ABSENCE OF SEX BIAS IN THE REFERRAL OF PATIENTS FOR CARDIAC CATHETERIZATION

Daniel B. Mark, M.D., M.P.H., Linda K. Shaw, B.A., Elizabeth R. DeLong, Ph.D., Robert M. Califf, M.D., and David B. Pryor, M.D.

Abstract *Background.* It has been suggested that women with clinical evidence of coronary artery disease are less often referred for cardiac catheterization than are men. To determine whether there is sex-related bias in referral for cardiac catheterization, we prospectively studied a cohort of 410 symptomatic outpatients (280 men and 130 women) who were being evaluated with exercise testing for possible coronary artery disease.

Methods. Before the patients underwent exercise testing, 15 cardiologists from an academic medical center were asked to predict the probability that the patients they saw in the cardiology clinic would have angiographic evidence of any obstructive coronary disease (stenosis of 75 percent or more); the probability of severe coronary disease (three-vessel or left main coronary artery disease); the probability of left main coronary artery disease; and the probability of survival one, three, and five years after the evaluation. Similar predictions were generated by previously validated statistical models with use of data collected before exercise testing from the history, physical examination, and 12-lead electrocardiography with the patient at rest.

Results. Overall, women were referred for cardiac catheterization significantly less often than men (18 percent vs. 27 percent, P = 0.03). As compared with men, women had a significantly lower pretest probability of coronary disease (as estimated by their physicians) and a lower rate of positive exercise-test results. After accounting for differences in these two factors, sex was not an independent predictor of referral for catheterization. Comparing physicians' estimates of outcome with those generated by the statistical models revealed no evidence that the physicians were underestimating the risk of coronary disease in women. Furthermore, physicians' predictions did not underestimate the probability of any obstructive coronary disease in men and women who subsequently underwent catheterization.

Conclusions. Academic cardiologists made appropriately lower pretest predictions of categories of disease in women with possible coronary artery disease than in men, and these assessments, along with women's lower rate of positive exercise tests, rather than bias based on sex, accounted for the lower rate of catheterization among women. (N Engl J Med 1994;330:1101-6.)

RECENT reports have called attention to differences in the diagnostic and therapeutic approach of physicians to men and women with known or suspected coronary artery disease.[1-7] Tobin and colleagues found that only 4 percent of women with an abnormal radionuclide scan during exercise were referred by their physicians for cardiac catheterization, as compared with 40 percent of men with similar results.[1] Subsequent studies have found a lower rate of referral for cardiac catheterization among women than among men hospitalized for myocardial infarction[2,3,6,7] and other manifestations of coronary disease.[3] Although women do differ from men in having a later onset of coronary disease and a lower prevalence of the disease at any given age,[8-11] attempts to control

From the Division of Cardiology, Department of Medicine (D.B.M., L.K.S., R.M.C., D.B.P.), and the Division of Biometry, Department of Community and Family Medicine (E.R.D.), Duke University Medical Center, Durham, N.C. Address reprint requests to Dr. Mark at Duke University Medical Center, Box 3485, Durham, NC 27710.

for these factors did not eliminate the observed differences, leaving open the possibility that differences in physicians' decision making based on the sex of the patient were responsible.

Providing definitive evidence of sex bias would require demonstrating that physicians made different decisions about management for patients who were similar except for their sex.[12] Understanding the causes of such bias would require an evaluation of whether physicians had erroneous or biased perceptions of the probability of coronary disease or the benefits of therapy (or both) in women.

Between 1983 and 1985, we prospectively studied the ability of physicians to make accurate predictions regarding diagnosis and outcome for a large consecutive series of outpatients referred to the exercise laboratory for evaluation of suspected coronary disease. Such predictions, which summarize the physician's subjective impression of the patient's diagnosis and risk level, were made before the current attention to sex bias arose; these data therefore offer an unusual opportunity to evaluate factors in both patients and physicians that affect referral patterns. The purpose of

this study was to use these data in determining whether there were differences based on sex in physicians' decisions to refer patients for cardiac catheterization.

METHODS

Study Population

The 410 study patients were drawn from 1030 consecutive outpatients with suspected coronary artery disease who were seen at Duke University Medical Center and were referred for exercise testing as part of their clinic evaluation between March 1983 and January 1985.[13] Patients who had previously undergone cardiac catheterization or had evidence of substantial valvular, congenital, or cardiomyopathic disease were not eligible for this study. In addition, patients were excluded if they were referred directly to the exercise laboratory without an evaluation in the cardiology clinic by a Duke cardiologist or if we did not obtain pretest estimates of outcomes related to coronary disease from the attending cardiologist.

Collection of Data

For each patient, a cardiac history was obtained and a physical examination and 12-lead electrocardiography were performed by the cardiologist as part of the clinic evaluation. Selected portions of this evaluation were repeated by the cardiology fellow or physician's assistant who supervised the exercise test. These data, along with the results of exercise testing, were entered prospectively into a computerized medical information system.[13]

Predictions by Physicians

Every cardiologist at the medical center who referred patients to the exercise laboratory was asked to use a standard form to record key elements of each patient's history (including descriptions of chest pain) before testing, along with his or her subjective estimate of the probability that angiography would show any obstructive coronary artery disease, severe coronary artery disease, and left main coronary artery disease and the probability of survival after one, three, and five years of follow-up. A total of 15 cardiologists participated in this study. Angiographic evidence of any obstructive coronary artery disease was defined as stenosis of 75 percent or more in at least one of the three major epicardial coronary artery systems.[14] Severe coronary disease was defined as three-vessel or left main coronary artery disease (with ≥75 percent stenosis).

Exercise Testing and Cardiac Catheterization

Decisions about exercise testing and subsequent cardiac catheterization were made by each patient's attending cardiologist in consultation with the patient and the physician who had referred the patient to the medical center's cardiology clinic. Treadmill testing was performed according to the standard Bruce protocol. A positive test was one in which there was 1 mm or more of exercise-induced ST-segment deviation at 0.06 second after the J point, relative to the PR segment.[15] Both first-pass radionuclide angiography and gated blood-pool scanning were done during exercise on an upright bicycle ergometer, as previously described.[16] For each of these studies, a positive test was defined as one in which there was a new exercise-induced wall-motion abnormality.

Predictive Models

We had previously developed multivariable models to estimate the probability of any obstructive coronary artery disease, severe coronary artery disease, and left main disease and one-, three-, and five-year survival and had validated these models in a study of consecutive patients referred for cardiac catheterization between 1969 and 1983.[13,17] These models provide objective summaries of the probability of coronary disease (by logistic regression) and of survival outcomes (by Cox proportional-hazards regression) that can be compared with physicians' subjective estimates to determine whether physicians are systematically less or more accurate in pre-

dicting outcomes for women than for men. Participating physicians in this study were not given access to these models during the course of the study.

Statistical Analysis

This study had three objectives. First, in order to understand the determinants of referral for catheterization and whether those determinants vary according to sex, we created a series of stepwise multivariable logistic-regression models with referral for catheterization as the dependent variable and an entry significance level of P<0.05. Initially, all available pretest data from the history, physical examination, and electrocardiogram were used as candidate independent variables. In the second phase of modeling, we expanded the pool of candidate variables by adding physicians' predictions of the patient's diagnosis and outcome as well as information about whether the attending cardiologist personally performed the cardiac catheterization. In the final phase, we again expanded the pool of candidate variables by adding the results of the patient's exercise test (classified as positive or not positive). In each of the three phases, we wished to identify the variables that were most strongly associated with the physician's decision regarding referral. Since sex was not a significant independent predictor in any phase of this analysis, we forced this variable into each model and calculated an odds ratio for men as compared with women and the corresponding 95 percent confidence interval.

Our second objective was to determine whether physicians' predictions showed evidence of bias according to the patient's sex when compared with the more objective predictions of our validated statistical models. To accomplish this goal, we calculated the arithmetic difference between the physicians' predictions and the model's, according to sex, for each outcome of interest.

Our final objective was to determine whether physicians' subjective predictions of the presence of any obstructive coronary artery disease were less accurate for women than for men when compared with the diagnoses established by catheterization in the subgroup of the patients who were referred for cardiac catheterization. The accuracy of the physicians' predictions was examined in terms of reliability (also called calibration, a measure of how closely predicted outcomes correspond to observed outcomes) and discrimination (a measure of the capacity to separate patients with and without a specific outcome), as previously described.[18]

RESULTS

Study Population

The base-line characteristics of the 410 study patients are shown according to sex in Table 1. As expected, the men were younger, more often had typical angina, were more apt to have a history of smoking, and more frequently had a history of myocardial infarction. The women were older, more often had atypical angina, and had more congestive heart failure. Overall, the rate of referral for cardiac catheterization within 90 days of the clinic evaluation was significantly higher for the men than the women (27 percent vs. 18 percent, P = 0.03).

Predictors of Referral for Catheterization

Predictors of referral for cardiac catheterization were identified in three sequential steps. When only variables from the clinical history, physical examination, and electrocardiogram were considered, four were independently predictive of referral: type of angina (typical angina, atypical angina, or nonanginal pain), smoking history, duration of symptoms of coronary disease, and a progressive course of angina (Ta-

Table 1. Base-Line Characteristics of the Study Population, According to Sex.*

CHARACTERISTIC	MEN (N = 280)	WOMEN (N = 130)
Age (yr) — median (25th–75th percentile)	56 (47–63)	58 (50–65)
Nonwhite race — %	9	13
Symptoms of coronary artery disease		
Duration (mo) — median (25th–75th percentile)	12 (2–36)	12 (4–48)
Typical angina — %	40	25
Atypical angina — %	39	50
Pain frequency/week — median (25th–75th percentile)	2 (1–4)	2.5 (1–5)
Stable symptoms — %	83	79
Progressive symptoms — %	17	21
Risk factors — %		
History of smoking	51	26
Diabetes mellitus	8	9
Hypertension	37	41
Hyperlipidemia	13	16
Other clinical factors — %		
History of MI	26	15
Q waves on ECG	13	6
History of CHF	4	15
S₃ gallop	0.7	2.3
Peripheral vascular disease	2	5
Cerebrovascular disease	1	2
Referred for catheterization — %	27	18
Referring cardiologist performed catheterization — %	19	19
Type of exercise test — %		
Treadmill	59	55
First-pass RNA	18	22
MUGA	16	20
Treadmill and RNA or MUGA	7	3
Exercise test positive — %	27	12

*MI denotes myocardial infarction, ECG electrocardiogram, CHF congestive heart failure, RNA radionuclide angiography, and MUGA gated blood-pool scan.

ble 2). Sex was not an independent predictor of referral (adjusted odds ratio for referral, men vs. women: 1.30; 95 percent confidence interval, 0.73 to 2.33; P = 0.36).

When all the clinical variables were considered together with physicians' diagnostic and survival predictions and a variable indicating whether the predicting physician personally performed the cardiac catheterization (4 of the 15 participating physicians did so), the major independent predictors were the physician's estimate of the probability of any obstructive coronary disease and whether the cardiologist performed cardiac catheterization. Also predictive were the type of angina, the duration of chest-pain symptoms, and a progressive anginal course. Once again sex was not an independent predictor (adjusted odds ratio for men vs. women, 1.13; 95 percent confidence interval, 0.62 to 2.07; P = 0.69).

In the final phase of modeling, we included the results of the patient's exercise test (coded as positive or not positive) along with the variables considered in the previous steps (Table 2). Among patients with a positive exercise test, 48 percent of the men and 44 percent of the women were referred for catheterization

(P = 0.79). All the variables from the previous stage entered the model; in addition, whether the exercise test was positive was a strong independent factor determining referral for catheterization. The adjusted odds ratio for referral among men as compared with women in this model was 1.02 (95 percent confidence interval, 0.55 to 1.91; P = 0.95).

Comparison of Physicians' Predictions with the Results of Modeling

In order to compare physicians' predictions with a reference standard that was available for the entire study population, we paired each prediction by a physician with the corresponding prediction from our statistical models and calculated the arithmetic difference. Figure 1 shows that for predictions of angiographic evidence of any obstructive coronary disease, there was a higher prevalence of overestimation among the women (for 47 percent of them the physician's prediction of the likelihood of disease was more than 10 percentage points higher than the model's, as compared with 20 percent of the men). The pattern of differences between the model's and the physician's predictions was significantly different for men and women (P<0.001 by the Wilcoxon test). For severe coronary disease (Fig. 2), agreement was actually better for the women, whereas there was a trend for greater underestimation of severity in the men (33 percent had a physician's estimate more than 10 percentage points lower than the model's, as compared

Table 2. Predictors of Referral for Cardiac Catheterization.*

Clinical variables only	Model χ^2 = 63 (6 df)
Type of angina (2 df)	AROC = 0.743
History of smoking	
Duration of symptoms of CAD	
Progressive angina	
Sex	
Sex:beta = 0.2679; P = 0.36; odds ratio = 1.30 (95% CI, 0.73–2.33)	
Clinical variables and physician-specific variables	Model χ^2 = 101 (7 df)
	AROC = 0.810
Physician predicted any obstructive CAD	
Physician performed cardiac catheterization	
Type of angina (2 df)	
Duration of symptoms of CAD	
Progressive angina	
Sex	
Sex:beta = 0.1227; P = 0.69; odds ratio = 1.13 (95% CI, 0.62–2.07)	
Clinical variables, physician-specific variables, and exercise-test results	Model χ^2 = 117 (8 df)
	AROC = 0.839
Physician predicted any obstructive CAD	
Physician performed cardiac catheterization	
Positive exercise test	
Type of angina (2 df)	
Duration of symptoms of CAD	
Progressive angina	
Sex	
Sex:beta = 0.0207; P = 0.95; odds ratio = 1.02 (95% CI, 0.55–1.91)	

*AROC denotes area under the receiver-operating-characteristic curve, CAD coronary artery disease, and CI confidence interval. The odds ratios shown are the odds of being referred for cardiac catheterization among men as compared with women.

with 11 percent of the women; P<0.001). The distribution of predictions of survival at one, three, and five years showed smaller differences according to sex; slightly more women than men had their risk of death at all three time points overestimated by the physicians, as compared with the model (P<0.001 for all comparisons).

Accuracy of the Physicians' Diagnostic Predictions in Patients Who Underwent Catheterization

Since the comparison of the predictions made by the model and by the physicians did not eliminate the possibility that both could incorporate a sex bias (since both are based on the physicians' assessment of key variables), we also examined the accuracy of predictions that angiography would show evidence of any obstructive coronary artery disease in the subgroup of 99 patients (76 men and 23 women) who actually underwent cardiac catheterization within 90 days of enrollment in the study. Overall, the prevalence of angiographic evidence of any obstructive coronary disease was 78 percent for the men and 35 percent for the women. The discrimination of physicians' predictions was excellent for both men and women, with areas under the receiver-operating-characteristic curves of 0.91. There were too few women with severe coronary disease (8 percent) to evaluate physicians' discrimination in predicting this outcome. When predicting angiographic evidence of any obstructive coronary disease in men, the physicians did well in identifying the two groups with a high prevalence of disease (≥ 0.90) but overestimated the probability of disease in the group with intermediate prevalence (0.40) (Fig. 3). When predicting outcomes for the women, the physicians

Figure 2. Differences in the Predictions of the Probability That Angiography Would Show Evidence of Severe Coronary Artery Disease Made by the Attending Physician and the Statistical Model for Each Study Patient.

Severe coronary artery disease was defined as three-vessel disease or left main coronary artery disease. The distribution of arithmetic differences in the predictions (the model's minus the physician's) is shown for each sex. Negative differences indicate that the physician's prediction was higher than the model's; positive differences indicate that the physician's prediction was lower. The category −0.10 to 0.09 represents agreement. The numbers above the bars indicate the percentage of patients in the given category.

showed a trend toward consistently overestimating the true prevalence of disease.

DISCUSSION

We confirmed previous observations that women being evaluated for chest pain in the outpatient cardiac clinic are referred for cardiac catheterization significantly less often than are men,[1] but we found that this difference was accounted for by a lower pretest probability of coronary disease and a lower rate of positive exercise-test results among women. By examining physicians' predictions about diagnosis and outcome for these patients, we were able to exclude the possibility that a substantial bias on the part of physicians affected their predictive accuracy and thus accounted for the difference in referral rates. The availability of these prospectively collected, patient-specific estimates by physicians allowed us, in essence, to study physicians' thinking about the relation of sex to diagnosis and outcome unobtrusively during a period before the current widespread interest in sex-related bias emerged. Of course, because our study involved 15 experienced cardiologists practicing at one tertiary care hospital in the southeastern United States, we cannot exclude the possibility that studies of other populations or other physicians in other practice settings would yield different results. The physicians in this study have had in-depth exposure to the data available in the Duke Cardiovascular Disease Databank, and it is possible that they have become more accurate in predicting outcomes of coronary disease than clinicians without this information.

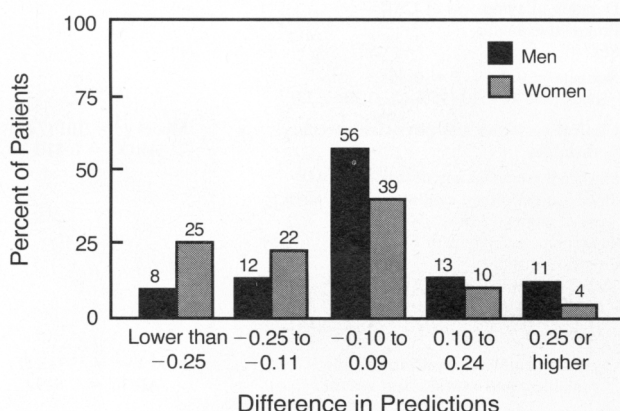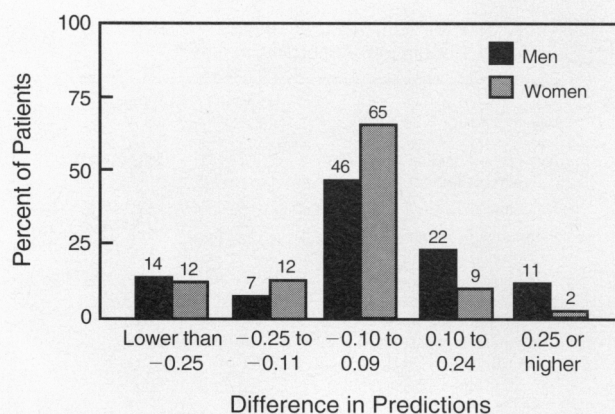Recent interest in sex bias in the treatment of pa-

Figure 1. Differences in the Predictions of the Probability That Angiography Would Show Evidence of Any Obstructive Coronary Artery Disease Made by the Attending Physician and the Statistical Model for Each Study Patient.

The distribution of arithmetic differences in the predictions (the model's minus the physician's) is shown for each sex. Negative differences indicate that the physician's prediction was higher than the model's; positive differences indicate that the physician's prediction was lower. The category −0.10 to 0.09 represents agreement. The numbers above the bars indicate the percentage of patients in the given category.
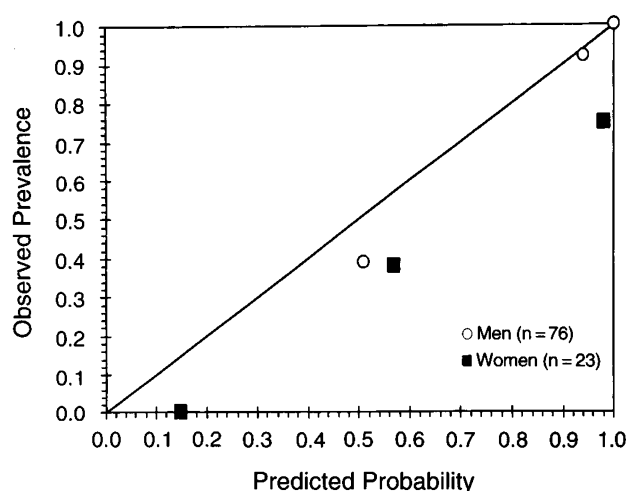
Figure 3. Reliability (Calibration) Plots of Physicians' Predictions of the Probability That Angiography Would Show Evidence of Any Obstructive Coronary Artery Disease.

The plot was created by arranging physicians' predictions from lowest to highest, forming three equal-sized groups for each sex, and plotting the mean physicians' prediction for that group against the observed prevalence of any obstructive coronary artery disease. The predictions for the men were well calibrated for the two high-prevalence groups, but they slightly overestimated the rate of disease in the intermediate-prevalence group. The predictions for the women showed a consistent trend toward slight overestimation of the rate of disease in the one low-prevalence group and the two intermediate-prevalence groups. The diagonal line shows perfect calibration.

tients with suspected or known coronary disease was aroused by the report of Tobin and colleagues,[1] who found that only 4 percent of the women with abnormal radionuclide exercise scans were referred for cardiac catheterization, as compared with 40 percent of the men (P<0.001). Furthermore, after controlling for age, previous myocardial infarction, typical and atypical angina, and abnormal test results, they found that men were still over six times more likely than women to be referred for catheterization.

The rest of the literature on sex-based differences in the management of coronary disease deals with hospitalized patients. Among patients who had had myocardial infarctions who were enrolled in the multicenter Survival and Ventricular Enlargement (SAVE) trial, Steingart and colleagues found that before the index infarction, the women participants were less likely than the men to have undergone cardiac catheterization (5.9 percent vs. 12.7 percent, P<0.001), despite their similar histories of angina and greater functional disability.[2] This difference persisted after adjustment for age, history of myocardial infarction, and cardiac risk factors. In contrast, after the index infarction, the rates of catheterization among the men and women participants were the same, a finding recently confirmed by Krumholz et al.[19] but one that conflicts with the results from the Myocardial Infarction Triage and Intervention Registry[6] and from the 1987 Medicare data base.[7] Using data on state insurance claims to study differences in rates of coronary

angiography in patients hospitalized for coronary heart disease, Ayanian and Epstein found that the overall rate was 15 to 28 percent higher among men than among women — a difference that persisted after adjustment for age.[3]

Unless an appropriate biologic basis for differences in management can be demonstrated, clinical diagnostic and therapeutic decision making for patients with coronary artery disease should not vary according to sex.[12,20] Thus, decisions about referral for cardiac catheterization should ideally be the same for "similar" men and women. The chief difficulty in studying sex bias, therefore, is ensuring that women are being compared with appropriate male counterparts. In this regard, the well-known differences in the presentation and prevalence of coronary disease between men and women are quite important.

In this study, we performed several analyses in an attempt to understand the link between sex and the decision to refer a patient for cardiac catheterization. In our initial multivariable analysis, we found four independent predictors of referral, but sex was not one of them. In subsequent modeling steps, we found that the three most important determinants of referral for catheterization were the physician's estimate, made before the exercise test, of the probability that angiography would show any obstructive coronary disease; whether the physician personally performed cardiac catheterization; and whether the patient had a positive exercise test. Again, sex was not an independent predictor, because the predictive information provided by the patient's sex was accounted for by differences in physicians' predictions for men and women and by the different rates of positive exercise-test results.

It is certainly logical that physicians' subjective estimates of outcomes for individual patients should be a strong predictor of referral. We therefore evaluated whether such predictions were biased or less accurate for women than for men in two ways. First, we compared physicians' predictions with the predictions generated by previously validated diagnostic and prognostic models; we found that physicians had a tendency to overestimate the likelihood of any obstructive coronary disease in women, whereas they tended to underestimate the likelihood of severe coronary disease in men. The comparison of predictions of outcomes showed a slight but significant trend toward overestimating the likelihood of death among women. Thus, these data showed that the study physicians were not underestimating the probability of coronary disease or of adverse outcomes in women. However, it is possible that our statistical models incorporated some sex-related bias, since their predictions are based on data collected from physicians. Therefore, we also examined physicians' accuracy in making predictions for the 99 study patients referred for catheterization. This analysis showed that the degree to which physicians' predictions could separate patients with and without coronary disease was high for both sexes.

In addition, physicians tended to overestimate the true prevalence of disease among women, although this trend should not be overinterpreted in view of the small numbers represented.

Several limitations of our study should be noted. First, we did not consider several factors likely to be important in the decision to refer a patient for catheterization, including the presence of coexisting diseases, the influence of the patient's primary care physician, and the patient's own preferences. Second, we classified results of exercise tests as positive or not positive, whereas the physicians participating in this study probably used more detailed test results in making their decisions. Finally, we did not examine directly the effects of the results of exercise tests on physicians' estimates, so we cannot exclude the possibility that physicians combined exercise-test data with clinical data differently for men and for women.

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