

Referral for Coronary Artery Revascularization Procedures After Diagnostic Coronary Angiography: Evidence for Gender Bias?

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Objectives. We sought to determine whether there is a gender bias in the selection of patients for coronary revascularization once the severity of the underlying coronary artery disease has been established with angiography.

Background. It has been suggested that women with coronary artery disease are less likely to be referred for coronary angiography and coronary artery bypass surgery than men. Whether such a referral bias for revascularization procedures, including coronary angioplasty, is present once angiography has been performed is not clear.

Methods. We retrospectively analyzed 22,795 patients with suspected coronary artery disease who underwent coronary angiography between 1981 and 1991 and compared the numbers of women and men who underwent either coronary artery bypass surgery or coronary angioplasty within 30 days of coronary angiography.

Results. Angiography revealed significant (one-vessel or more) disease in 15,455 patients (52% of women, 76% of men). Despite

worse symptoms, women had less extensive coronary disease than men as judged by the number of vessels diseased. Women were also more likely to have other co-morbid diseases. An equal proportion of women (54%) and men underwent revascularization procedures. After adjustment for baseline differences and age, differences in the two individual revascularization strategies were very small: More women tended to have coronary angioplasty ([absolute difference \pm 1 SD] $+3.3 \pm 0.7\%$, $p < 0.0001$), but fewer had coronary artery bypass surgery than men ($-2.5 \pm 0.8\%$, $p = 0.003$). When the two revascularization strategies were considered together, there was no significant gender difference in overall adjusted use of revascularization ($+0.8 \pm 0.9\%$, $p = 0.41$).

Conclusions. Once diagnostic coronary angiography had been performed, no major differences in the overall utilization of revascularization procedures were noted for women compared with men.

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Coronary artery disease is the most frequent cause of death among women in the United States (1), yet recent studies (2,3) have suggested that women with suspected coronary artery disease are less likely to be referred for coronary angiography and revascularization procedures than men. This observation appears to be true even after positive radionuclide exercise test results (4). Coronary angiography is also less frequently performed in women after acute myocardial infarction (5), although conflicting data have also been reported (6). These observations have fueled debate about possible treatment bias against women or, alternatively, raised the question of overutilization of procedures in men (7-10). The possibility of real gender differences in the pathogenesis and clinical presentation of coronary artery disease might also contribute to these

observations. Less frequent referral for revascularization among women may be due to the perceived higher mortality among women undergoing coronary artery bypass surgery (11-13) or percutaneous transluminal coronary angioplasty (14-17) than among men, although recent studies (12,14,18) have emphasized that this difference in mortality is largely explained by the more advanced age and disease severity in women than men at the time of treatment. One possible implication of the latter observation may be that women are treated at a later stage in their illness than men, but whether or not this has resulted from an investigational or treatment bias is not known.

Although it appears that gender differences in the management of coronary artery disease probably do exist, it is not clear whether significant differences exist once coronary angiography has been performed. In a study by Ayanian and Epstein (3), it was observed that women hospitalized for coronary artery disease underwent fewer diagnostic and revascularization procedures (coronary angioplasty or bypass surgery) than men but the observations were not stratified according to whether coronary angiography had been performed. In another important study, Steingart et al. (2) observed that there was no significant difference in the use of bypass surgery

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among men and women with angina, although there was a trend toward its greater use in men; however, the use of coronary angioplasty was not investigated. Therefore, the purpose of this study was to examine referral rates for revascularization procedures (bypass surgery or angioplasty) among a large population of women and men who had coronary angiography performed for suspected coronary artery disease.

Methods

Patient selection. All patients ≥ 18 years old who underwent initial diagnostic coronary angiography at the Mayo Clinic between 1981 and 1991, inclusive, were considered for this study. Coronary angiography was performed to evaluate known or suspected coronary artery disease in patients with symptoms or objective evidence of myocardial ischemia, or both, as well as in patients with significant valvular or congenital heart disease, cardiomyopathy of any etiology or clinically significant arrhythmias. Patients who had undergone previous angiography at this institution or previous coronary angioplasty or bypass surgery were excluded. Patients were identified from our cardiac catheterization laboratory's computerized data base and then matched to our institution's Diagnostic Medical Index, which provided additional demographic information. After exclusion of 808 patients with incomplete data, 22,795 (15,237 men, 7,558 women) were identified for further analysis.

Referral for coronary revascularization. For the purpose of this study, we examined the frequency of coronary revascularization within 30 days of the baseline coronary angiogram. For each patient, only one revascularization procedure was counted: For example, a patient referred for coronary angioplasty who subsequently underwent coronary artery bypass surgery within 30 days of angiography was included only in the angioplasty group.

Angiographic analysis. Severity of coronary artery disease was assessed from the coronary angiogram by visual inspection or with hand-held calipers by the cardiologist who performed the procedure and was immediately entered into the data base. Extent of coronary disease was defined according to the Coronary Artery Surgery Study (CASS) investigators (19). Briefly, significant disease of the right, left anterior descending and circumflex coronary arteries was defined by a $\geq 70\%$ luminal diameter stenosis in these vessels or their major branches, whereas significant disease of the left main coronary artery was defined by $\geq 50\%$ diameter stenosis. In a right-dominant circulation, one-vessel disease was defined by significant disease in one of the three major coronary arteries or their branches; two- and three-vessel disease was defined by significant disease in two and three of these vessels, respectively. In a left-dominant circulation, the three coronary vessels involved in one-, two- and three-vessel disease were the left anterior descending coronary artery, the proximal circumflex coronary artery with its marginal branches and the distal circumflex coronary artery and its posterolateral branches. Patients with significant left main coronary artery disease were

defined as having two-vessel disease when the circulation was right dominant and three-vessel disease when it was left dominant. Patients meeting none of these definitions were classified as having no significant coronary artery disease.

Left ventricular ejection fraction was obtained at ventriculography and determined from 30° right anterior oblique projections. Ejection fraction data were available only for patients who had angiography performed since 1987.

Patient demographics and clinical characteristics. Demographic and clinical data were obtained using the Diagnostic Medical Index of the Mayo Clinic. Significant concomitant disease was considered to be present when one or more of the following diseases appeared on this index: cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, renal disease, diabetes mellitus and hypertension. Functional class of angina was categorized according to the Canadian Cardiovascular Society (CCS) (20). Functional class of patients was recorded in the surgical data base according to the New York Heart Association, but for the purpose of the present study it is reported as angina class. It was necessary to interpret functional class I (asymptomatic) as corresponding to angina class I (angina with strenuous exertion), but classes II to IV of both classifications reflect essentially the same level of symptoms.

Although the functional class of patients and other detailed clinical characteristics were recorded in the coronary angioplasty and surgical data bases, they were not routinely recorded in the diagnostic angiography data base. The functional class of patients who did not undergo revascularization was analyzed after detailed review of the histories of a random sample of 300 patients stratified by number of diseased vessels.

Statistical analysis. Descriptive data are presented as mean value ± 1 SD or percent. Characteristics were compared between genders by either *t* tests for continuous variables or chi-square tests for dichotomous variables. Rates of revascularization were compared between genders among patients with significant coronary disease and then stratified by extent of coronary disease. A multiple linear regression model was used to estimate the independent effect of gender on choice of revascularization. This analysis was performed using binary (dichotomous) revascularization variables of coronary angioplasty, bypass surgery or any revascularization as the dependent variables, and age (continuous), gender (binary), year of angiography (continuous), number of concomitant diseases (continuous) and number of diseased vessels (continuous) as the independent variables. In a subgroup of patients with available ejection fraction data (see Angiographic analysis), a separate model was analyzed that included this variable as well. The computations were performed using SAS statistical software. Because the functional class of patients and other detailed clinical characteristics were not recorded in the diagnostic angiography data base, functional class was not entered into the linear regression model; statistical significance was assumed at $p = 0.05$.

Table 1. Summary of Findings at Diagnostic Coronary Angiography in 22,795 Patients

No. of Vessels Diseased	No. (%) of Men (n = 15,237)	No. (%) of Women (n = 7,558)
0	3,735 (24)	3,605 (48)
1	1,908 (13)	834 (11)
2	3,287 (22)	1,141 (15)
3	6,307 (41)	1,978 (26)

The observed difference in prevalence of significant coronary artery disease between men and women was statistically significant ($p < 0.0001$).

Results

Patient population. The mean age of the study population was 63 ± 12 years. On average, women were slightly older than men (64 ± 12 vs. 62 ± 11 years, respectively, $p < 0.0001$). Women were also slightly more likely than men to have at least one additional concomitant disease (30% vs. 28%, $p = 0.0009$). The extent of coronary disease according to gender is shown in Table 1. There were 7,340 patients without significant coronary disease (24% of men vs. 48% of women who underwent baseline angiography). Overall, men tended to have more extensive coronary disease than women ($p < 0.0001$). For subsequent analyses, only the 15,455 patients with at least one-vessel disease were analyzed with respect to subsequent performance of revascularization procedures. Among these were 11,502 men and 3,953 women whose previously observed baseline differences remained consistent: Women were older than men (67 ± 10 vs. 63 ± 10 years, $p < 0.0001$), and more women had one or more concomitant diseases (36% vs. 30%, $p < 0.0001$). Women were more likely to have cerebrovascular disease, peripheral vascular disease, diabetes mellitus and hypertension than men but less likely to have chronic pulmonary disease or malignancy (Table 2).

Comparison of revascularization procedures. Among patients with significant coronary artery disease, the overall revascularization rates were equal for both genders: 6,238 men (54%) and 2,153 women (54%) underwent revascularization procedures. Revascularization rates according to the number of vessels diseased are shown in Table 3. Among patients with one-vessel disease, 45% of men and 47% of women underwent

Table 2. Comparison of Gender Differences for Concomitant Disease Present at Baseline Diagnostic Angiography

Disease	No. (%) of Men (n = 11,502)	No. (%) of Women (n = 3,953)	p Value
Cerebrovascular	609 (5.3)	254 (6.4)	0.008
Peripheral vascular	938 (8.2)	397 (10.0)	<0.0001
COPD	596 (5.2)	143 (3.6)	<0.0001
Malignancy	744 (6.5)	217 (5.5)	0.03
Renal	291 (2.5)	115 (2.9)	0.20
Diabetes mellitus	874 (7.6)	455 (11.5)	<0.0001
Hypertension	1,790 (15.6)	895 (22.6)	<0.0001

COPD = chronic obstructive pulmonary disease.

Table 3. Frequency of Revascularization by Gender According to Extent of Coronary Artery Disease

	No. (%) of Men (n = 11,502)	No. (%) of Women (n = 3,953)	p Value
One-vessel disease			
No revascularization	1,057 (55)	439 (53)	0.19
Revascularization	851 (45)	395 (47)	
CABG	168 (9)	77 (9)	0.72
PTCA	683 (36)	318 (38)	0.24
Two-vessel disease			
No revascularization	1,671 (51)	538 (47)	0.03
Revascularization	1,616 (49)	603 (53)	
CABG	848 (26)	304 (27)	0.58
PTCA	768 (23)	299 (26)	0.06
Three-vessel disease			
No revascularization	2,536 (40)	823 (42)	0.27
Revascularization	3,771 (60)	1,155 (58)	
CABG	3,174 (50)	886 (45)	<0.001
PTCA	597 (10)	269 (14)	<0.001
Total			
No revascularization	5,264 (46)	1,800 (46)	0.80
Revascularization	6,238 (54)	2,153 (54)	
CABG	4,190 (36)	1,267 (32)	<0.001
PTCA	2,048 (18)	886 (22)	<0.001

CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty.

revascularization ($p = 0.19$). Coronary angioplasty was used in 36% of men versus 38% of women, whereas bypass surgery was performed in 9% of both men and women. Among patients with two-vessel disease, 49% of men underwent revascularization (23% with angioplasty, 26% with bypass surgery) compared to 53% of women (26% with angioplasty, 27% with bypass surgery) ($p = 0.03$). Similar proportions of men and women with three-vessel disease underwent revascularization (60% and 58%, respectively, $p = 0.27$). However, in this group, bypass surgery was more likely to be used in men than in women (50% vs. 45%, respectively, $p < 0.001$), whereas angioplasty was less likely to be used in men than in women (10% vs. 14%, respectively, $p < 0.001$).

There were significant differences observed in baseline characteristics between men and women who underwent revascularization procedures: Women were older and more likely to have angina class III or IV symptoms and more likely to have other medical diseases (Table 4). These differences were observed regardless of the revascularization strategy chosen.

After adjustment for age, year of angiography, number of concomitant medical illnesses and extent of coronary artery disease, we found that women were more likely to undergo coronary angioplasty than men (absolute difference $+3.3 \pm 0.7\%$, $p < 0.0001$), whereas the converse was true for bypass surgery (absolute difference $-2.5 \pm 0.8\%$, $p = 0.003$). Although these differences are very small, they are statistically significant because of the very large sample size. However, when use of angioplasty or bypass surgery was considered (i.e.,

Table 4. Baseline Demographic Data by Gender in Patients Undergoing Revascularization

	PTCA		CABG		PTCA or CABG	
	Men (n = 2,048)	Women (n = 886)	Men (n = 4,190)	Women (n = 1,267)	Men (n = 6,238)	Women (n = 2,153)
Mean (±SD) age (yr)	61 ± 11	67 ± 11*	65 ± 10	68 ± 9*	63 ± 10	68 ± 10*
CCS class III or IV (%)	62	76*	82	86†	75	82*
One or more concomitant disease (%)	27	35*	31	36‡	29	35*

*p < 0.0001. †p < 0.005. ‡p < 0.001. CCS = Canadian Cardiovascular Society; other abbreviations as in Table 3.

any revascularization), there was no significant difference between overall use of revascularization procedures between genders (absolute difference of 0.8 ± 0.9%, p = 0.41).

Medical treatment group. Comparison of the functional class of patients who were treated medically was derived from the random sample of 300 patients representing 4.1% of all patients treated medically. Sixty-seven percent of women had class III or IV symptoms compared with 41% of men (p < 0.001). This difference was apparent for patients with one-, two- and three-vessel disease. These data were not included in the multivariate analysis because functional class was not recorded for all medically treated patients.

Left ventricular ejection fraction. For patients who underwent angiography between 1987 and 1991, left ventricular ejection fraction was measured in 6,337 patients who had at least one-vessel disease. The distribution of ejection fraction according to gender and treatment strategy demonstrates that patients with a higher ejection fraction were more likely to undergo revascularization (Table 5). The proportion of patients, stratified by ejection fraction, who underwent revascularization is shown in Table 6. There was a slight trend toward women undergoing less bypass surgery and more coronary angioplasty than men, but overall revascularization rates were equivalent. Multivariate analysis based on these 6,337 selected patients adjusted for age, year of angiography, number of concomitant medical illnesses, extent of coronary artery disease and left ventricular ejection fraction revealed that women were still more likely to undergo coronary angioplasty than

men (absolute difference +2.6 ± 1.2%, p = 0.03) and less likely to undergo bypass surgery (-3.0 ± 1.2%, p = 0.01). The overall adjusted revascularization rates were similar (absolute difference between women and men -0.4 ± 1.4%, p = 0.77). Thus, although ejection fractions were slightly higher among women and were positively associated with revascularization, the effect on revascularization choices after adjustment for ejection fraction was negligible.

Discussion

Study findings. In the present study, 22,795 patients (33% women) underwent coronary angiography for suspected coronary artery disease. Of these, 15,455 patients (26% women) were found to have significant coronary artery disease. We found that there was no difference in revascularization frequency between men and women with one- or three-vessel disease. Among patients with two-vessel disease, women did in fact undergo revascularization slightly more frequently than men (Table 2). After adjusting for age, year in which angiography was performed, number of concomitant diseases present and extent of coronary artery disease, we found that there was no significant difference in the referral of men and women for coronary revascularization, although there were small differences in gender regarding the use of coronary angioplasty or bypass surgery.

Table 5. Left Ventricular Ejection Fraction Distribution by Gender According to Treatment Selected

Treatment	No. of Pts	Left Ventricular Ejection Fraction		
		≤ 0.35	0.36-0.49	≥ 0.50
PTCA				
Men	1,229	41 (3%)	157 (13%)	1,031 (84%)
Women	510	15 (3%)	54 (11%)	441 (86%)
CABG				
Men	1,412	105 (7%)	267 (19%)	1,040 (74%)
Women	469	28 (6%)	80 (17%)	361 (77%)
Medical treatment				
Men	1,975	196 (10%)	356 (18%)	1,423 (72%)
Women	742	74 (10%)	109 (15%)	559 (75%)

Data obtained from 6,337 patients with one or more diseased coronary artery and available left ventricular ejection fraction data; number (%) of patients (Pts). Other abbreviations as in Table 3.

Table 6. Proportion of Patients Who Underwent Revascularization, Stratified by Left Ventricular Ejection Fraction

	Left Ventricular Ejection Fraction		
	≤ 0.35	0.36-0.49	≥ 0.50
Men (n = 4,616)			
PTCA	12%	20%	27%
CABG	31%	34%	31%
Either	43%	54%	57%
CABG (% of revascularization procedures)	72%	63%	53%
Women (n = 1,721)			
PTCA	13%	22%	30%
CABG	24%	33%	27%
Either	37%	55%	57%
CABG (% of revascularization procedures)	65%	60%	48%

Data based on those in Table 5. Abbreviations as in Table 3.

Women were slightly less frequently referred for bypass surgery but more frequently referred for coronary angioplasty, but the specific reasons for choosing either revascularization technique could not be determined for the present study. However, physician and patient preference were generally the most important factors in view of the lack of data from randomized trials of coronary angioplasty versus bypass surgery. Because the operative mortality rate for bypass surgery is higher in women than men (11-13), physicians may have recommended coronary angioplasty as a lower risk procedure for women more frequently than for men. However, higher complication and in-hospital mortality rates among women than men after coronary angioplasty were documented in the mid to late 1980s (15,17,21). Women had a higher prevalence of diabetes, which may have been associated with smaller coronary vessels that were suboptimal for bypass surgery; their higher prevalence of cerebrovascular and peripheral vascular disease may also have influenced the decision not to proceed with bypass surgery.

Alternatively, differences in left ventricular ejection fraction between genders may have influenced revascularization choices. Women tend to have better left ventricular function at baseline in reported studies of revascularization outcomes (12-14,16), and it is therefore conceivable that more men were referred for surgical revascularization than women on this basis. However, we found no significant difference in the probability of referral for either bypass surgery or coronary angioplasty after adjusting for ejection fraction. Our analysis of ejection fraction data pertained only to patients studied since 1987, although it is unlikely that the overall findings would have been different if all patients had been included.

Our study therefore supports the hypothesis that once coronary angiography has been performed in patients with coronary artery disease, referral for revascularization is essentially similar among women and men. Any significant difference or bias in the management of women and men is likely to have occurred up to and including the decision to proceed with angiography (2-5).

Previous studies. Although previous studies have addressed the issue of different rates of revascularization for men and women, referral patterns after coronary angiography have not been clearly defined. Using statewide hospital discharge data for patients hospitalized with coronary artery disease in Massachusetts and Maryland, Ayanian and Epstein (3) found significantly higher rates of angiography and revascularization for men than women but did not determine whether revascularization rates differed once angiography had been performed. Steingart et al. (2) found that among 2,231 patients in the Survival and Ventricular Enlargement (SAVE) trial, women with angina were less likely to have undergone coronary angiography than men before enrollment in the trial. Once angiography had been performed, there was no gender-related difference in the use of bypass surgery; however, the use of coronary angioplasty, now the most common method of coronary revascularization in the United States, was not explored.

Important differences between our study and these earlier studies should be emphasized. Our study represents a consecutive series of patients investigated at a single institution over a period of 11 years. Identification of the patient population in the study by Ayanian and Epstein (3) relied on statewide abstracted discharge diagnoses provided by an outside agency. The SAVE study population was highly selected and nonconsecutive (2), whereas Krumholz et al. (6) included a highly selected group of patients with myocardial infarction. Nevertheless, our results are consistent with these last two studies; that is, once coronary angiography has been performed, the subsequent utilization of revascularization procedures is essentially similar for women and men.

Our results thus provide further insight into the issue of gender-related differences in referral for revascularization procedures among patients with suspected coronary artery disease. These findings should be distinguished from the observations that once women have had a cardiac event, such as an acute myocardial infarction, frequency of revascularization is similar to that in men (6). This observation has been coined the "Yentl" syndrome by Healy (9) and suggests that only when women are found to have severe coronary artery disease or a myocardial infarction are they treated as men would be. Although our results do not necessarily support the contention of the "Yentl" syndrome at work, they do support the fact that women and men with a wide variety of coronary artery disease syndromes are treated similarly after coronary angiography.

Severity of symptoms in women. Consistent with the angiographic findings of earlier studies (22), we observed that women with suspected coronary artery disease were less likely than men to have angiographically significant coronary artery disease. The data clearly demonstrate that women are more likely to have Canadian Cardiovascular Society class III or IV symptoms than men—this was true for patients who underwent revascularization and those treated medically. Similar observations have been made by others (12-15,17,23), although the explanation for this is not well understood. There is a higher prevalence of hypertension and left ventricular hypertrophy among women (24) as well as a higher mortality among women with coronary artery disease and diabetes mellitus than men with diabetes (25); our results confirm these gender differences in the presence of these diseases (Table 2). It is therefore possible that the effects of hypertension, left ventricular hypertrophy and diabetes mellitus on the microcirculation contribute to a greater degree of myocardial ischemia for any given degree of epicardial coronary artery narrowing. Alternative explanations are that women are sicker than men at the time of angiography because of delayed presentation to their physician after symptom onset or that there is a higher threshold among physicians for referral for angiography (4). Only with carefully designed and prospective studies will this important and perplexing issue be resolved.

Study limitations. The present study was a retrospective one and as such has certain limitations. The lack of functional classification and other clinical data among patients who did

not undergo revascularization was addressed earlier. Many patients underwent functional stress testing before angiography, but an analysis of these results among this very large population was not possible. Such an analysis may have lent insight into the lower frequency of significant coronary artery disease among women at angiography, despite their more prominent symptoms, although this finding is consistent with that of an earlier large study (22). The specific indications for selecting the various treatment strategies were not recorded and could not be ascertained for the present study. Although our study included some patients who underwent angiography and subsequent investigation for other cardiac diseases, our population consisted predominantly of patients with evidence of coronary artery disease. Therefore, our findings can probably be generalized to patients undergoing evaluation for coronary artery disease. Whether the results from this single large tertiary referral institution can be extrapolated to the community in general is unknown, but our findings appear to be consistent with other recent reports.

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