Gender Differences and Temporal Trends in Clinical Characteristics, Stress Test Results and Use of Invasive Procedures in Patients Undergoing Evaluation for Coronary Artery Disease

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OBJECTIVES   This study examined gender differences and temporal changes in the clinical characteristics of patients referred for nuclear stress imaging, their imaging results and subsequent utilization of coronary angiography and revascularization.

BACKGROUND   Gender bias may influence resource utilization in patients with coronary artery disease (CAD). No study has analyzed gender differences and time trends in patients referred for noninvasive testing and subsequent use of invasive procedures.

METHODS   Between January 1986 and December 1995, 14,499 patients (5,910 women and 8,589 men) without established CAD underwent stress myocardial perfusion imaging. The clinical characteristics, imaging results, coronary angiograms and revascularization outcomes were compared in women and men over time.

RESULTS   The mean pretest probability of CAD was lower in women (45%) than in men (70%) (p < 0.001). More women (69%) than men (42%) had normal nuclear images (p < 0.001). Men (17%) were more likely than women (8%) to undergo coronary angiography (p < 0.001). Male gender was independently associated with referral for coronary angiography (multivariate model: chi-square = 16, p < 0.001) but was considerably weaker than the imaging variables (summed reversibility score: chi-square = 273, p < 0.001). Revascularization was performed in more men (46% of the population undergoing angiography) than women (39%) (p = 0.01), but gender was not independently associated with referral to revascularization. There were no significant differences in clinical, imaging or invasive variables between the genders over time.

CONCLUSIONS   There was little evidence for a bias against women in this study. Women were somewhat less likely to undergo coronary angiography but were referred for stress perfusion imaging more liberally. Practice patterns remained constant over this 10-year period. (J Am Coll Cardiol 2001;38:690–7) © 2001 by the American College of Cardiology

Studies designed to examine gender differences in patients undergoing evaluation for coronary artery disease (CAD) have been controversial. Resource use has been reported to be lower (1–12) or no different (13–22) in women than in men. A small number of studies have reported lower utilization of only certain resources in women (23–27), suggesting that gender bias might influence the clinical decision-making process at different nodal points. Only two studies have examined time trends in resource utilization patterns (13,25). These studies focused on selected subsets of patients with established CAD and examined their resource use between the 1970s and 1980s. Since then, many commentaries have been published addressing gender bias (28–35). No study has examined gender differences and time trends in a more recent cohort of patients referred for stress testing with follow-up coronary revascularization.

This study was designed to examine whether there were gender differences and temporal changes over the 10-year period of 1986 to 1995 in: 1) the clinical characteristics of the population referred for stress single-photon emission computed tomography (SPECT); 2) the results of SPECT imaging; 3) the SPECT findings associated with subsequent referral to cardiac catheterization; and 4) the catheterization findings associated with referral to revascularization.

METHODS

Study population. Imaging with SPECT was first utilized at the Mayo Clinic in January 1986. Between January 1986 and December 1995, 36,504 thallium-201 (Tl-201) or technetium-99m (Tc-99m) sestamibi imaging studies were performed. Patients were excluded from these studies for the following reasons (some patients had more than one criterion): 1) established CAD on the basis of a history of documented myocardial infarction (MI), previous coronary artery bypass graft surgery (CABG) or previous percutaneous transluminal coronary angioplasty (PTCA) (n = 17,436); 2) left bundle branch block or paced ventricular

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
SPECT = single-photon emission computed tomography
SRS = summed reversibility score
SSS = summed stress score
Tc-99m = technetium-99m
Tl-201 = thallium-201

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rhythm (n = 2,587); 3) clinically significant valvular heart disease (n = 3,031); 4) rest study only (n = 813); 5) stress modality dobutamine infusion (n = 539) or cycle ergometry (n = 13); and 6) refusal of research authorization (n = 57). Because this study was designed to focus on testing for diagnostic purposes, patients with established CAD were excluded. Patients with left bundle branch block, paced ventricular rhythm or valvular heart disease were excluded, because these entities have been associated with false-positive perfusion studies (36–38). Because dobutamine or cycle ergometry was used in relatively few patients who did not qualify for more conventional forms of stress, these patients were also excluded. Only the first study was analyzed in patients with multiple studies (n = 1,031). The study population consisted of 14,499 patients. Baseline clinical data were collected at the time of stress testing and entered into a computer database. Chest pain was graded according to the criteria of Diamond (39).

Stress SPECT imaging. This method has been described previously (40–42). Patients underwent treadmill (n = 10,898) or pharmacologic (n = 3,601) SPECT imaging. Treadmill testing was performed using the Bruce or Naughton protocol until standard end points were reached. Pharmacologic stress testing was performed with intravenous administration of adenosine (140 μg/kg per min over 6 min; n = 1,545) or dipyridamole (0.56 mg/kg for 4 min; n = 2,056). The stress electrocardiogram was interpreted as positive for ischemia if there was ≥1.0 mm horizontal or downsloping ST segment depression 80 ms after the J point, compared with baseline. The radioisotope was injected during the last 60 to 90 s of exercise, at 3 min of the adenosine infusion or 3 to 4 min after termination of the dipyridamole infusion.

Thallium-201 imaging was performed as a one-day protocol. During stress, 3 to 4 mCi of Tl-201 were injected. Imaging with SPECT began 10 to 15 min later by using the "step-and-shoot" method. Delayed rest imaging was performed 3 to 4 h later. Patients imaged after January 1, 1990 underwent re-injection with 1 mCi of Tl-201 before delayed imaging. Technetium-99m sestamibi was first used in 1991. Sestamibi imaging was generally performed as a two-day protocol, with rest imaging on the first day and stress imaging on the second day; 15 mCi of Tc-99m

sestamibi were injected during stress and 30 mCi at rest. The same SPECT method for Tl-201 was used for Tc-99m sestamibi, except that imaging started 45 to 60 min after the sestamibi injection. The images were processed and reconstructed using standard procedures (40–42).

The images were interpreted by consensus of two experienced observers. These observers were aware of each patient's gender. The stress and rest images were displayed side by side in three planes (short-axis, horizontal long-axis and vertical long-axis), divided into 24 segments. Uptake in each segment was graded on a 5-point scale (0 = absent uptake; 1, 2 and 3 = severely, moderately and mildly diminished uptake, respectively; and 4 = normal uptake). For the purposes of this study, only the scoring in the 14 short-axis segments was used. Mild fixed defects (scores of 3 stress and 3 delayed) were considered normal, because most of these defects are due to soft-tissue attenuation. Summed stress and rest scores were calculated as the summation of the uptake in each of the 14 short-axis segments on the stress and rest images, respectively (43). The summed stress score (SSS) for a normal image is 56 (14 × 4). The Cedars-Sinai laboratory has reported that cut-points for SSS (an equivalent score ≤47 using our scoring system) can identify high-risk patients (43). The summed reversibility score (SRS) was calculated as the difference between the summed rest and stress scores. A nonischemic image has a score of 0. Left ventricular size was assessed subjectively and coded as enlarged or not enlarged.

Coronary angiography. Coronary angiography was reported if it occurred within three months after the stress test. The angiographers were aware of each patient's gender and the results of SPECT imaging. The angiograms were coded according to Coronary Artery Surgery Study criteria (≥50% diameter narrowing of the left main coronary artery or ≥70% diameter narrowing of the left anterior descending, left circumflex or right coronary artery or their major branches was considered significant) (44).

Revascularization. Coronary angioplasty and CABG were reported if they were performed within three months of angiography. For patients with multiple procedures, only the first procedure was counted.

Statistical analysis. The SAS software (Cary, North Carolina) was used. Comparisons between men and women were completed using the Wilcoxon rank-sum test for continuous variables and the chi-square test (for independence) for categorical variables. For symptomatic patients <70 years old, the pretest probability of CAD was estimated on the basis of age, gender and chest pain type (no data are provided for estimating the probability in asymptomatic patients or those >70 years old) (45). Logistic regression models were used to assess factors related to referral to coronary angiography and revascularization (46). Multivariate models to predict these end points were developed using the stepwise selection technique. The entire study population was analyzed for the angiographic model. The variables considered included age, gender, symptom status, chest pain

Table 1. Clinical Characteristics

Year	No. of Studies		Mean Age (years)		Chest Pain (%)		Typical Angina (%)		Smoking History (%)		Hypertension (%)		Hyperlipidemia (%)		Diabetes (%)	
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
1986	59	112	60.2	58.9	75	54	19	20	56	70	44	45	37	28	8	10
1987	217	350	62.7	59.9	75	58	19	19	43	67	57	46	45	33	15	14
1988	381	665	61.1	59.3	77	55	19	16	36	65	51	47	44	39	14	13
1989	627	907	62.3	61.0	77	56	19	23	39	65	50	46	46	41	13	15
1990	634	1,000	62.2	61.3	76	63	20	23	34	63	52	46	44	36	17	13
1991	836	1,183	63.5	61.4	73	58	19	23	37	57	54	48	51	40	13	16
1992	826	1,137	62.9	61.5	73	58	19	20	39	62	53	46	55	44	17	14
1993	740	1,033	62.9	61.3	73	58	21	20	38	62	56	50	53	44	15	18
1994	791	1,058	64.2	61.7	68	53	19	20	38	59	56	49	54	48	18	19
1995	799	1,144	62.6	61.7	67	51	18	18	38	60	56	51	53	50	20	17
Mean value	591*	859	62.8*	61.2	73*	57	19†	20	38*	62	54*	48	50*	43	16†	16

*$p < 0.001$, women vs. men; †p = NS, women vs. men.

type, smoking history, hypertension (by history or repeated blood pressure >140/90 mm Hg), hyperlipidemia (by history or cholesterol or triglyceride levels >90th percentile for age and gender), diabetes (by history or repeated fasting glucose levels >120 mg/dl), type of stress test (pharmacologic or exercise), SSS, SRS and left ventricular enlargement. Only patients who underwent coronary angiography were included in the revascularization model. The variables considered for the revascularization model included the same aforementioned variables and also the extent of CAD on angiography. Differences between the genders over time were investigated using a gender-time interaction term in the logistic regression models. The C-index was used to measure the classification ability of the models. Bootstrapping was performed to confirm the stability of the estimates in each model by running 1,000 samples, with replacement of the 14,499 observations in the angiography data set and the 1,905 observations in the revascularization data set, and then running the logistic stepwise procedure on each of the 1,000 samples. The number of times each factor came into the final model was tabulated. For all analyses, $p < 0.05$ was considered significant.

RESULTS

Stress test patterns and patient characteristics. Overall, 5,910 women and 8,589 men underwent stress SPECT (Table 1). At all time points, more men than women were tested. The number of studies increased during the first five years and remained relatively constant thereafter. More women (30%) than men (21%) were imaged with Tc-99m sestamibi ($p < 0.001$), reflecting our laboratory's recommendation to clinicians to use this agent in women in whom a breast artifact on the images was anticipated. More women (31%) than men (20%) underwent pharmacologic stress testing ($p < 0.001$). Mean age was slightly higher in women and remained constant throughout the study. More women than men had symptoms of chest pain, but the percentages of patients with typical angina were similar. A

minority of patients (10%) underwent evaluation of exertional dyspnea. More men (33%) than women (17%) were asymptomatic ($p < 0.001$). There was no change in symptom status in either gender over time. The average calculated pretest probability of CAD in symptomatic patients remained constant in both genders throughout the study (Fig. 1). More men than women had a history of cigarette smoking. More women than men were hypertensive or hyperlipidemic. There was no difference between the genders for diabetes. The mean number of risk factors increased slightly over time in women, from 1.5 between 1986 and 1990 to 1.6 between 1991 and 1995 ($p < 0.001$), and also in men, from 1.6 between 1986 and 1990 to 1.7 between 1991 and 1995 ($p < 0.001$). The difference between the genders was not significant. The consistency of age, symptom status and risk factor profile indicates that there was no important gender-related change in clinical characteristics during the time course of this study.

Stress SPECT results. Abnormal scans were more common in men (58%) than in women (31%) ($p < 0.001$) (Table 2). The percentage of normal studies over time remained constant in women, but decreased slightly in men ($p = 0.02$). This difference between the genders was not significant, however. The summed stress and reversibility scores were also significantly worse in men. A "high-risk" scan (SSS ≤47) was present in 1,942 men and 471 women. The SSS remained constant over time in men, but decreased slightly in women ($p = 0.03$). In both genders, there were also small but statistically significant increases in SRS over time ($p = 0.003$ for men; $p < 0.001$ for women).

Coronary angiography. More men (n = 1,418; 17% of the male study population) than women (n = 487; 8% of the female population) were referred for coronary angiography ($p < 0.001$) (Fig. 2, Table 3). Over time, there was a slight increase in the percentage of women, but not men, referred ($p = 0.04$). Although there was a significant difference between men and women in the overall rate of referral to angiography, this difference did not change significantly
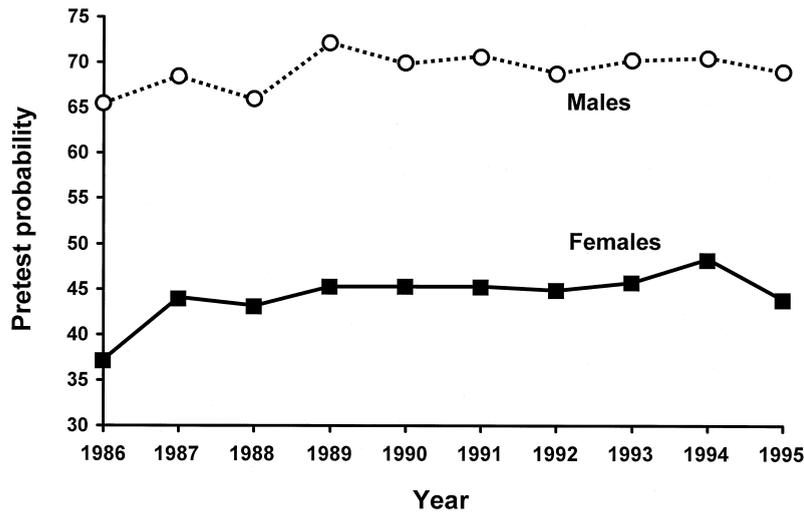
Figure 1. Mean pretest probability of coronary artery disease in females **(squares)** and males **(circles)** <70 years old with symptoms of chest pain, plotted over time.

over time (p = NS). In patients with a "high-risk" SSS, 46% of men and 51% of women were referred to angiography. In the univariate analysis, all variables analyzed were significantly associated with referral to angiography. In the multivariate analysis, the nuclear imaging variables were much more powerful than the clinical variables. Gender was an independent but relatively weak predictor in the multivariate model. There was no interaction between gender and time in the multivariate model. On angiography, more men (76%) than women (62%) had significant CAD (p < 0.001). Triple-vessel CAD was also more prevalent in men (25%) than in women (19%) (p = 0.005). The percentages of patients with significant CAD and the extent of CAD remained constant in both genders over time.

Revascularization. Procedures were performed in 192 women (102 had PTCA and 90 had CABG) and 655 men (268 had PTCA and 387 had CABG) (Fig. 3, Table 4) The type of procedure was more likely to be PTCA in women and

CABG in men (p = 0.003). Expressed as a percentage of the patients who underwent angiography, 39% of women versus 46% of men were referred for revascularization (p = 0.01). In neither gender was there a significant change in the percentages of patients referred for revascularization over time. Gender was significantly associated with referral to revascularization in the univariate analysis, but not in the multivariate analysis.

DISCUSSION

Many studies have addressed gender bias and resource utilization in patients with CAD (1–27). The majority of these studies have limited their analyses to the subset of patients with acute MI referred for invasive procedures. The "upstream" use of tests impacts the "downstream" use of more invasive procedures (47,48). Therefore, this study was designed to encompass patients presenting for noninvasive stress testing and following them to revascularization to address the possibility of gender bias at multiple steps in the

Table 2. Single-Photon Emission Computed Tomographic Results

Year	Normal Images (%)		At Least One Reversible Segment (%)		SSS*		SRS†	
	Women	Men	Women	Men	Women	Men	Women	Men
1986	86	60	14	37	54.8	52.9	1.0	1.6
1987	71	45	26	48	54.2	51.9	1.1	2.1
1988	72	45	27	50	54.3	51.2	1.0	2.7
1989	68	36	30	60	53.8	50.3	1.6	3.4
1990	70	40	28	55	53.8	50.6	1.5	3.5
1991	71	42	27	54	54.1	50.6	1.4	3.6
1992	68	42	30	54	53.8	50.9	1.5	3.4
1993	70	45	29	51	53.8	51.0	1.6	3.2
1994	65	42	33	52	53.7	51.1	1.7	3.1
1995	66	39	33	55	53.8	50.6	1.6	3.5
Mean value	69‡	42	30‡	54	53.9‡	50.9	1.5‡	3.3

*A summed stress score (SSS) of 56 represents a normal image; †a summed reversibility score (SRS) of 0 represents a nonischemic image; ‡p < 0.001, women vs. men.
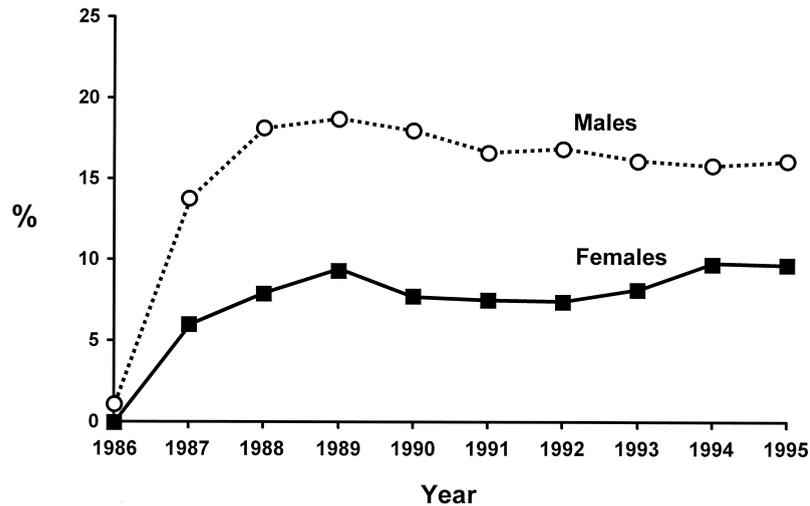
Figure 2. Percentages of females **(squares)** and males **(circles)** referred for coronary angiography from the total study population, plotted by year.

decision-making process. Women appear to have been referred for stress SPECT imaging more frequently than men, on the basis of their lower pretest probability of CAD and higher percentage of normal SPECT images. The only step in which women were less likely to be evaluated was coronary angiography. Male gender was an independent predictor of referral to angiography, but was considerably weaker than the SPECT variables. Overall, there was little evidence for a bias against women in this study. Analysis of time trends indicated that practice patterns remained remarkably constant. Several editorials on gender bias were published during the 10-year study period (28–34). The increasing attention directed to gender bias did not have an impact on practice patterns.

The controversy of gender bias. In a meta-analysis examining patient outcomes after MI, Vaccarino et al. (49) noted that the higher early crude mortality rates in women often disappear after controlling for age and other factors. Similarly, some studies have noted that the lower crude rates of coronary angiography in women no longer persist after

adjustment for confounding variables or appropriateness of its use (14,18,20,21,27). If gender bias does exist, it appears to have more of an impact on the use of diagnostic testing and administration of thrombolytic therapy (1,2,4–12,23–26). Once coronary angiography is performed, most (13,14,16,17,19,20,22–26), but not all (2,3,6,8,9,27), studies have found no gender difference in referral to revascularization.

Time trends. Only two studies have examined gender differences and time trends in patients with CAD. Bickell et al. (13) studied referral to CABG for three periods: 1969 to 1974, 1975 to 1979 and 1980 to 1984. Although there was no gender difference for the entire study population, among low-risk patients, men were more likely to be referred during the most recent period. Chiriboga et al. (25) examined utilization of several cardiac services in patients with acute MI during six different years between 1975 and 1988. Over time, there was an increase in the use of invasive procedures in both genders, with men more likely to undergo coronary angiography and PTCA in the

Table 3. Referral to Coronary Angiography

Variable	Univariate Analysis			Multivariate Analysis*		
	Chi-Square	p Value	OR (95% CI)	Chi-Square	p Value	OR (95% CI)
SSS† (5-point decrease)	2,066	< 0.001	2.4 (2.3–2.5)	147	< 0.001	1.5 (1.4–1.6)
SRS‡ (1-point increase)	2,020	< 0.001	1.3 (1.29–1.32)	273	< 0.001	1.18 (1.17–1.20)
Cardiac enlargement	502	< 0.001	3.9 (3.3–4.3)	—	—	—
Gender (male)	202	< 0.001	2.2 (2.0–2.5)	16	< 0.001	1.3 (1.1–1.5)
Chest pain class	62	< 0.001	1.2 (1.1–1.2)	—	—	—
Diabetes	56	< 0.001	1.3 (1.2–1.4)	—	—	—
Smoking	23	< 0.001	1.2 (1.1–1.3)	4	0.047	1.1 (1.0–1.2)
Symptom status	22	< 0.001	1.3 (1.2–1.5)	17	< 0.001	1.3 (1.2–1.5)
Pharmacologic stress	14	< 0.001	1.2 (1.1–1.4)	9	0.003	1.2 (1.1–1.4)
Age (10-year increase)	10	0.002	1.07 (1.03–1.11)	27	< 0.001	0.87 (0.82–0.91)
Hypertension	9	0.004	1.2 (1.1–1.3)	—	—	—
Hyperlipidemia	5	0.034	1.1 (1.0–1.2)	—	—	—

*Variables without numbers in the multivariate analysis did not meet the entry criteria into the final model; †a summed stress score (SSS) of 56 represents a normal image; ‡a summed reversibility score (SRS) of 0 represents a nonischemic image. Final model: chi-square = 3,051, p < 0.001, C-index = 0.87. Bootstrapping analysis SSS and SRS came into every model, symptom status in >99% of the models, gender in 97%, pharmacologic stress in 81% and age in 79%.

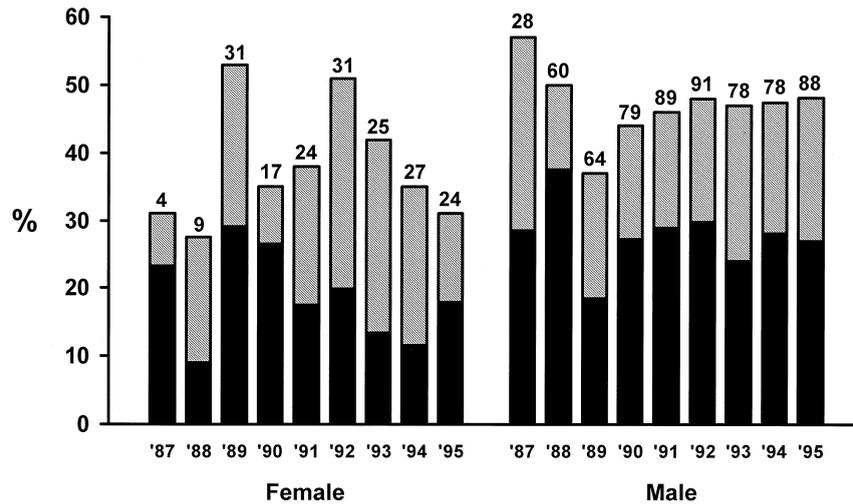CI = confidence interval; OR = odds ratio.

Figure 3. Percentages of patients referred for revascularization from the angiographic population, plotted by year. The **numbers at the top of the columns** represent the absolute number of revascularization procedures done each year. **Solid bars** = bypass surgery; **stripped bars** = percutaneous interventions.

later years, but there was no gender difference in referral to CABG.

Study limitations. This study has several limitations. First, the cohort was comprised of patients referred for SPECT at a tertiary-care center. This study cannot address whether there was gender bias in more "upstream" decision-making involving the entire population of patients presenting for evaluation of CAD at our institution. In an earlier population-based study of Olmsted County residents, we reported that women were less likely than men to undergo stress testing (10). Second, physicians were aware of each patient's gender when interpreting the test results, which could have introduced bias in their reports. If such bias existed, it did not change over time. Third, certain potentially important variables, such as patient preference for a specific treatment, socioeconomic status and left ventricular ejection fraction, were either not collected or not collected

in a uniform fashion in the data base. Analysis of such variables could alter the results of the statistical modeling. Finally, no follow-up data were collected to determine whether there was a gender difference in the patients' outcome as a measure of the "correctness" of medical decision-making.

Conclusions. The issue of gender bias in patients with CAD remains controversial. In this study, there was little evidence for lower utilization of diagnostic and therapeutic services in women. Practice patterns remained constant, despite increasing medical reports raising concern about possible gender bias.

Table 4. Referral to Revascularization

	Univariate Analysis			Multivariate Analysis*		
Variable	Chi-Square	p Value	OR (95% CI)	Chi-Square	p Value	OR (95% CI)
Extent of CAD	385	< 0.001	2.8 (2.5–3.1)	267	< 0.001	2.5 (2.3–2.8)
SRS† (1-point increase)	207	< 0.001	1.13 (1.11–1.15)	57	< 0.001	1.07 (1.06–1.09)
SSS‡ (5-point decrease)	186	< 0.001	1.5 (1.4–1.6)	—	—	—
Chest pain class	114	< 0.001	1.5 (1.4–1.7)	62	< 0.001	1.4 (1.3–1.6)
Age (10-year increase)	54	< 0.001	1.4 (1.3–1.5)	—	—	—
Symptom status	49	< 0.001	2.3 (1.8–2.9)	—	—	—
Hyperlipidemia	14	< 0.001	1.4 (1.2–1.7)	—	—	—
Cardiac enlargement	9	0.003	1.4 (1.1–2.6)	—	—	—
Gender (male)	7	0.010	1.3 (1.1–1.6)	—	—	—
Pharmacologic stress	7	0.010	0.8 (0.6–0.9)	6	0.014	0.7 (0.6–0.9)
Hypertension	6	0.02	1.2 (1.0–1.5)	—	—	—
Smoking	1	NS	1.1 (0.9–1.2)	—	—	—
Diabetes	< 1	NS	0.9 (0.8–1.1)	—	—	—

*Variables without numbers in the multivariate analysis did not meet the entry criteria into the final model; †a summed reversibility score (SRS) of 0 represents a nonischemic image; ‡a summed stress score (SSS) of 56 represents a normal image. Final model: chi-square = 652, p < 0.001; C-index = 0.82. Bootstrapping analysis the extent of CAD came into every model, SRS and chest pain class in 98% of the models and pharmacologic stress in 64%. In the initial multivariate stepwise analysis, symptom status just met the entry criteria into the model (chi-square = 4, p = 0.038). In the bootstrapping analysis, it came into only 13% of the models. This variable was therefore eliminated from the final multivariate model.
   CAD = coronary artery disease; other abbreviations as in Table 3.

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