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Practical Applications in Stress Echocardiography

Risk Stratification and Prognosis in Patients With Known or Suspected Ischemic Heart Disease

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OBJECTIVES The purpose of this study was to define appropriate parameters for risk stratification and prognosis in patients undergoing stress echocardiography.

BACKGROUND Stress echocardiography is an established technique for the diagnosis of coronary artery disease. However, current data on risk stratification of patients undergoing stress echocardiography are limited.

METHODS We evaluated 1,500 patients (59 ± 13 years old; 51% male) undergoing stress echocardiography (34% with treadmill exercise and 66% with dobutamine). Resting left ventricular ejection fraction (EF) and regional wall motion were assessed by the consensus of two echocardiographers. Follow-up (mean 2.7 ± 1.0 years) for confirmed non-fatal myocardial infarction (n = 31) and cardiac death (n = 44) were performed.

RESULTS By univariate analysis, both the peak wall motion score index (WMSI) ($p < 0.0001$) and EF ($p < 0.0001$) were significant predictors of cardiac events. Peak WMSI effectively risk stratified patients into low (0.9%/year), intermediate (3.1%/year), and high (5.2%/year) risk groups ($p < 0.0001$). A threshold of 45% EF provided further risk stratification of all WMSI groups. By multivariate logistic regression analysis, peak WMSI (relative risk [RR] 2.1, 95% confidence interval [CI] 1.0 to 4.4; p = 0.04) and EF (RR 1.0, 95% CI 0.9 to 1.0; p = 0.01) were both predictors of cardiac events.

CONCLUSIONS Stress echocardiography yields prognostic information for risk stratification of patients with known or suspected ischemic heart disease. A normal stress echocardiographic study (peak WMSI = 1.0) confers a benign prognosis (0.9%/year cardiac event rate). Peak WMSI >1.7 and EF ≤45% are independent markers of patients at high risk of an adverse clinical outcome. (J Am Coll Cardiol 2003;42:1084–90) © 2003 by the American College of Cardiology Foundation

Stress echocardiography is routinely used for the diagnosis of coronary artery disease (CAD) in patients with anginal symptoms (1,2). However, an equally important objective of noninvasive testing is to identify patients at risk of future cardiac events. The application of prognostic testing is based on the premise that patients identified as being at highest risk of adverse outcomes can be intervened upon to alter the natural history of their disease process, thereby reducing subsequent risk. Prospective, randomized clinical trials have shown that medical therapy and coronary revascularization can reduce cardiac mortality in subsets of selected patients (3,4). Recent trials of medical therapy have demonstrated reductions in both fatal and non-fatal myocardial infarction (MI) rates and cardiac death (5–9).

Stress echocardiographic results are traditionally interpreted as binary (normal or abnormal). Risk stratification and prognosis based on this approach indicate that a normal study portends a good prognosis (low risk), and an abnormal study is associated with an increased risk of cardiac events (high risk). However, *abnormal* stress echocardiographic studies should be further risk stratified: a patient with only apical ischemia (single-vessel CAD) is at substantially lower (intermediate) risk than a patient with both anterior and inferolateral ischemia and cavity dilation after stress (multivessel CAD, deemed high risk). Thus, if stress echocardiography could better risk stratify patients into three groups (low, *intermediate*, and high risk) and accurately predict cardiac events, potential cost savings could be realized by targeting appropriate treatment strategies and more appropriate referral to catheterization for the highest risk patients.

Thus, the objectives of the present study were threefold: 1) to define the prognostic value of stress echocardiography for the prediction of cardiac events; 2) to define the ability of stress echocardiography to risk stratify patients into low- (<1%/year), intermediate- (1% to 5%/year), and high-risk (>5%/year) groups for cardiac events; and 3) to evaluate the prognostic value of resting ejection fraction (EF) and peak left ventricular (LV) wall motion scores, together, in predicting cardiac events in a large, unselected population of patients referred for stress echocardiographic testing.

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Abbreviations and Acronyms

CAD	= coronary artery disease
EF	= ejection fraction
LV	= left ventricle/ventricular
MI	= myocardial infarction
WMSI	= wall motion score index

METHODS

Study population. We identified 1,607 patients who underwent either exercise or pharmacologic stress echocardiography between January 1, 1996, and November 30, 2000. Successful follow-up (98%) for cardiac events ≥1 year after testing was obtained. Patients with nonischemic cardiomyopathy (n = 41) were excluded, and patients revascularized within 60 days after stress echocardiography (n = 66) were censored from the prognostic portion of the analysis, which left a cohort of 1,500 patients.

Exercise echocardiography protocol. Maximal exercise treadmill testing was performed using a standard Bruce protocol. Patients exercised to general fatigue, with premature termination for severe angina, ventricular tachycardia, hemodynamically significant arrhythmias, or hemodynamic instability. Post-exercise echocardiographic images were acquired within 30 to 60 s after termination of treadmill exercise. Failure to achieve 85% of the age-predicted maximal heart rate was followed by conversion to a dobutamine stress echocardiographic study (~3% to 5% of treadmill stress echocardiographic studies).

Dobutamine echocardiography protocol. Dobutamine was administered intravenously beginning at a dose of 5 to 10 μg/kg per min and increased by 5 to 10 μg/kg per min every 3 min, up to a maximum of 50 μg/kg per min or until a study end point was achieved. The end points for termination of the dobutamine infusion included development of new segmental wall motion abnormalities, attainment of 85% of age-predicted maximum heart rate, or development of significant adverse effects related to the dobutamine infusion. Atropine was administered intravenously in 0.25-mg increments every 3 min, up to a maximum of 2.0 mg if a study end point was not achieved at the maximum dobutamine dose.

During both types of stress, transthoracic echocardiographic images were obtained using standard views with commercially available ultrasound equipment (Hewlett-Packard Sonos 2500, Andover, Massachusetts). Echocardiographic images were acquired at baseline, with each increment of dobutamine infusion, and during the recovery phase.

Echocardiographic image analysis. The LV was divided into 16 segments, as recommended by the American Society of Echocardiography (10), and a score was assigned to each segment at baseline, with each stage of stress (dobutamine only), and during recovery. Each segment was scored as follows: 1 = normal; 2 = mild to moderate hypokinesia (reduced wall thickening and excursion); 3 = severe hypokinesia (marked reduced wall thickening and excursion); 4 = akinesia (no wall thickening and excursion); and 5 = dyskinesia (paradoxical wall motion away from the center of the LV during systole) (11). All echocardiograms were interpreted by the consensus of two experienced echocardiographers blinded to the patients' treatment and outcome.

A normal response to stress was defined as normal wall motion at rest, with an increase in wall thickening and excursion during stress. An abnormal response to stress was defined as: 1) a LV wall segment that did not increase in thickness and excursion during stress (fixed wall motion abnormality); 2) deterioration of LV segment wall thickening and excursion during stress (increase in wall motion score of ≥1 grade); and 3) a biphasic response with dobutamine stress. The peak wall motion score index (WMSI) following stress was derived from the cumulative sum score of 16 LV wall segments divided by the number of visualized segments. The stress echocardiogram with a peak WMSI of 1.0 was considered normal, 1.1 to 1.7 was mild to moderately abnormal, and >1.7 was markedly abnormal. Resting EF used in the study analysis was an average visual estimation (12) from two experienced echocardiographers.

Patient follow-up. Serial prospective follow-up was obtained by means of a physician-directed telephone interview using a standardized questionnaire. If the patient died after the stress echocardiographic study, the closest surviving relative and the patient's physician were interviewed to determine the cause of death. Cardiac death was confirmed by a review of the hospital medical records and/or death certificate. Autopsy records were reviewed when available.

The primary end point of the study was the initial follow-up event: non-fatal MI or cardiac death. Non-fatal MI was documented by evidence of an appropriate combination of clinical symptoms, electrocardiographic (ECG) findings, and cardiac enzyme changes.

Statistical analysis. Continuous data are expressed as the mean value ± SD. Differences in categorical variables among groups were assessed by chi-square analysis. Receiver-operating characteristic (ROC) curve analysis was used to determine the peak WMSI grouping and EF cutoff value, with the maximal informational content (area beneath the ROC curve), which optimized accuracy in predicting cardiac events. Univariate analysis was performed to determine the relationship between clinical and echocardiographic variables and cardiac events. Univariate variables that were predictive of cardiac events were considered in the multivariate logistic regression analysis. Kaplan-Meier cumulative survival analysis with stratification by peak WMSI and EF was performed; a comparison of survival between the groups was made using the Mantel-Cox test. Statistical significance was set at $p < 0.05$. All analyses were performed using commercially available statistical software (SPSS for Windows, version 10.0.5).

Table 1. Patient Characteristics by Type of Stress

	Exercise Stress (n = 514)	Dobutamine (n = 986)	p Value
Age (yrs)	54 ± 12	61 ± 12	<0.0001
Male gender	273 (53%)	489 (49%)	0.49
History of MI	43 (8%)	205 (21%)	<0.0001
History of PCI	39 (7%)	89 (9%)	0.40
History of bypass surgery	29 (5%)	103 (10%)	<0.01
History of hypertension	281 (55%)	690 (71%)	<0.01
History of diabetes	99 (19%)	301 (31%)	<0.0001
Number of cardiac risk factors	1.7 ± 1.1	1.9 ± 1.1	<0.001
Beta-blockers	106 (20%)	242 (25%)	0.16
Abnormal rest ECG	170 (34%)	480 (49%)	<0.0001
%Max HR (beats/min)	95 ± 10	87 ± 13	<0.0001
Peak wall motion score index	1.1 ± 0.3	1.4 ± 0.7	<0.0001
Number of new reversible wall motion abnormalities	0.8 ± 2.3	2.2 ± 3.2	<0.0001
Ejection fraction (%)	57 ± 5	51 ± 13	<0.0001
Follow-up (yrs)	2.7 ± 0.9	2.7 ± 0.9	0.22
Myocardial infarction	4 (1%)	27 (3%)	0.02
Cardiac death	4 (1%)	39 (4%)	<0.001

Data are presented as the mean value ± SD or number (%) of patients.
ECG = electrocardiogram; %Max HR = percent maximal predicted-heart rate achieved; MI = myocardial infarction; PCI = percutaneous coronary intervention.

RESULTS

Patient characteristics. From the study cohort of 1,500 patients, 514 (34%) underwent treadmill exercise and 986 (66%) underwent pharmacologic stress. The demographics are characterized in Table 1. Patients who underwent dobutamine stress were older and more often had a history of previous MI and bypass surgery, more cardiac risk factors (hyperlipidemia, hypertension, diabetes, smoking, and family history of premature CAD), more frequent abnormal resting ECGs, a higher peak WMSI, a greater number of new reversible wall motion abnormalities, worse LV systolic function, and greater subsequent rates of adverse cardiac events than patients undergoing exercise stress testing.

Outcome events of stress echocardiography. Patients were followed for up to five years (mean 2.7 ± 1.0 years), and 98% of patients were followed for at least one year. Among the study cohort of 1,500 patients, 75 coronary events (5%) occurred during the follow-up period. These included 31 non-fatal MIs (2.1%) and 44 cardiac deaths (2.9%).

Univariate analysis. Descriptive patient characteristics and exercise and stress echocardiographic variables in patients with and without cardiac events on follow-up are shown in Table 2. Patients with cardiac events on follow-up were older, more often had a history of previous MI and more frequent abnormal rest ECGs, and were less likely to undergo exercise stress (Table 2) than patients without cardiac events. With respect to echocardiographic variables (Table 2), patients with cardiac events had a higher peak

Table 2. Patient Characteristics

	Cardiac Events (n = 75)	No Events (n = 1425)	p Value
Age (yrs)	64 ± 12	58 ± 12	< 0.01
Male gender	43 (57%)	719 (50%)	0.58
History of hypertension	57 (79%)	914 (65%)	0.35
History of diabetes	28 (38%)	372 (26%)	0.06
History of MI	25 (36%)	223 (16%)	< 0.001
Abnormal rest ECG	48 (69%)	602 (44%)	0.03
Exercise	5 (6%)	476 (33%)	< 0.0001
Peak wall motion score index	1.8 ± 0.9	1.2 ± 0.6	< 0.0001
Number of new reversible wall motion abnormalities	4.2 ± 4.7	1.6 ± 3.4	< 0.001
Ejection fraction (%)	43 ± 19	54 ± 10	< 0.0001

Data are presented as the mean value ± SD or number (%) of patients.
Abbreviations as in Table 1.

WMSI, a greater number of new reversible wall motion abnormalities, and worse LV systolic function.

Peak WMSI, EF, and cardiac events. The annual cardiac event rate increased as a function of the extent and severity of abnormal wall motion response during stress and increasing peak WMSI (Fig. 1). A normal wall motion (peak WMSI = 1.0) response during stress echocardiography was associated with a benign prognosis (0.9%/year), whereas mild to moderate (peak WMSI = 1.1 to 1.7) and severe wall motion (peak WMSI >1.7) abnormalities resulted in higher cardiac event rates (3.1%/year and 5.2%/year, respectively; p < 0.0001 vs. normal wall motion). Figure 2 illustrates the cardiac event rate as a function of peak WMSI and EF. An EF >45% demonstrated an intermediate cardiac event rate, even in patients with a peak WMSI of 1.1 to 1.7 (2.0%/year) or >1.7 (2.3%/year). An EF ≤45% and peak WMSI of 1.1 to 1.7 (6.2%/year) or >1.7 (5.6%/year) were associated with a high cardiac event rate. There is a significant correlation between peak WMSI and EF (r = 0.83, p <

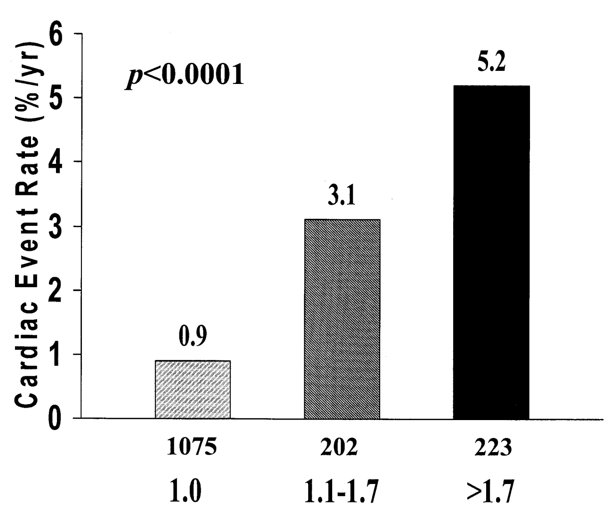

Figure 1. Cardiac event rate per year as a function of wall motion score index (WMSI). The number of patients within each WMSI category is shown **below each column**. Statistical significance increases as a function of the WMSI result.

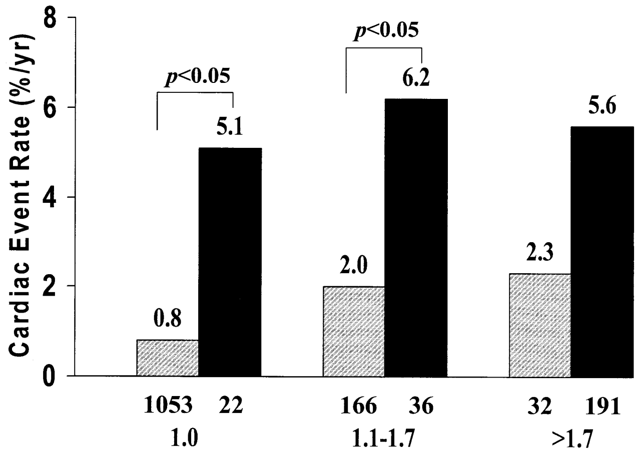

Figure 2. Cardiac event rate per year as a function of wall motion score index and ejection fraction (EF). The number of patients within each category is indicated **below each column**. **Shaded columns** = EF >45%; **solid columns** = EF ≤45%.

0.0001), such that a higher peak WMSI was associated with a lower resting EF.

Exercise versus dobutamine stress. There were eight cardiac events among patients who underwent treadmill stress and 67 events among patients who underwent dobutamine stress (0.6%/year vs. 2.5%/year, $p < 0.0001$). Patients with EF ≤45% had significantly higher cardiac event rates, both in the exercise and dobutamine groups. Patients with abnormal exercise or abnormal dobutamine stress studies had significantly higher cardiac event rates than corresponding patients with normal exercise (1.4%/year vs. 0.2%/year, $p < 0.05$) or normal dobutamine (4.7%/year vs. 0.8%/year, $p < 0.0001$) studies.

Predictors of cardiac events. Univariate predictors of cardiac events are shown in Table 3. Clinical and echocardiographic variables significant by univariate analysis were considered in the multivariate analysis. On multivariate logistic regression analysis, peak WMSI (relative risk [RR] 2.1, 95% confidence interval [CI] 1.0 to 4.4; $p = 0.04$) and

Table 3. Univariate and Multivariate Predictors of Cardiac Events

Variable	RR	95% CI	p Value
Univariate predictors of cardiac events			
Age	0.96	0.94–0.98	0.001
Hypertension	1.99	1.11–3.56	0.01
Diabetes mellitus	1.74	1.06–2.83	0.02
Smoking	1.62	0.99–2.64	0.05
History of MI	2.91	1.74–4.85	0.0001
Abnormal rest ECG	2.82	1.67–4.77	0.0001
%Max HR	1.02	1.00–1.04	0.004
Ejection fraction	1.05	1.03–1.06	0.0001
Peak WMSI	4.64	2.87–7.53	0.0001
Multivariate predictors of cardiac events			
Peak WMSI	2.08	1.01–4.42	0.04
Ejection fraction	0.97	0.94–0.99	0.01

CI = confidence interval; RR = risk ratio; other abbreviations as in Table 1.

EF (RR 1.0, 95% CI 0.9 to 1.0; $p = 0.01$) were both predictors of cardiac events.

Kaplan-Meier survival analysis: risk stratification using peak WMSI and EF. Figures 3 and 4 show cumulative survival curves in patients as a function of peak WMSI (Fig. 4) abnormalities and EF. A peak WMSI of 1.0 or EF >45% identified patients at low risk. Cumulative survival was progressively worse with a higher peak WMSI. A peak WMSI >1.7 or EF ≤45% identified patients at highest risk of cardiac events.

DISCUSSION

This study assessed the prognostic value of stress echocardiography in patients with known or suspected CAD. A normal stress echocardiographic study portends an excellent prognosis. Univariate regression showed that peak WMSI and EF were independent predictors of cardiac events. Stress echocardiography can risk stratify patients not only into high- and low-risk groups, but also into an intermediate risk group (1% to 5%) for cardiac events. Findings from this study show that peak WMSI >1.7 and EF ≤45% identified patients at highest risk of adverse cardiac events.

Prognostic implications of a normal stress echocardiogram. Previous studies have examined the prognostic value of a normal stress echocardiogram (13–21). It has been demonstrated that normal stress echocardiography is associated with a benign prognosis (16,20,21). However, a few studies have reported intermediate cardiac event rates in patients with a normal stress echocardiogram (13–15,17–19). These studies with higher event rates included patients with resting wall motion abnormalities and were performed before the routine use of harmonic imaging and contrast agents. The results of the present study are concordant with current published data in that a normal stress echocardiogram confers a benign prognosis. This low event rate of 0.9%/year over the ensuing year approaches that of a normal age-matched population and also of patients with normal coronary angiograms (22). The higher cardiac event rates in patients undergoing dobutamine stress are related to the worse clinical, wall motion, and overall LV systolic function characteristics of these patients (Table 1). The results of the present study compare favorably with those of normal myocardial perfusion studies (thallium-201 or technetium-99m sestamibi), associated with a benign prognosis (23).

Prognostic value of peak WMSI: risk stratification. The diagnosis of CAD is the first step in the appropriate evaluation of a patient with anginal symptoms. However, for proper management and appropriate decision analysis, additional information on risk stratification and prognosis is necessary (24). Peak WMSI is quantitated by stress echocardiographic interpretation and incorporates both the extent and severity of wall motion abnormalities at peak stress. In this study, peak WMSI was able to effectively risk stratify patients into three groups: low- (0.9%/year), intermediate-

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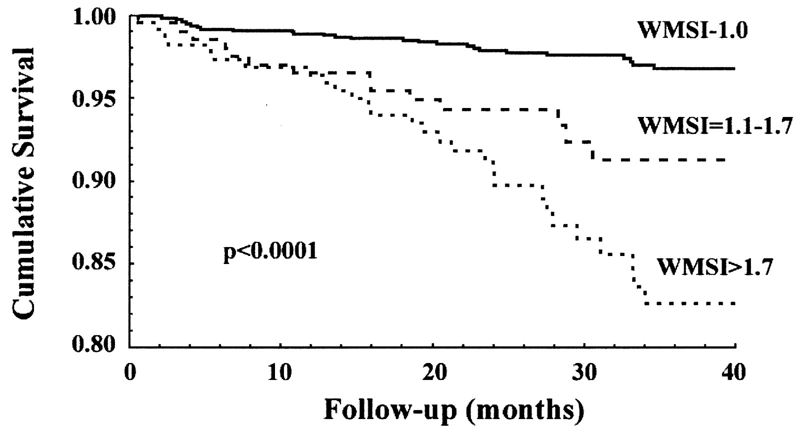


—— WMSI=1.0	1075	1054	876	567	322
---- WMSI=1.1-1.7	202	1911	58	86	45
····· WMSI>1.7	223	211	171	101	54

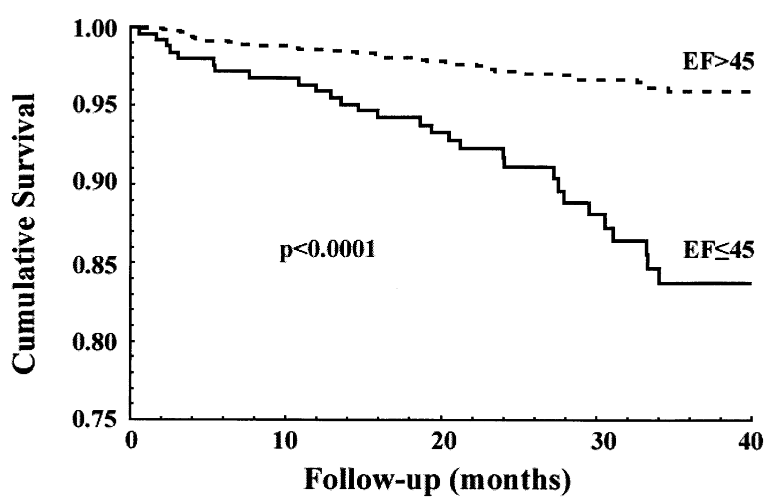
Figure 3. Cumulative survival as a function of wall motion score index (WMSI) using cardiac events as an end point.

(3.1%/year), and high-risk (5.2%/year) groups for cardiac events.

Prognostic value of EF. Multiple studies have shown that EF is a powerful predictor of cardiac events (25,26). Angiographically measured EF has been previously reported as a better predictor of survival, compared with the angiographically demonstrated number of diseased coronary vessels in medically treated patients (26). In the present study, an EF threshold of 45% provided appropriate further risk stratification of patients. Patients with an EF >45% had a low to intermediate cardiac event rate, regardless of the extent of peak WMSI abnormality.

Peak WMSI and EF data provided appropriate risk stratification of patients undergoing stress echocardiography. Peak WMSI and EF were concordantly identified by multivariate analyses as the best predictors of cardiac events. Of note, there were 22 patients with a peak WMSI of 1.0 and EF ≤45%. These patients had resting global LV hypokinesia but a normal peak WMSI of 1.0 (inotropic contractile reserve), suggestive of nonischemic cardiomyopathy. Despite normal peak WMSI, a worse prognosis was conferred in the subgroup of patients with EF ≤45%.

Study significance and implications for the use of stress echocardiographic testing. In contrast to previous studies (27–34) assessing the prognostic value of wall motion or EF variables, this is the first study to evaluate risk stratification and prognosis together in a large patient population referred for stress echocardiography. This is the first stress echocardiographic study to define an intermediate-risk group and demonstrate risk stratification into three groups (low-, intermediate-, and high-risk groups). This study incorporates wall motion and EF into prognostic risk stratification



---- EF>45	1250	1220	1007	642	365
—— EF≤45	250	236	198	112	56

Figure 4. Cumulative survival stratified into ejection fraction (EF) >45% and EF ≤45% using cardiac events as an end point.

as separate and combined end points. Thus, the results of this study may be applicable to the general population of patients typically referred for stress echocardiography.

In the present study, the presence of normal wall motion (peak WMSI = 1.0) during stress echocardiography conferred a benign prognosis. These low-risk patients generally only require counseling with regard to risk factor modification. Patients with mild to moderate wall motion abnormalities (peak WMSI = 1.1 to 1.7) had an intermediate risk of cardiac events. The ideal management strategy for these patients is unclear. Rather than an invasive management approach of catheterization and revascularization, with its inherent risks, patients with an intermediate risk of cardiac events may perhaps experience lowering of their risk of future cardiac events by aggressive risk factor modification and referral to catheterization, only if they have refractory symptoms. In addition, resting EF should have an important influence on the appropriate management approach in such patients. An initial noninvasive management strategy may be cost-effective and avoid unnecessary invasive procedures (35). Conversely, high-risk patients with WMSI >1.7 and especially those with EF ≤45% are at a significant risk of cardiac events. Such high-risk patients should be appropriately referred for consideration of cardiac catheterization and potential coronary revascularization to modify and reduce their risk.

Study limitations. The prognostic analysis of the study was limited by the study population. Among the 1,500 patients included in this study, 1,075 (71.6%) had a normal response to stress (WMSI = 1.0). There were only 75 coronary events (1.9%/year) during the follow-up period. Thus, due to a limited number of hard events, the study combined analysis of exercise and dobutamine stress patients. This is not ideal, but probably acceptable, as patients could be individually risk stratified (abnormal vs. normal) by either exercise or dobutamine stress echocardiographic studies. In addition, although patients were followed for up to five years, one-year follow-up was incomplete in 2% of patients. Furthermore, this low-risk patient population provided a limited number of patients with WMSI of 1.1 to 1.7 and >1.7 for substratification by EF. The frequency of cardiac death was higher than that of non-fatal MI in this population. This unexpected finding may be due to difficulty in confirming MI and our higher success rate in defining cardiac death in each patient. Another potential limitation is that the cutoff values for WMSI and EF in this study could be subject to patient referral bias relative to the constitution of our patient population.

The patients in this study were typical in terms of age, gender, and demographics of a population referred for testing at a large tertiary-care hospital, and the results may be generalizable to this setting. However, the subjective nature of wall motion analysis and visual EF measurement, with its dependence on the expertise of the observer, presents a limitation with respect to the extrapolation of our results to those of other centers (36,37).

Conclusions. On the basis of this and other reported studies, it is clear that a normal stress echocardiogram confers a benign prognosis (<1%/year). Peak WMSI can effectively risk stratify patients into low- (0.9%/year), intermediate- (3.1%/year), and high-risk (5.2%/year) groups for cardiac events. Resting EF, as assessed by echocardiography, provides further risk stratification of patients with known or suspected CAD, in addition to peak WMSI alone. Thus, the information provided by stress echocardiography, peak WMSI, and EF should be used together in identifying high-risk patients for appropriate referral to catheterization and consideration of coronary revascularization.

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