE (6.6% cumulative HE rate), and the 80 patients with normal studies immediately after PTCA (excluded from this study) experienced 5 HE (6.3% cumulative HE rate). Thus, the 15,475 patients tested during this time interval experienced a cumulative HE rate of 4.0% (613 total HE).

For purposes of analysis, patients with normal MPS were separated into those without (6,046 patients; 41 HE, 0.7% cumulative rate) and with known CAD (1,330 patients; 37 HE, 1.3% cumulative rate).

Clinical characteristics. The clinical characteristics of these two groups are shown in Tables 1 and 2. Patients without previous CAD were evenly split by gender (Table 1), predominantly underwent exercise, and infrequently had diabetes or a history of smoking. Intermediate numbers had hypertension, a family history of CAD, or elevated cholesterol. About a third were asymptomatic, smaller numbers had nonanginal chest discomfort or atypical angina, and fewer had typical angina or dyspnea. The pre-scan likelihood of CAD was low-intermediate. Half had abnormal rest ECG, and few were using anti-ischemic medications.

Patients with known CAD (Table 2) were more often male. One-third of patients had nonanginal chest discomfort, 28% were asymptomatic, and smaller proportions had atypical angina, typical angina, or dyspnea. The pre-scan likelihood of ischemia was low-intermediate. Few patients were taking anti-ischemic medications.

Univariate predictors of outcomes. The observed, attributable, and relative risks associated with these clinical characteristics are shown in Tables 1 and 2. In patients without known CAD (Table 1), increased age, diabetes, and dyspnea were associated with a greater observed risk of cardiac death or HE. The use of calcium channel blockers was also associated with higher observed risk of HE.

Table 3. Demographic, Clinical, and Risk Factor Characteristics and Hard Event Rates by Presenting Symptoms in Patients With No History of Previous CAD

	Presenting Symptoms				
	Asymptomatic	**NACP**	**Atypical Angina**	**Typical Angina**	**Dyspnea**
n (HE rate)	1,989 (0.4%)	1,757 (0.5%)	1,595 (0.9%)	490 (0.8%)	215 (2.8%)
Male gender	66% (1,306)	49% (865)	40% (643)	35% (173)	39% (83)
	0.3% (0.6%)	0.7% (1.3%)	0.3% (2.3%)	0.0% (0.3%)	3.6% (1.3%)*
Age (yrs)	22% (428)	21% (377)	26% (407)	25% (122)	48% (104)
	1.4% (0.1%)	0.5% (0.3%)	2.5% (0.9%)	2.5% (0.5%)	4.8% (0.3%)*
	61 ± 12	60 ± 13	61 ± 13	62 ± 13	69 ± 13*
Exercise stress	79% (1,572)	75% (1,406)	80% (1,201)	73% (357)	61% (131)
	0.3% (1.0%)	0.4% (2.8%)	0.2% (6.0%)	0.0% (0.9%)	0.8% (3.0%)*
Hypertension	37% (744)	39% (682)	45% (711)	48% (233)	49% (105)
	0.5% (0.3%)	0.6% (0.8%)	1.0% (1.8%)	1.3% (0.5%)	3.8% (0.4%)*
Diabetes mellitus	9% (183)	8% (134)	117 (772)	11% (55)	16% (34)
	1.1% (0.3%)	0.0% (0.6%)	3.5% (1.7%)	3.6% (0.6%)	8.8% (0.5%)*
Family history	22% (446)	21% (363)	23% (361)	27% (134)	21% (45)
	0.2% (0.5%)	0.3% (1.1%)	0.0% (2.9%)	0.7% (0.6%)	2.2% (0.8%)*
Smoking	13% (264)	14% (242)	13% (213)	13% (66)	13% (29)
	0.0% (0.5%)	0.4% (0.7%)	1.9% (3.2%)	1.5% (0.5%)	0.0% (0.7%)
Increased cholesterol	39% (773)	42% (744)	43% (688)	42% (204)	36% (77)
	0.4% (0.4%)	0.4% (1.1%)	0.6% (3.6%)	1.5% (0.6%)	1.3% (0.3%)*
Likelihood of CAD	11% (214)	10% (177)	44% (708)	82%	9% (20)
	1.9% (0.2%)	1.7% (0.3%)	1.6% (2.6%)	1.0% (0.4%)	5.0% (0.0%)
	0.15 ± 0.21	0.16 ± 0.20	0.39 ± 0.28	0.72 ± 0.27	0.15 ± 0.18
Beta-blockers	5.6% (112)	5.5% (97)	6.0% (96)	9.4% (46)	7.0% (15)
	1.8% (0.3%)	1.0% (0.9%)	0.0% (3.0%)	0.0% (0.5%)	0.0% (0.9%)*
CCB	5% (107)	6% (108)	8% (133)	15% (75)	13% (27)
	0.0% (0.0%)	1.9% (0.5%)	3.8% (0.0%)	1.3% (0.4%)	3.7% (0.8%)*
NTG	0.6% (12)	2.1% (3)	5.0% (80)	8.0% (39)	5.1% (11)
	0.0% (0.4%)	0.0% (0.8%)	1.3% (2.9%)	0.0% (0.5%)	0.0% (0.9%)*
Abnormal rest ECG	55% (1,092)	47% (832)	50% (803)	52% (253)	64% (137)
	0.7% (0.0%)	0.6% (0.5%)	1.2% (0.0%)	0.8% (0.4%)	4.4% (0.8%)*

For each variable, the values on the upper line represent the frequency of the variable within each symptom category and number of patients [% (n)], the lower line shows the hard event rate for patients with the variable (and without the variable) over the follow-up interval. Continuous variables are dichotomized at the level of the 75th percentile.
*$p < 0.05$ within categories of presenting symptom.
Abbreviations as in Table 1.

Attributable risk was greatest for increasing age, exercise (a protective effect), diabetes, and dyspnea with respect to both HE and cardiac death. Higher relative risks for HE were noted for age, diabetes, and symptoms of dyspnea, with relatively high values present for pre-scan likelihood of CAD, calcium channel blockers, and abnormal rest ECG. Strikingly low relative risks were associated with exercise stress and smoking, and to a lesser extent, with family history of CAD. The relative risk for cardiac death was low for exercise and high for diabetes, dyspnea, and age.

In patients with known CAD (Table 2), the clinical characteristics associated with greater observed risk of HE or cardiac death included age, hypertension, diabetes, and dyspnea. The use of beta-blockers and nitrates was also associated with higher observed risk of HE. Attributable risk was greatest for age, dyspnea, and nitrate use with respect to cardiac death and age, abnormal rest ECG, and previous angiography for HE. Increased relative risk of HE was noted for age, dyspnea, nitrate use, abnormal rest ECG, and previous angiography. Low relative risks were associated with exercise, smoking, hypercholesterolemia, presentation without symptoms, typical angina, and calcium channel blockers.

Risk and percent maximal heart rate achieved. Of the 5,533 patients who underwent exercise stress, 4,937 (89%) attained target heart rate (≥85% of maximal predicted heart rate [MPHR]). In addition, 7% achieved 80% to 85%, 3% attained 70% to 80%, and 2.9% achieved <70% of MPHR. The HE rates in these four subgroups of patients were 0.7%, 0.5%, 1.1%, and 2.9%, respectively. This suggests that prognostically, achieving ≥80% of MPHR is sufficient, but lower MPHR are associated with worse prognosis.

Clinical characteristics and predictors of outcomes as a function of presenting symptoms. As a function of presenting symptoms (Table 3), significant differences in HE rates were found in all variables examined except for smoking and likelihood of CAD. Significant differences were present as a function of age, gender, type of stress, hypertension, diabetes, family history, cholesterol levels, anti-ischemic medication use, and rest ECG.

HE rates in patient subgroups. A significant difference was present with respect to HE rates between patients with versus without a history of CAD ($p < 0.001$; 1.4% vs. 0.4% per year, respectively) (Fig. 2). No such differences were present as a function of type of stress or patient gender. Comparing rates of HE in men and women with versus

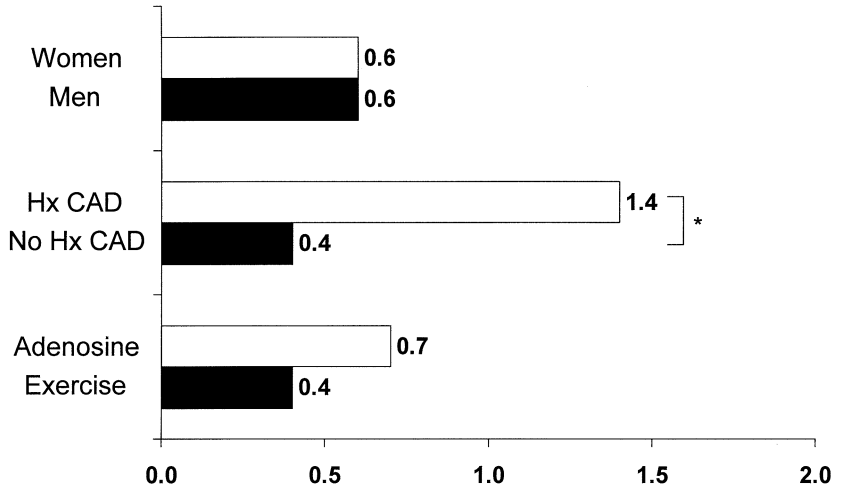

Figure 2. Hard event rates (% per year) in women versus men, patients with versus without history (Hx) of previous coronary artery disease (CAD), and patients undergoing adenosine versus exercise stress. *$p < 0.001$.

without diabetes (Fig. 3), diabetic women had a HE rate of 1.8%/year, with lower rates in the other subgroups. No difference was present in HE rates between men and women either with or without diabetes. However, a difference was present between women with versus without diabetes ($p = 0.007$), although no such difference was present in men. No difference in HE rates was present between patients with versus without known CAD with adenosine stress (Fig. 4), but a significant difference was present with exercise stress ($p < 0.001$).

Multivariable survival analysis. Cox proportional hazards analysis identified stress type, CAD history, diabetes, gender, and age as the model most predictive of HE. Interactions were present between type of stress and history of CAD as well as between the presence of diabetes and gender (Table 4).

The final model for prediction of time to HE in patients with no previous CAD included age and gender, the presence of diabetes, and the type of stress. This model included a nonlinear term for age and an interaction between gender and diabetes. In patients with previous CAD, the final model of time to HE included age, gender, diabetes, and previous catheterization. Significant interactions were present between age and gender and between diabetes and gender.

As the model for patients with known CAD did not include stress type but the model for patients without CAD did, the results of subsequent analyses shown in Tables 5 through 8 will show separate results for exercise and adenosine stress patients without CAD but a single set of results in patients with known CAD.

Changes in risk with time: event rates as a function of increments of follow-up time. To better understand the temporal change in risk as a function of patient characteristics, we estimated the predicted HE rate at six-month intervals for the first two years after the index study (first,

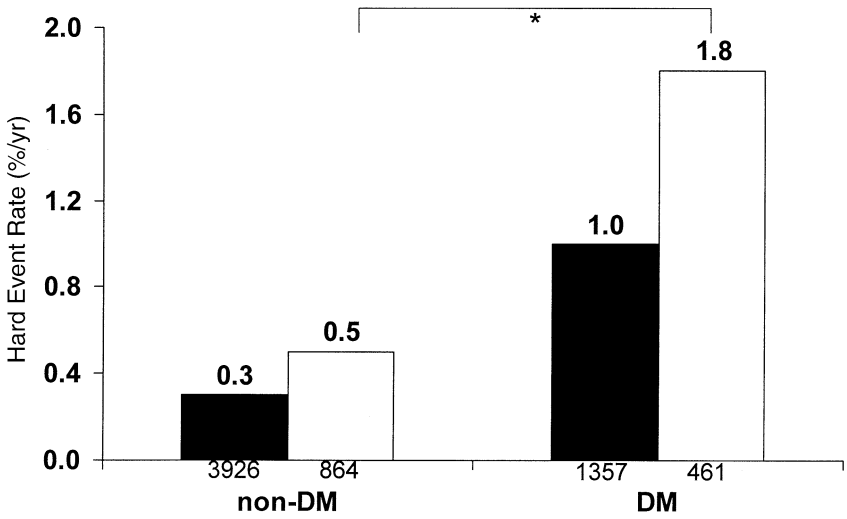

Figure 3. Hard event rates (% per year) in men **(black bars)** and women **(white bars)** with **(right)** versus without **(left)** diabetes. **Numbers under bars** represent number of patients within category. *$p = 0.007$. DM = diabetes mellitus.

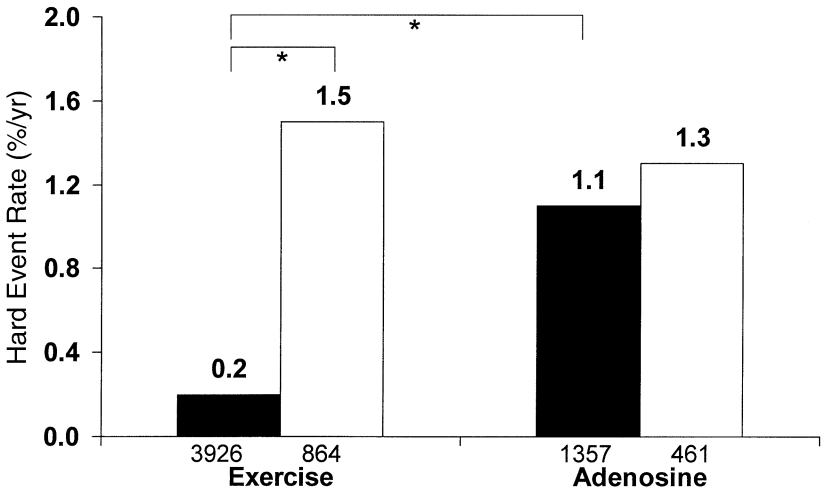

Figure 4. Hard event rates (% per year) in patients without **(black bars)** versus with **(white bars)** history of known coronary artery disease undergoing exercise **(left)** or adenosine **(right)** stress. **Numbers under bars** represent number of patients within category. *$p < 0.001$.

second, third, and fourth 6-month intervals), and summed these to show predicted event rates in the first versus second years of follow-up as well as the overall two-year predicted event rates (Table 5).

In patients with no previous CAD undergoing exercise, non-diabetic women had very low predicted event rates at all ages for all six-month intervals examined. These rates were similarly very low in both diabetic and non-diabetic men until age 80, at which point event rates were still relatively low, despite being 2 to 3 times greater than event rates at younger ages. Diabetic women had predicted HE rates that were 4- to 5-fold greater, and, by age 80, reached rates of 1% or more in two of four six-month intervals examined. Patients undergoing adenosine stress had a similar pattern of predicted HE rates (no significant temporal change with a significant age-related trend), but with significantly greater absolute rates of HE.

In comparison to patients without previous CAD, patients with known CAD at the time of SPECT (Table 6) had a similar pattern of increasing risk with age, but greater predicted event rates in all time intervals except in the setting of elderly female diabetics. Patients with known CAD also differed from patients without previous CAD in that female diabetics had event rates similar to male diabetics and non-diabetics; however, non-diabetic women had lower event rates.

Table 4. Final Cox Proportional Hazards Model for Hard Events

Factors	Chi-Square	p Value
Exercise stress (factor + higher order factors)	14.4	0.0008
All interactions	13.7	0.0002
History of CAD (factor + higher order factors)	30.1	<0.0001
All interactions	13.7	0.0002
DM (factor + higher order factors)	14.8	0.0006
All interactions	4.8	0.0291
Male (factor + higher order factors)	5.4	0.0672
All interactions	4.8	0.0291
Age (yrs)	26.0	<0.0001
Exercise stress * history of CAD (factor + higher order factors)	13.7	0.0002
DM * male (factor + higher order factors)	4.8	0.0291
Total interaction	18.9	0.0001
Total	81.0	<0.0001

"All interactions" refers to the statistical significance of the interactions for each variable.

Abbreviations as in Table 1.

The most striking finding in patients with known CAD was that patient risk increased in all patient subgroups in each successive time interval. Comparing the first to the fourth six-month interval, patient risk increased approximately 2 to 2.5 times, and event rates in the first year were lower than in the second year. Hence, risk appears to accelerate over time in patients with known CAD (Fig. 5).

To further understand the temporal characteristics of risk as a function of patient characteristics, we estimated the predicted time *to* 0.5%, 1.0%, 1.5%, and 2.0% risk based on the multivariable models, as well as the time *from* the index study to 0.5% risk, 0.5% to 1.0% risk, 1.0% to 1.5% risk, and 1.5% to 2.0% risk (Tables 7 and 8). The latter was performed to determine whether the risk of HE changed over time.

In patients without previous CAD (Table 7), predicted time to any level of risk was extremely long in men both with and without diabetes, as well as in non-diabetic women, until advanced age. In these three patient subgroups, time to risk was relatively long (time to 1% risk occurring well beyond 1 year) even at age 80. In diabetic women, however, time to risk was significantly shortened at each age level and reached short intervals (1% risk at <1 year) by age 80. Examining time to each level of risk reveals that in all four patient subgroups, time to risk shortened only minimally with increasing risk level, implying that risk did not change over time.

In patients with known CAD (Table 8), time to any level of risk was long in non-diabetic women but was relatively shorter in the three other subgroups at most ages examined

Table 5. Predicted Rates of Hard Events by Six-Month Intervals in Patients With No History of Previous CAD

	Age (yrs)	First Six Months (%)	Second Six Months (%)	Third Six Months (%)	Fourth Six Months (%)	First Year (%)	Second Year (%)	Two-Year Sum (%)
Exercise stress								
Male	50	0.03	0.03	0.05	0.08	0.06	0.13	0.19
Non-DM	60	0.05	0.05	0.06	0.10	0.10	0.16	0.26
	70	0.10	0.08	0.13	0.20	0.18	0.33	0.51
	80	0.36	0.23	0.35	0.52	0.59	0.87	1.46
Female	50	0.01	0.02	0.03	0.04	0.03	0.07	0.10
Non-DM	60	0.02	0.02	0.03	0.05	0.04	0.08	0.12
	70	0.04	0.04	0.06	0.10	0.08	0.16	0.24
	80	0.17	0.12	0.19	0.29	0.29	0.48	0.77
Male	50	0.03	0.02	0.04	0.07	0.05	0.11	0.16
DM	60	0.04	0.03	0.05	0.09	0.07	0.14	0.21
	70	0.09	0.06	0.11	0.17	0.15	0.28	0.43
	80	0.30	0.20	0.31	0.46	0.50	0.77	1.27
Female	50	0.17	0.12	0.19	0.29	0.29	0.48	0.77
DM	60	0.22	0.15	0.23	0.36	0.37	0.59	0.96
	70	0.45	0.28	0.41	0.62	0.73	1.03	1.76
	80	1.31	0.69	0.97	1.34	2.00	2.31	4.31
Adenosine stress								
Male	50	0.12	0.14	0.14	0.14	0.26	0.28	0.54
Non-DM	60	0.15	0.17	0.18	0.18	0.32	0.36	0.68
	70	0.27	0.31	0.31	0.32	0.58	0.63	1.21
	80	0.70	0.77	0.80	0.81	1.47	1.61	3.08
Female	50	0.08	0.08	0.08	0.09	0.16	0.17	0.33
Non-DM	60	0.10	0.10	0.11	0.12	0.20	0.23	0.43
	70	0.17	0.19	0.20	0.21	0.36	0.41	0.77
	80	0.44	0.49	0.50	0.52	0.93	1.02	1.95
Male	50	0.13	0.14	0.15	0.15	0.27	0.30	0.57
DM	60	0.16	0.18	0.18	0.19	0.34	0.37	0.71
	70	0.29	0.31	0.33	0.33	0.60	0.66	1.26
	80	0.73	0.80	0.83	0.84	1.53	1.67	3.20
Female	50	0.41	0.46	0.47	0.49	0.87	0.96	1.83
DM	60	0.51	0.57	0.60	0.60	1.08	1.20	2.28
	70	0.92	1.01	1.03	1.05	1.93	2.08	4.01
	80	2.34	2.52	2.55	2.55	4.86	5.10	9.96

CAD = coronary artery disease; DM = diabetes mellitus.

Table 6. Predicted Rates of Hard Events by Six-Month Intervals in Patients With History of Known CAD

	Age (yrs)	First Six Months (%)	Second Six Months (%)	Third Six Months (%)	Fourth Six Months (%)	First Year (%)	Second Year (%)	Two-Year Sum (%)
Male	50	0.33	0.56	0.70	0.80	0.89	1.50	2.39
Non-DM	60	0.39	0.66	0.82	0.94	1.05	1.76	2.81
	70	0.46	0.77	1.00	1.10	1.23	2.10	3.33
	80	0.54	0.91	1.14	1.30	1.45	2.44	3.89
Female	50	0.01	0.01	0.01	0.02	0.02	0.03	0.05
Non-DM	60	0.03	0.05	0.07	0.08	0.08	0.15	0.23
	70	0.15	0.25	0.32	0.36	0.40	0.68	1.08
	80	0.70	1.17	1.45	1.65	1.87	3.10	4.97
Male	50	0.34	0.57	0.72	0.83	0.91	1.55	2.46
DM	60	0.41	0.71	0.87	1.00	1.12	1.87	2.99
	70	0.53	0.90	1.11	1.27	1.43	2.38	3.81
	80	0.68	1.15	1.41	1.62	1.83	3.03	4.86
Female	50	0.44	0.74	0.92	1.06	1.18	1.98	3.16
DM	60	0.45	0.76	0.95	1.09	1.21	2.04	3.25
	70	0.46	0.79	0.97	1.11	1.25	2.08	3.33
	80	0.48	0.80	1.00	1.14	1.28	2.14	3.42

CAD = coronary artery disease; DM = diabetes mellitus.

Table 7. Time (Days) From Index Test to 0.5%, 1.0%, 1.5%, and 2.0% Predicted Risk of Hard Events in Patients With No History of Previous Coronary Artery Disease

		Time To:				Time From:			
	Age (yrs)	0.5% Risk	1.0% Risk	1.5% Risk	2.0% Risk	Test to 0.5%	0.5% to 1.0%	1.0% to 1.5%	1.5% to 2.0%
Exercise stress									
Male non-diabetic	50	1,725	3,287	4,801	6,292	1,725	1,562	1,514	1,491
	60	1,406	2,679	3,914	5,129	1,406	1,273	1,235	1,215
	70	815	1,553	2,269	2,974	815	738	716	705
	80	336	641	936	1,226	336	305	295	290
Male diabetic	50	1,691	3,222	4,707	6,168	1,691	1,531	1,485	1,461
	60	1,378	2,626	3,837	5,028	1,378	1,248	1,211	1,191
	70	799	1,523	2,225	2,915	799	724	702	690
	80	330	628	918	1,202	330	298	290	284
Female non-diabetic	50	2,680	5,106	7,459	9,774	2,680	2,426	2,353	2,315
	60	2,184	4,162	6,080	7,967	2,184	1,978	1,918	1,887
	70	1,266	2,413	3,525	4,619	1,266	1,147	1,112	1,094
	80	522	995	1,454	1,905	522	473	459	451
Female diabetic	50	549	1,046	1,529	2,003	549	497	483	474
	60	448	853	1,246	1,633	448	405	393	387
	70	260	495	722	947	260	235	227	225
	80	107	204	298	390	107	97	94	92
Adenosine stress									
Male non-diabetic	50	677	1,290	1,885	2,470	677	613	595	585
	60	552	1,052	1,537	2,014	552	500	485	477
	70	320	610	891	1,168	320	290	281	277
	80	132	252	367	482	132	120	115	115
Male diabetic	50	664	1,265	1,848	2,422	664	601	583	574
	60	541	1,031	1,506	1,974	541	490	475	468
	70	314	598	873	1,145	314	284	275	272
	80	129	247	360	472	129	118	113	112
Female non-diabetic	50	1,052	2,005	2,929	3,838	1,052	953	924	909
	60	858	1,634	2,387	3,128	858	776	753	741
	70	497	947	1,384	1,814	497	450	437	430
	80	205	391	571	748	205	186	180	177
Female diabetic	50	215	409	597	782	215	194	188	185
	60	176	335	489	641	176	159	154	152
	70	102	194	284	372	102	92	90	88
	80	42	80	117	153	42	38	37	36

(rate of risk >1% per year). Examining the time intervals between levels of risk, each 0.5% level of predicted risk occurred at shortening intervals, indicating an increase in risk with time after a normal MPS in patients with known CAD ($p < 0.001$).

DISCUSSION

We followed a cohort of patients after normal MPS to determine 1) whether clinical factors altered the risk for HE, 2) which factors were predictive of risk, and 3) whether a significant change in risk over time occurred after a normal MPS. Univariable analysis revealed that HE rates were greater in diabetic versus non-diabetic women. Compared with patients without previous CAD undergoing exercise stress, patients with known CAD undergoing exercise stress or patients undergoing adenosine stress were found to have significantly higher event rates. With respect to patients undergoing exercise stress, the risk associated with normal MPS was similar in patients who achieved ≥85% and 80% to 85% of MPHR, but HE rates were higher in patients who achieved <80% of MPHR.

Multivariable survival models revealed that clinical factors dramatically altered both the risk of HE and its temporal characteristics, suggesting that clinical information yields incremental prognostic value over MPS data in patients with normal scans. Cox proportional hazards analysis identified adenosine stress, CAD history, diabetes, gender, and increasing age as the model most predictive of HE, with significant interactions between type of stress and CAD history (lower risk in patients without previous CAD undergoing exercise stress in comparison to all other patients) as well as between the presence of diabetes and patient gender (higher risk in female diabetic patients compared with all other patients). Parametric survival analysis in patients without previous CAD revealed that increasing age, gender, the presence of diabetes, and adenosine stress best predicted HE (with significant interactions between the presence of diabetes and patient gender [higher

Table 8. Time (Days) From Index Test to 0.5%, 1.0%, 1.5%, and 2.0% Predicted Risk of Hard Events in Patients With Known Coronary Artery Disease

		Time To:				Time From:			
	Age (yrs)	0.5%	1.0%	1.5%	2.0%	Test to 0.5%	0.5% to 1.0%	1.0% to 1.5%	1.5% to 2.0%
Male non-diabetic	50	246	397	527	645	246	152	130	118
	60	218	353	468	573	218	135	115	105
	70	194	314	416	509	194	120	102	93
	80	173	279	370	453	173	106	91	83
Female non-diabetic	50	3,781	6,114	8,111	9,922	3,781	2,333	1,997	1,811
	60	276	2,064	2,737	3,349	1,276	787	674	611
	70	431	696	924	1,130	431	266	227	206
	80	145	235	312	381	145	90	77	70
Male diabetic	50	252	408	541	661	252	156	133	121
	60	211	341	452	553	211	130	111	101
	70	176	285	378	463	176	109	93	84
	80	147	238	316	387	147	91	78	71
Female diabetic	50	199	322	427	522	199	123	105	95
	60	197	319	423	518	197	122	104	94
	70	196	316	420	513	196	121	103	94
	80	194	314	416	509	194	120	102	93

risk in female diabetics compared with all other patients]). In patients with previous CAD, the final model of time to HE included increased age and gender, diabetes, and previous catheterization.

Based on the parametric survival models, in patients without previous CAD, predicted risk increased (and time to any level of risk decreased) significantly with age, with diabetes in women, and with adenosine stress. For any combination of clinical factors, the level of risk in these patients appeared to stay uniform with time (e.g., the risk in the first 12 months post-MPS was the same as the second 12 months post-MPS). In patients with known CAD, predicted risk also increased (and time to any level of risk decreased) with age and in female diabetics. Importantly, for any combination of clinical factors in patients with CAD, risk increased with time. That is, the risk in the first year was less than in the second year, hence, a dynamic temporal component of risk was present. Of note, absolute predicted risk was greater in patients with known CAD than in patients without previous CAD.

Incremental prognostic value of clinical data. We previously suggested (4) that clinical characteristics influence patient outcome after a normal scan based on the finding of a trend of increasing HE rates in patients with normal scans with post-ETT likelihood, Duke treadmill score, or increasing age. Numerous studies have described the incremental

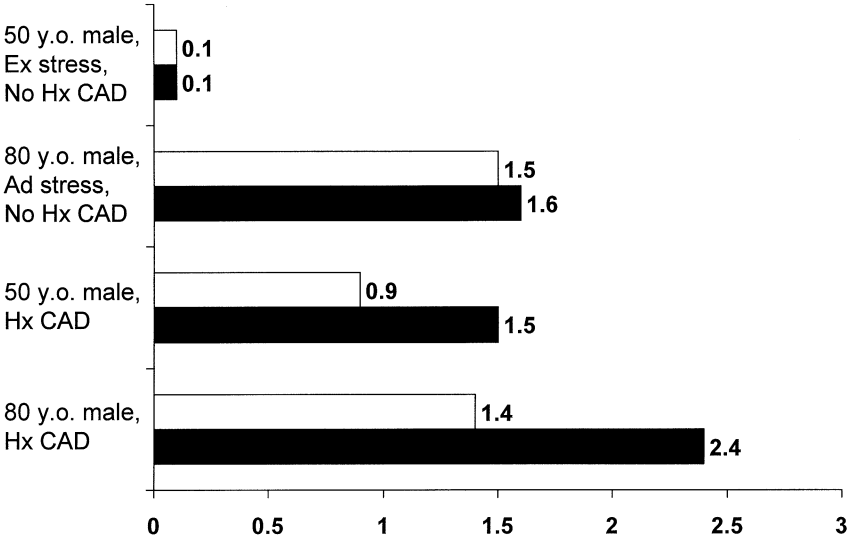

Figure 5. Examples of predicted event rates in the first and second years after the index single photon emission computed tomography study. The **top pair of bars** represents first- and second-year event rates in a 50-year-old male with no known coronary artery disease (CAD) undergoing exercise stress. In comparison, an 80-year-old male with no known CAD undergoing adenosine stress would have significantly greater first- and second-year event rates. Of note, although the risk increases, the rates in the first and second years are not different. On the other hand, the counterparts of these two patients with CAD, as shown in the **bottom two pairs of bars**, would have significantly greater risk, the rate in the second year would exceed that in the first year, and the change in risk between year 1 and year 2 would increase as a function of age in the setting of known CAD. **Black bars** = year 2 predicted hard event rate. **White bars** = year 1 predicted hard event rate. Ad = adenosine; Ex = exercise; Hx = history; y.o. = year old.

prognostic value of MPS data over clinical, historical, and treadmill data for prediction of adverse events. The current study reinforces the importance of the converse of this finding—clinical and historical clinical information yields incremental information over MPS data alone. This indicates that for a normal MPS result, actual patient risk will vary with clinical and historical data. This is consistent with clinical intuition; with normal MPS, an elderly patient with known CAD and revascularization who is unable to perform exercise stress would have a greater risk than a young patient with good exercise tolerance without previous CAD. This information has long been incorporated in clinical practice, as shown by the value of clinical data for predicting referral to catheterization after MPS.

Previous studies: prediction of low risk versus defining time intervals with low risk. Although a low risk is associated with normal MPS (1–3,5–13), several recent studies have reported somewhat higher event rates (14–18). These rates are generally reported as both cumulative and annualized event rates. As previously stated, an event rate of 3% over a three-year period may be due to: 1) a low constant event rate, 2) an event rate of <1% in the first year and increasing event rates in subsequent years, or 3) a much higher event rate initially and a lower rate subsequently. To date, post-MPS risk has not been reported as rates within circumscribed time intervals after the index study, an approach that would yield insight into both the change in risk over time and the duration of time after the study that risk remains low. Although previous studies have reported longer follow-ups (12,17), no previous reports have assessed the change in risk over time.

Clinical implications. The relative differences between therapeutic modalities with respect to mortality or cost vary as a function of the post-intervention timepoint at which they are examined. Although previous studies have shown reductions in short- and long-term costs of care with the addition of nuclear testing to a clinical strategy (1–3), these studies assumed that patients would undergo no further testing after a normal MPS. If repeat testing is needed or resource utilization increases at a certain time interval after a normal scan, the clinical- and cost-effectiveness of strategies incorporating nuclear testing would be significantly altered. However, to fully understand the cost implications for testing strategies, inquiry into temporal variations in risk with alternative testing strategies is necessary.

The finding that patients with a low likelihood of disease referred to MPS are at low risk for a considerable time interval after a normal study implies that these patients probably do not require repeat testing for a number of years. That patient characteristics alter the rate at which risk develops after normal scans suggests that under certain circumstances a reported annualized event rate may misestimate the actual risk. If risk is non-constant over the follow-up period, the annualized event rate will differ from the event rate in each year of the study. A non-constant event rate was present in the current study in patients with known CAD.

Study limitations. The patients in this study are those referred to a university-affiliated referral center, potentially limiting generalizability. The scintigraphic studies were assessed by experienced observers using a standardized, semiquantitative approach to visual interpretation (5,20). The visual approach was used because at the time of collection of the SPECT studies, we did not have a quantitative analysis technique operating on all of our camera/computer systems. However, the reliance upon the expertise of the observer limits the extrapolation of our results to those of other centers.

Although parametric survival models can accurately estimate predicted time to risk and levels of risk at specific time intervals, the limited number of events in this study compromises the precision of the estimates of risk and time to risk in the current study. In the current study, these estimates are intended to demonstrate the impact of the variables in the model as confounders of risk and time to risk in patients with normal scans.

Conclusions. The risk of HE after a normal MPS, and its change over time, are a function of the clinical and historical factors of the patients tested. Hence, clinical factors add incremental value over MPS data alone and alter the time at which repeat testing might be appropriate, hence establishing the existence of a "warranty" period for normal MPS studies.

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

REFERENCES

1. 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.
2. Berman DS, Hachamovitch R, Kiat H, et al. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography [published erratum appears in J Am Coll Cardiol 1996; 27:756]. J Am Coll Cardiol 1995;26:639–47.
3. Shaw LJ, Hachamovitch R, Berman DS, et al. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group. J Am Coll Cardiol 1999; 33:661–9.
4. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation 1996;93:905–14.
5. Berman DS, Kang X, Van Train KF, et al. Comparative prognostic value of automatic quantitative analysis versus semiquantitative visual analysis of exercise myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol 1998;32:1987–95.
6. Abdel Fattah A, Kamal AM, Pancholy S, et al. Prognostic implications of normal exercise tomographic thallium images in patients with

angiographic evidence of significant coronary artery disease. Am J Cardiol 1994;74:769–71.
7. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. Circulation 1991;83:363–81.
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. Gibbons RJ, Hodge DO, Berman DS, et al. Long-term outcome of patients with intermediate-risk exercise electrocardiograms who do not have myocardial perfusion defects on radionuclide imaging. Circulation 1999;100:2140–5.
10. Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 1993;22:665–70.
11. Ladenheim ML, Kotler TS, Pollock BH, Berman DS, Diamond GA. Incremental prognostic power of clinical history, exercise electrocardiography and myocardial perfusion scintigraphy in suspected coronary artery disease. Am J Cardiol 1987;59:270–7.
12. Machecourt J, Longere P, Fagret D, et al. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect: study in 1,926 patients with follow-up at 33 months. J Am Coll Cardiol 1994;23:1096–106.
13. Shaw LJ, Miller DD, Romeis JC, et al. Prognostic value of noninvasive risk stratification in younger and older patients referred for evaluation of suspected coronary artery disease. J Am Geriatr Soc 1996;44:1190–7.
14. Stratmann HG, Tamesis BR, Younis LT, Wittry MD, Miller DD. Prognostic value of dipyridamole technetium-99m sestamibi myocardial tomography in patients with stable chest pain who are unable to exercise. Am J Cardiol 1994;73:647–52.
15. 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.
16. 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.
17. Parisi AF, Hartigan PM, Folland ED. Evaluation of exercise thallium scintigraphy versus exercise electrocardiography in predicting survival outcomes and morbid cardiac events in patients with single- and double-vessel disease. Findings from the Angioplasty Compared to Medicine (ACME) study. J Am Coll Cardiol 1997;30:1256–63.
18. Calnon DA, McGrath PD, Doss AL Harrell FE Jr., Watson DD, Beller GA. Prognostic value of dobutamine stress technetium-99m-sestamibi single-photon emission computed tomography myocardial perfusion imaging: stratification of a high-risk population. J Am Coll Cardiol 2001;38:1511–7.
19. 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.
20. Berman DS, Kiat H, Van Train KF, Germano G, Maddahi J, Friedman JD. Myocardial perfusion imaging with technetium-99m-sestamibi: comparative analysis of available imaging protocols. J Nucl Med 1994;35:681–8.
21. Diamond GA, Staniloff HM, Forrester JS, Pollock BH, Swan HJ. Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. J Am Coll Cardiol 1983;1:444–55.
22. Lawless J. Statistical Models and Methods for Lifetime Data. New York, NY: John Wiley and Sons, 1982.
23. Harrell FE Jr. Predicting Outcomes: Applied Survival Analysis and Logistic Regression. Charlottesville, VA: University of Virginia, 2000.
24. Harrell FE Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.

Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: What is the warranty period of a normal scan?

Rory Hachamovitch, Sean Hayes, John D. Friedman, Ishac Cohen, Leslee J. Shaw, Guido Germano and Daniel S. Berman

J. Am. Coll. Cardiol. 2003;41;1329-1340
doi:10.1016/S0735-1097(03)00125-6