

Impact of Gender on Risk Stratification by Stress Echocardiography

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ABSTRACT

OBJECTIVE: To compare the prognostic value of stress echocardiography results in men and women with known and suspected coronary artery disease.

METHODS: We analyzed the data of 8737 patients (5529 men and 3208 women) who underwent stress echocardiography (exercise in 523 patients, dipyridamole in 6227 patients, dobutamine in 1987) for evaluating known (n = 3857) or suspected (n = 4880) coronary artery disease. Patients were followed up for the occurrence of overall mortality or nonfatal myocardial infarction.

RESULTS: During a median follow-up of 25 months, 1218 cardiac events (693 deaths and 525 infarctions) occurred. Moreover, 2263 patients (1731 men [31%] and 532 women [17%]; $P < .0001$) underwent coronary revascularization and were censored. Stress echocardiography results added prognostic information to that of clinical findings and resting wall motion score index in men and women with both known and suspected coronary artery disease. In patients with known coronary artery disease, women had a higher ($P = .01$) event rate than men in the presence of ischemia. The annual event rate was worse for nondiabetic women ($P = .007$) but not diabetic women; age had a neutral prognostic effect in the 2 sexes. In patients with suspected coronary artery disease, men without ischemia had a higher ($P < .0001$) event rate than women. The annual event rate was worse in men aged less than 65 years ($P < .0001$) or more than 65 years ($P = .04$), and those with ($P = .03$) or without ($P < .0001$) diabetes.

CONCLUSION: Prognosis is at least comparable in men and women with ischemia and in those with coronary artery disease and no ischemia at stress echocardiography. In these clinical settings, availability for major procedures should be similar for both genders.

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KEYWORDS: Gender gap; Prognosis; Stress echocardiography; Women

Coronary artery disease is the single leading cause of mortality in both sexes.¹ Cardiovascular mortality in the United States has declined substantially, but this improvement in prognosis has been restricted to men.² However, younger women have substantially higher mor-

tality rates than men after myocardial infarction and coronary bypass surgery.¹ Several factors, although not completely understood, might account for the higher mortality rates in women. Women with myocardial infarction are older and have more comorbidity and risk factors, such as diabetes, hypertension, renal insufficiency, and congestive heart failure.³ Selective underuse, underdiagnosis, and undertreatment of women with abnormal test results may explain the suboptimal diagnostic accuracy of noninvasive testing.^{4,5} Interest has grown in the use of stress echocardiography for evaluating coronary artery disease in women because of proved cost-effectiveness⁶⁻⁸ and high diagnostic⁹⁻¹³ and prognostic¹⁴⁻²¹ value, incremental to that of exercise electrocardiography.¹⁷ The aim of this multicenter, observational study

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was to compare the prognostic value of stress echocardiography results in a large cohort of male and female patients with known or suspected coronary artery disease.

MATERIALS AND METHODS

Patients

From the prospective databases of 3 different Italian institutions (Lucca, Pisa, Milan), 8940 patients who underwent stress echocardiography between 1995 and 2006 were selected initially. Exclusion criteria were significant valvular or congenital heart disease, significant comorbidity reducing life expectancy to less than 1 year, and inadequate acoustic window. Of these patients, 203 (2%) were lost to follow-up. The remaining 8737 patients (5529 men and 3208 women) had complete follow-up information and formed the study population.

Therefore, this is a retrospective analysis of a prospectively collected database. Indication to stress echocardiography was suspected coronary artery disease in 4880 subjects (56%) and risk stratification of known coronary artery disease in 3857 subjects (44%). Coronary artery disease was defined as recent or a history of acute coronary syndromes (ST-elevation myocardial infarction or non-ST-elevation myocardial infarction) or coronary revascularization and/or the presence of more than 1 angiographically documented coronary stenosis greater than 50%. The stressor used (523 exercise, 6227 dipyridamole, and 1987 dobutamine) was chosen on the basis of specific contraindications, local facilities, and physician's preference. Pharmacologic stress echocardiography was used when the exercise electrocardiography result was nondiagnostic or inconclusive. The choice of the pharmacologic stressor was made on the basis of potential relative contraindications of one over the other and on a gradient of safety (dipyridamole is safer than dobutamine). Stress echocardiography was performed on antianginal medical therapy in 3005 patients (34%) (β -blockers in 1395 patients, calcium antagonists in 1179 patients, or nitrates in 1572 patients) and off therapy in 5732 patients (66%). Informed consent was obtained from all patients before testing, and the study protocol was approved by the institutional ethical committee. Stress echocardiography data were collected and analyzed by stress echocardiographers not involved in patient care. All investigators of contributing centers passed quality-control criteria for regional wall motion before entering the study as previously described.²² Diabetes mellitus,²³ arterial hypertension,²⁴ and hypercholesterol-

emia²⁵ were defined according to standard definitions. All patients were followed up for a median of 25 months (first quartile 6 months, third quartile 58 months) with a minimum predefined follow-up time of 3 months.

CLINICAL SIGNIFICANCE

- There is no gender gap in the prognostic power of stratification of physical or pharmacologic stress echocardiography. The survival rate is comparable between men and women.
- Stress echocardiography is an equal opportunity approach for prognostic purposes in women.
- Women have a higher event rate than men in the presence of ischemia and known coronary artery disease.

Stress Protocol

Exercise stress echocardiography was conducted using a semi-supine bicycle ergometer with 25 W incremental loading every 2 minutes. Dipyridamole (up to 0.84 mg for 10 minutes with co-administration of atropine up to 1 mg or up to 0.84 mg for 6 minutes) and dobutamine (up to 40 mg/kg/min with co-administration of atropine up to 1 mg) stress echocardiography were performed according to well-established protocols.²⁶

Echocardiographic Analysis

Echocardiographic images were semiquantitatively assessed using a 17-segment, 4-point scale model of the left ventricle.²⁶ A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced new or worsening of preexisting wall motion abnormality or biphasic response (ie, low-dose improvement followed by high-dose deterioration). Necrotic pattern was akinetic or dyskinetic myocardium with no thickening during stress. A test was normal in case of no rest and stress wall motion abnormality.

Follow-up

Outcome was determined from patients' interviews at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient, his/her close relative, or referring physician. Death and nonfatal myocardial infarction were registered as clinical events. Coronary revascularization (surgery or angioplasty) also was recorded. To avoid misclassification of the cause of death,²⁷ overall mortality was considered. Myocardial infarction was defined by typical symptoms, electrocardiographic, and cardiac enzyme changes. Follow-up data were analyzed for the prediction of hard events (death or nonfatal myocardial infarction).

Statistical Analysis

Continuous variables are expressed as mean \pm standard deviation. Differences between groups were compared using the Student *t* and chi-square test, as appropriate. Survival rates were estimated with Kaplan–Meier curves and compared by the log-rank test. Patients undergoing coronary revascularization were censored at the time of the proce-

ture. Only the first event was taken into account. Annual event rates were obtained from Kaplan-Meier estimates to take censoring of the data into account. The association of selected variables with outcome were assessed with the Cox's proportional hazard model using univariate and stepwise multivariate procedures. A significance of .05 was required for a variable to be included into the multivariate model, whereas 0.1 was the cutoff value for exclusion. Hazard ratios with the corresponding 95% confidence interval were estimated. Statistical significance was set at *P* less than .05. Moreover, clinical findings, resting wall motion score index, and ischemia at stress echocardiography were sequentially included in the model. Global chi-square value of the model was calculated from the log-likelihood ratio; a significant increase after the addition of further variables indicated incremental prognostic value. To evaluate the ability of stress echocardiography to classify risk, we plotted receiver operating characteristic (ROC) curves for the clinical variables included in the analysis. The C statistics, a measure of the area under the ROC curve, was calculated with and without the stress echocardiography positivity. We also evaluated the ability of stress echocardiography to reclassify risk across categories with the use of the approach, as suggested by Pencina et al.²⁸ The Statistical Package for the Social Sciences (release 13.0, SPSS Inc, Chicago, Ill) was used for analysis.

RESULTS

Inducible ischemia was assessed in 2760 patients (32%), 2000 of whom were men and 760 of whom were women (36% vs 24%; *P* < .0001). Wall motion score index at peak of ischemia was similar in men and women (1.54 ± 0.33 vs 1.53 ± 0.34 , *P* = .53). A necrotic pattern was observed in 1668 men and 672 women (30% vs 21%, *P* < .0001); resting wall motion score index was 1.56 ± 0.38 in men and 1.53 ± 0.36 in women (*P* = .12). Test results were normal in 1861 men and 1776 women (34% vs 55%, *P* < .0001). Table 1 shows the main clinical and echocardiographic findings for male and female patients with known and suspected coronary artery disease.

Outcomes

During a median follow-up of 25 months (first quartile 6 months, third quartile 58 months), 1218 patients (14%) had a cardiac event (693 deaths and 525 nonfatal myocardial infarctions). A total of 533 events occurred in the 2968 men and 172 occurred in the 889 women with known coronary artery disease (18% vs 19%; *P* = .63). A total of 319 events occurred in 2561 men and 194 events occurred in 2319 women with suspected coronary artery disease (12% vs 8%; *P* < .0001).

Table 1 Clinical and Echocardiographic Characteristics of Men and Women with Known and Suspected Coronary Artery Disease

	Known CAD			Suspected CAD		
	Men (n = 2968)	Women (n = 889)	<i>P</i> Value	Men (n = 2561)	Women (n = 2319)	<i>P</i> Value
Age (y)	62 ± 11	68 ± 10	<.0001	61 ± 11	62 ± 11	.003
Clinical history						
Prior myocardial infarction	2507 (84%)	668 (75%)	<.0001	—	—	—
Prior CABG	396 (13%)	101 (11%)	.12	—	—	—
Prior PCI	825 (28%)	268 (30%)	.17	—	—	—
Left bundle branch block	57 (2%)	22 (2%)	.41	116 (5%)	128 (6%)	.11
Diabetes mellitus	577 (19%)	221 (25%)	.0006	462 (18%)	370 (16%)	.05
Arterial hypertension	1380 (46%)	557 (63%)	<.0001	1291 (50%)	1178 (51%)	.79
Hypercholesterolemia	1505 (51%)	527 (59%)	<.0001	984 (38%)	955 (41%)	.05
Smoking habit	1587 (53%)	194 (22%)	<.0001	1146 (45%)	618 (27%)	<.0001
Anti-ischemic therapy at the time of test						
β-blockers	630 (21%)	178 (20%)	.45	347 (14%)	240 (10%)	.0006
Calcium antagonists	572 (19%)	171 (19%)	.99	350 (14%)	246 (11%)	.001
Nitrates	826 (28%)	233 (26%)	.35	344 (13%)	169 (7%)	<.0001
At least 1 medication	1268 (43%)	372 (42%)	.65	810 (32%)	555 (24%)	<.0001
Echocardiogram						
Resting WMA	2212 (75%)	568 (64%)	<.0001	632 (25%)	552 (24%)	.48
Resting WMSI	1.37 ± 0.37	1.32 ± 0.35	<.0001	1.14 ± 0.31	1.12 ± 0.27	.04
Exercise	193 (7%)	30 (3%)	.0005	210 (8%)	90 (4%)	<.0001
Dobutamine	547 (18%)	200 (23%)	.007	512 (20%)	728 (31%)	<.0001
Dipyridamole	2228 (75%)	659 (74%)	.57	1839 (72%)	1501 (65%)	<.0001
Ischemia at stress echocardiography	1242 (41%)	299 (34%)	<.0001	758 (30%)	461 (20%)	<.0001
Peak WMSI	1.47 ± 0.38	1.40 ± 0.39	<.0001	1.21 ± 0.32	1.16 ± 0.30	<.0001

Data presented are mean value ± standard deviation or number (%) of patients. CAD = coronary artery disease; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; WMA = wall motion abnormality; WMSI = wall motion score index.

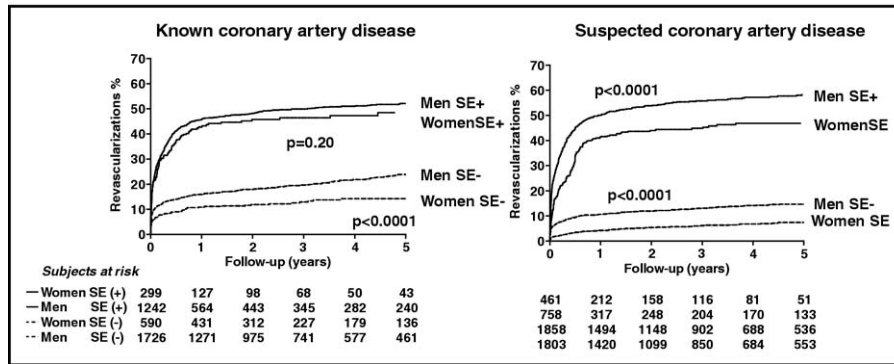


Figure 1 Revascularization rate for women and men with known and suspected coronary artery disease separated on the basis of presence (+) and absence (–) of ischemia at stress echocardiography. Number of patients per year is shown. SE = stress echocardiography.

According to the physician’s judgment, 2263 patients (26%) (1731 men [31%] and 532 women [17%]; $P < .0001$) underwent coronary revascularization (796 underwent surgery and 1467 underwent angioplasty) after a median of 45 days (first quartile 7 days, third quartile 212 days) from the index stress echocardiography. **Figure 1** shows the rates of revascularization in men and women with known and suspected coronary artery disease according to the presence or absence of inducible ischemia. In the group with known coronary artery disease, revascularization rate was higher ($P < .0001$) in men than in women without ischemia. In the group with suspected coronary artery disease, the revascularization rate was higher ($P < .0001$) in men regardless of the stress echocardiography result.

Outcome Prediction

The annual hard event rate was 5.8% in men and 7.0% in women with coronary artery disease ($P = .08$). The annual hard event rate was 3.6% in men and 2.4% in women with suspected coronary artery disease ($P < .0001$). **Figures 2** and **3** show the incremental model of prediction in known and suspected coronary artery disease separated on gender.

The univariate and multivariable prognostic indicators in patients with known and suspected coronary artery disease are reported in **Table 2**. In the subset of women with known coronary artery disease and a positive test result for myocardial ischemia, the event rate was higher than in men ($P = .01$). No gender difference was observed in the subset of patients with a negative test result for inducible myocardial ischemia $P = .30$ (**Figure 4**). On analysis of data (**Figures 5** and **6**) according to prognostically important clinical covariates, such as age and diabetes mellitus, only nondiabetic women had a higher risk than men with a history of known coronary artery disease and inducible ischemia ($P = .007$) (**Figure 6**). The annual event rate in a normal test was 2.6% in men and 1.6% in women ($P < .0001$). In the nonischemic group, the annual event rate was worse in men aged less than 65 years ($P < .0001$) and more than 65 years ($P = .04$) (**Figure 5**), as well as in those with ($P = .03$) or

without $P < .0001$) diabetes (**Figure 6**). We constructed ROC curves for the model incorporating established risk factors with and without inclusion of the stress echocardiography result using the incidence of events as the outcome. The C statistic (area under the ROC curve) for hard events was 0.66 for the risk model that included the stress echocardiography test result (**Figure 7**). When we used the net reclassification index²⁸ to account for the correct movement in categories (higher risk for subjects in whom events occurred and lower risk for subjects free of events), there was a significant improvement in risk classification according to the model that incorporated the stress echocardiography test result compared with the model that included conventional clinical risk factors or the model that included conventional risk factors and rest wall motion score index (**Table 3**).

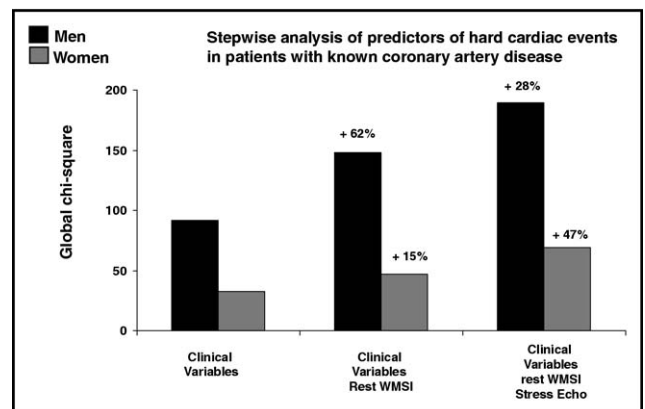


Figure 2 In patients with known coronary artery disease, global chi-square of clinical model for predicting hard events was 91.5 ($P < .0001$) in men and 32.4 ($P < .0001$) in women; sequential inclusion of resting wall motion score index and ischemia at stress echocardiography increased it by 62% (148.0; $P < .0001$) and 28% (189.6; $P < .0001$) in men and by 15% (47.0; $P < .0001$) and 47% (69.2; $P < .0001$) in women. WMSI = wall motion score index.

Figure 3 In patients with suspected coronary artery disease, the clinical model had a global chi-square of 129.9 ($P < .0001$) in men and 70.6 ($P < .0001$) in women; after the addition of resting wall motion score index and ischemia at stress echocardiography, it increased by 8% (140.9; $P < .0001$) and 33% (187.1; $P < .0001$) in men and by 39% (98.2; $P < .0001$) and 69% (166.4; $P < .0001$) in women. WMSI = wall motion score index.

DISCUSSION

Although coronary artery disease generally becomes clinically evident at least 10 years later in women than in men, once it is manifest more adverse outcomes have been reported for women.²⁹⁻³¹ Indeed, 49% of overall mortality due to coronary artery disease is observed in the female population.¹ Thus, recognizing coronary artery disease in women

and identifying those at increased risk of future cardiac events is an emerging point in contemporary cardiology. Unfortunately, diagnostic workup in female patients may be limited by clinical misperception of a lower pretest probability of coronary artery disease by the physician and by suboptimal diagnostic accuracy reported with various non-invasive cardiac tests.^{5,6} Stress echocardiography is a recognized equal opportunity approach, providing useful results for both diagnostic⁹⁻¹³ and prognostic¹⁴⁻²⁶ purposes in women. A recent report from the Agency for Health-Related Quality revealed that exercise echocardiography is highly accurate at detecting coronary artery disease in women with a sensitivity of 84% and a specificity of 76%.³² In addition, more recent evidence also supports the use of stress echocardiography for the estimation of prognosis in women.¹⁹⁻²¹ In a recent report in 4234 women, the extent of ischemic wall motion abnormalities was highly predictive of cardiac death.²⁰ For women undergoing exercise echocardiography, 5-year survivals were 99.4%, 97.6%, and 95% for those with no, single, and multivessel ischemia, respectively. Significantly higher cardiac death rates were noted for those women undergoing dobutamine stress echocardiography with annualized death rates ranging from 1% to 3% for 0- to 3-vessel ischemia.²⁰ From a clinical standpoint, to know whether these results also apply to populations of male and female patients with similar clinical characteristics would allow optimized patient management. Therefore, in this study on 8737 patients, we compared the prognostic value of stress echocardiography results in men and women in populations selected on the basis of history of coronary

Table 2 Univariate and Multivariate Predictors of Hard Events (Death, Myocardial Infarction) in Patients with Known and Suspected Coronary Artery Disease

	Known CAD				Suspected CAD			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (y)	1.03 (1.02-1.04)	<.0001	1.03 (1.02-1.04)	<.0001	1.05 (1.04-1.06)	<.0001	1.04 (1.03-1.05)	<.0001
Gender (male)	0.86 (0.72-1.02)	.08			1.51 (1.26-1.81)	<.0001	1.26 (1.05-1.52)	.01
Prior myocardial infarction	1.24 (1.00-1.55)	.05			—	—		
Prior CABG	1.02 (0.82-1.27)	.83			—	—		
Prior PCI	0.94 (0.79-1.12)	.50			—	—		
Left bundle branch block	2.11 (1.39-3.20)	<.0001			1.21 (0.81-1.88)	.39		
Diabetes mellitus	1.63 (1.37-1.93)	<.0001	1.40 (1.18-1.66)	<.0001	2.51 (2.06-3.07)	<.0001	1.90 (1.62-2.44)	<.0001
Arterial hypertension	1.21 (1.05-1.41)	.01			1.56 (1.31-1.87)	<.0001	1.25 (1.04-1.51)	.02
Hypercholesterolemia	0.98 (0.84-1.14)	.80			1.31 (1.10-1.57)	.003		
Smoking habit	0.83 (0.71-0.96)	.01			1.14 (0.95-1.36)	.15		
Therapy at the time of test	1.04 (0.89-1.21)	.62			1.77 (1.47-2.13)	<.0001	1.22 (1.00-1.49)	.05
Resting WMA	1.51 (1.26-1.82)	<.0001			2.15 (1.78-2.58)	<.0001		
Resting WMSI	2.49 (2.07-2.98)	<.0001	2.20 (1.83-2.66)	<.0001	2.38 (1.90-2.99)	<.0001		
Necrotic pattern	.87 (0.75-1.01)	.07			1.74 (1.41-2.14)	<.0001	1.90 (1.38-2.61)	<.0001
Ischemia at stress echocardiography	1.78 (1.53-2.07)	<.0001	1.83 (1.57-2.12)	<.0001	2.76 (2.30-3.31)	<.0001	3.30 (2.69-4.07)	<.0001
Peak WMSI	2.86 (2.40-3.41)	<.0001			3.50 (2.82-4.33)	<.0001		

CAD = coronary artery disease; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; WMA = wall motion abnormality; WMSI = wall motion score index; HR = hazard ratio; CI = confidence interval.

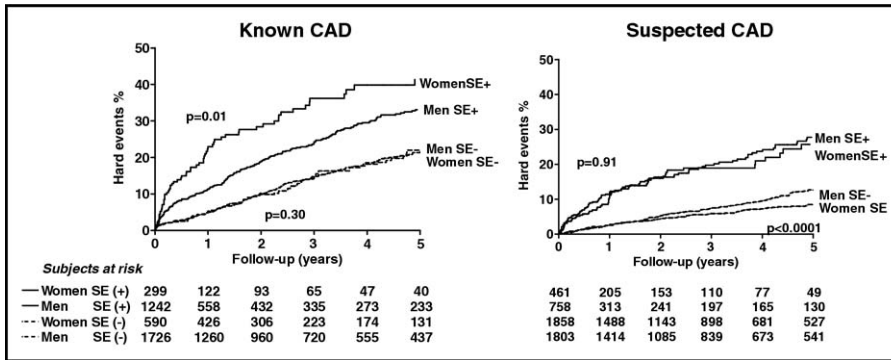


Figure 4 Hard event rate for women and men with known and suspected coronary artery disease separated on the basis of presence (+) and absence (-) of ischemia at stress echocardiography. Number of patients per year is shown. CAD = coronary artery disease; SE = stress echocardiography.

artery disease and prognostically important clinical parameters. We found age, diabetes mellitus, and ischemia at stress echocardiography to be strong and independent prognostic indicators in patients with known and suspected coronary artery disease. Moreover, inducible ischemia provided incremental value over clinical variables and resting left ventricular function for predicting death or myocardial infarction in both sexes regardless of history of coronary artery disease. Nevertheless, the prognostic information provided by both ischemic and nonischemic test results showed gender-related differences in different clinical settings. In particular, women had a similar and perhaps greater risk for adverse outcome than men when the diagnosis of coronary artery disease was documented or very likely. In fact, nondiabetic coronary artery disease women with ischemia fared worse than their male counterparts. Conversely, women with suspected coronary artery disease

and no ischemia had a better prognosis than men, regardless of age and history of diabetes. In keeping with previous results,³³ in our study women with coronary artery disease were more likely to be older and to have a history of diabetes mellitus, hypertension, and hypercholesterolemia, and less likely to be smokers than men. In addition, they had a better resting left ventricular function. Whether and to what extent these differences between genders may have contributed to prognosis is not clear. Notably, age and diabetes were not associated with different risk in men and women with and without ischemia. In the present study, women were less likely revascularized than men regardless of history of coronary artery disease. This is consistent with previous studies showing that women undergo cardiac catheterization and revascularization procedures less often than men in the case of manifest coronary artery disease.⁹⁻²¹ In a recent study,²⁹ less aggressive treatment strategy in women

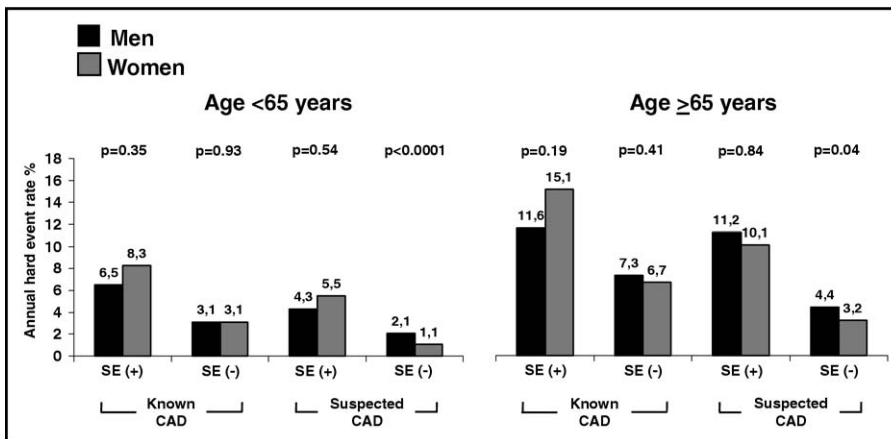


Figure 5 Annual hard event rate for women and men with known and suspected coronary artery disease according to the presence (+) and absence (-) of ischemia at stress echocardiography. The data were separately analyzed in patients aged less than 65 years and more than 65 years. CAD = coronary artery disease; SE = stress echocardiography.

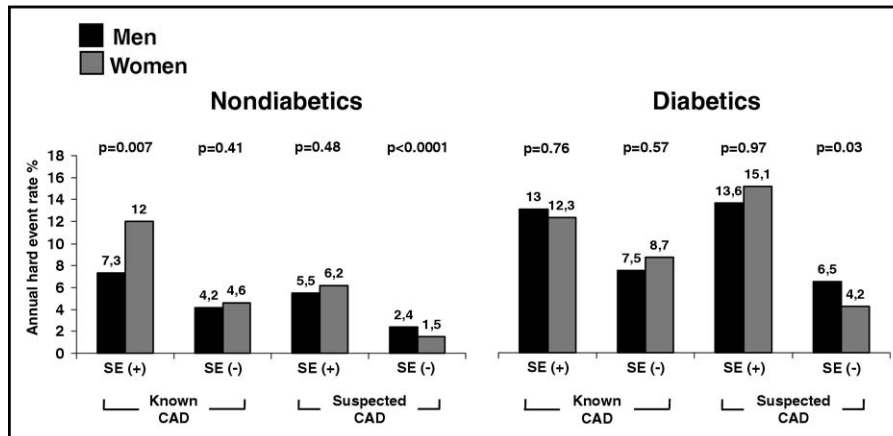


Figure 6 Annual hard event rate for women and men with known and suspected coronary artery disease, according to the presence (+) and absence (-) of ischemia at stress echocardiography. The data were separately analyzed in nondiabetic and diabetic patients. CAD = coronary artery disease; SE = stress echocardiography.

with stable angina was associated with a 2-fold greater risk of death or nonfatal myocardial infarction during the 1-year follow-up period. Because prognosis is at least comparable in men and women with ischemia and in those with coronary artery disease and no ischemia, sex referral bias is not

justified and availability for major procedures should be similar for both genders. The protective effect by revascularization has been documented in men and women.³⁴

STUDY LIMITATIONS

Dipyridamole was the most frequently used stressor in the echocardiography laboratories that were involved in the study. Although less used outside Europe, dipyridamole is as sensitive and accurate^{35,36} and exerts the same prognostic power³⁷⁻⁴⁰ as dobutamine when state of the art protocols are used as recommended by the European Association of Echocardiography.²⁶ Because of the long recruitment period, the outcome based on stress test results may have been potentially influenced by the evolution of methodology, technology, and expertise and advances in medical and interventional treatments. In this study, there was no central reading. Stress echocardiography was interpreted in the peripheral centers and entered directly in the database. This system allowed substantial sparing of human and technological resources, but it also was the logical prerequisite for a large-scale study designed to represent the realistic performance of the test rather than the results of a single laboratory, or even a single person, working in a highly dedicated echocardiography laboratory. Because the assessment of the echocardiograms was qualitative and subjective, variability in reading the echocardiograms might have modulated the results of individual centers.²⁶ However, all our readers in individual centers had lengthy experience in echocardiography and passed the quality control in stress echocardiography reading as previously described.²² Our study design was observational, not randomized, and the analysis was retrospective, although the data were acquired in a prospective fashion and entered into the databank at the time of initial assessment. The test results available to the referring physicians may have influenced the clinical management of

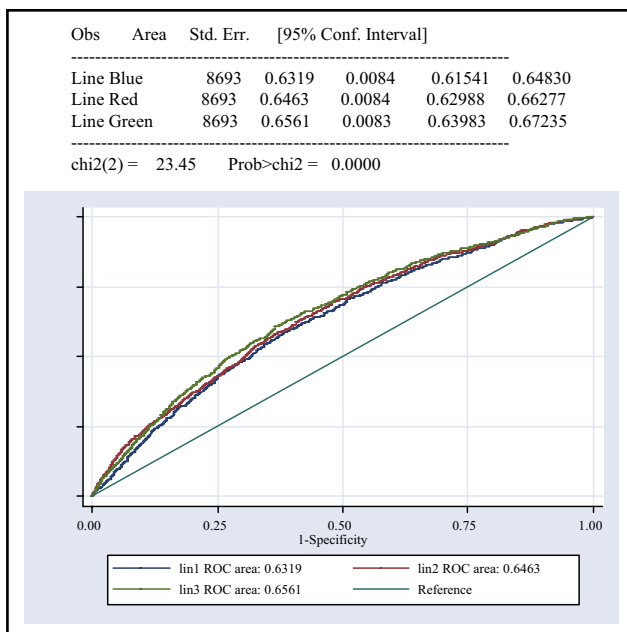


Figure 7 ROC curves for incident myocardial infarction or death during the follow-up. The curves are based on risk-prediction models incorporating conventional clinical risk factors (blue line) that included rest wall motion score index (red line) or stress echocardiography result (green line). The C statistics (area under the ROC curve) for hard events was significantly better when the stress echocardiography test result was included in the model. ROC = receiver operating characteristic.

Table 3 Reclassification Among Individuals Who Did and Did Not Have a Hard Event on Follow-Up

Model without Stress Echocardiography	Model with Rest WMSI and Ischemia			Total
	<4.36%	4.37%-13.0%	>13.0%	
Participants with Hard Event				
Frequency (Row %)				
<4.36%	263 (82, 45%)	55 (17, 24%)	1 (0, 31%)	319
4.37%-13.0%	41 (11, 20%)	254 (69, 40%)	71 (19, 40%)	366
>13.0%	0 (0, 0%)	81 (15, 17%)	453 (84, 83%)	534
Total	304	390	525	1219
Participants without Hard Event				
Frequency (Row %)				
<4.36%	2261 (90, 33%)	241 (9, 63%)	1 (0, 0.04%)	2503
4.37%-13.0%	359 (14, 34%)	1903 (76, 00%)	242 (9, 66%)	2504
>13.0%	0 (0, 0%)	551 (21, 94%)	1960 (78, 0.06%)	2511
Total	2620	2695	2203	7518

WMSI = wall motion score index.

the patients, especially regarding coronary revascularization, but this may have only decreased the prognostic power of the test, because patients were censored at the time of the procedure.

References

- American Heart Association. *Heart Disease and Stroke Statistics—2007 Update*. Dallas, TX: American Heart Association; 2007.
- Wenger NK, Shaw LJ, Vaccarino V. Coronary heart disease in women: update 2008. *Clin Pharmacol Ther*. 2008;83:37-51.
- Mosca L, Manson JE, Sutherland SE, et al. Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1997;96:2468-2482.
- Mieres JH, Shaw LJ, Arai A, et al; Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005;111:682-696.
- Bigi R, Cortigiani L. Stress testing in women: sexual discrimination or equal opportunity? *Eur Heart J*. 2005;26:423-425.
- Kwok Y, Kim C, Grady D, et al. A meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol*. 1999;83:660-666.
- Masini M, Picano E, Lattanzi F, et al. High-dose dipyridamole-echocardiography test in women: correlation with exercise-electrocardiography test and coronary angiography. *J Am Coll Cardiol*. 1988;12:682-685.
- 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;120:559-566.
- Sawada SG, Ryan T, Fineberg NS, et al. Exercise echocardiographic detection of coronary artery disease in women. *J Am Coll Cardiol*. 1989;14:1440-1447.
- Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. *J Am Coll Cardiol*. 1995;26:335-341.
- Ho YL, Wu CC, Huang PJ, et al. Assessment of coronary artery disease in women by dobutamine stress echocardiography: comparison with stress thallium-201 single-photon emission computed tomography and exercise electrocardiography. *Am Heart J*. 1998;135:655-662.
- Elhendy A, van Domburg RT, Bax JJ, et al. Noninvasive diagnosis of coronary artery disease in women with limited exercise capacity: comparison of dobutamine stress echocardiography and 99mTc sestamibi single-photon emission CT. *Chest*. 1998;114:1097-1104.
- Dionisopoulos PN, Collins JD, Smart SC, et al. The value of dobutamine stress echocardiography for the detection of coronary artery disease in women. *J Am Soc Echocardiogr*. 1997;10:811-817.
- Heupler S, Metha R, Lobo A, et al. Prognostic implications of exercise echocardiography in women with known or suspected coronary artery disease. *J Am Coll Cardiol*. 1997;30:414-420.
- Cortigiani L, Dodi C, Paolini EA, et al. Prognostic value of pharmacological stress echocardiography in women with chest pain and unknown coronary artery disease. *J Am Coll Cardiol*. 1998;32:1975-1981.
- Davar JI, Brull DJ, Bulugahipitiya S, et al. Prognostic value of negative dobutamine stress echo in women with intermediate probability of coronary artery disease. *Am J Cardiol*. 1999;83:100-102.
- Dodi C, Cortigiani L, Masini M, et al. The incremental prognostic value of pharmacological stress echo over exercise electrocardiography in women with chest pain of unknown origin. *Eur Heart J*. 2001;22:145-152.
- Cortigiani L, Gigli G, Vallebona A, et al. The stress echo prognostic gender gap. *Eur J Echocardiogr*. 2001;2:132-138.
- Arruda-Olson AM, Juracan EM, Mahoney DW, et al. Prognostic value of exercise echocardiography in 5,798 patients: is there a gender difference? *J Am Coll Cardiol*. 2002;39:625-631.
- Shaw LJ, Vassey C, Sawada S, et al. Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4,234 women and 6,898 men. *Eur Heart J*. 2005;26:447-456.
- Biagini E, Elhendy A, Bax JJ, et al. Seven-year follow-up after dobutamine stress echocardiography. Impact of gender on prognosis. *J Am Coll Cardiol*. 2005;45:93-97.
- Picano E, Landi P, Bolognese L, et al. Prognostic value of dipyridamole echocardiography early after uncomplicated myocardial infarction: a large scale multicenter trial. *Am J Med*. 1993;11:608-618.
- World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part I: Diagnosis and Classification of Diabetes Mellitus. WHO/NCD/NCS/99.2*. Geneva: World Health Organization; 1999.

24. European Society of Hypertension–European Society of Cardiology. Guidelines for the management of arterial hypertension. *J Hypertension*. 2003;21:1011-1053.
25. National cholesterol education program expert panel. Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Full Report. World Wide Web; 2001. Available at <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Last accessed January 10, 2009.
26. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement from the European Association of Echocardiography. *Eur J Echocardiogr*. 2008;9:415-437.
27. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol*. 1999;34:618-620.
28. Pencina MJ, D'Agostino RB, Sr, D'Agostino RB, Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157-172.
29. Daly CA, De Stavola B, Sendon JL, et al; Euro Heart Survey Investigators. Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study. *BMJ*. 2006;332:262-267.
30. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S, and the Israeli SPRINT Investigators. In-hospital and 1-year mortality in 1,524 women after myocardial infarction: comparison with 4,315 men. *Circulation*. 1991;83:484-491.
31. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med*. 1999;341:226-232.
32. Shaw LJ, Bairey Merz CN, Pepine CJ, et al; WISE Investigators. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006;47(3 Suppl):S4-S20.
33. Hochman JS, Tamis-Holland JE. Acute coronary syndromes: does sex matter? *JAMA*. 2002;288:3161-3164.
34. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA*. 2002;288:3124-3129.
35. Picano E, Molnaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. *Cardiovasc Ultrasound*. 2008;6:30.
36. Gershlick AH, de Belder M, Chambers J, et al. Role of non-invasive imaging in the management of coronary artery disease: an assessment of likely change over the next 10 years. A report from the British Cardiovascular Society Working Group. *Heart*. 2007;93:423-431.
37. Pingitore A, Picano E, Varga A, et al. Prognostic value of pharmacological stress echocardiography in patients with known or suspected coronary artery disease: a prospective, large-scale, multicenter, head-to-head comparison between dipyridamole and dobutamine test. *J Am Coll Cardiol*. 1999;34:1769-1777.
38. Schroeder K, Wieckhorst A, Voller H. Comparison of the prognostic value of dipyridamole and dobutamine stress echocardiography in patients with known or suspected coronary artery disease. *Am J Cardiol*. 1997;79:1516-1517.
39. Minardi G, Disegni M, Manzara C, et al. Diagnostic and prognostic value of dipyridamole and dobutamine stress echocardiography in patients with acute myocardial infarction. *Am J Cardiol*. 1997;80:847-851.
40. Cortigiani L, Bigi R, Sicari R, et al. Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease. *J Am Coll Cardiol*. 2006;47:605-610.