

SEX, CLINICAL PRESENTATION, AND OUTCOME IN PATIENTS WITH ACUTE CORONARY SYNDROMES

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FOR THE GLOBAL USE OF STRATEGIES TO OPEN OCCLUDED CORONARY ARTERIES
IN ACUTE CORONARY SYNDROMES IIb INVESTIGATORS

ABSTRACT

Background Studies have reported that women with acute myocardial infarction have in-hospital and long-term outcomes that are worse than those of men.

Methods To assess sex-based differences in presentation and outcome, we examined data from the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb study, which enrolled 12,142 patients (3662 women and 8480 men) with acute coronary syndromes, including infarction with ST-segment elevation, infarction with no ST-segment elevation, and unstable angina.

Results Overall, the women were older than the men and had significantly higher rates of diabetes, hypertension, and prior congestive heart failure. They had significantly lower rates of prior myocardial infarction and were less likely ever to have smoked. A smaller percentage of women than men had infarction with ST elevation (27.2 percent vs. 37.0 percent, $P < 0.001$), and of the patients who presented with no ST elevation (those with myocardial infarction or unstable angina), fewer women than men had myocardial infarction (36.6 percent vs. 47.6 percent, $P < 0.001$). Women had more complications than men during hospitalization and a higher mortality rate at 30 days (6.0 percent vs. 4.0 percent, $P < 0.001$) but had similar rates of reinfarction at 30 days after presentation. However, there was a significant interaction between sex and the type of coronary syndrome at presentation ($P = 0.001$). After stratification according to coronary syndrome and adjustment for base-line variables, there was a nonsignificant trend toward an increased risk of death or reinfarction among women as compared with men only in the group with infarction and ST elevation (odds ratio, 1.27; 95 percent confidence interval, 0.98 to 1.63; $P = 0.07$). Among patients with unstable angina, female sex was associated with an independent protective effect (odds ratio for infarction or death, 0.65; 95 percent confidence interval, 0.49 to 0.87; $P = 0.003$).

Conclusions Women and men with acute coronary syndromes had different clinical profiles, presentation, and outcomes. These differences could not be entirely accounted for by differences in base-line characteristics and may reflect pathophysiologic and anatomical differences between men and women. (N Engl J Med 1999;341:226-32.)

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CORONARY heart disease is the leading cause of morbidity and mortality among women as well as men in the West. Each year in the United States, there are 1.5 million hospitalizations for acute coronary syndromes, including unstable angina, myocardial infarction with no ST-segment elevation, and infarction with ST-segment elevation. Women with acute ischemic syndromes tend to be older than men with such syndromes, and they have higher rates of associated diabetes and hypertension.¹⁻²³ Studies report that women who present with acute myocardial infarction have worse in-hospital and long-term prognoses than men.^{1-5,7,8,12-18,21} It is uncertain whether these differences reflect differences in base-line characteristics or pathophysiologic distinctions between men and women. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) trial involves a large cohort of men and women who presented with acute coronary syndromes, therefore affording the opportunity to examine sex-based differences in presentation and outcome.

METHODS

Patients

Details of the GUSTO IIb trial have been reported previously.²⁴ The trial enrolled consecutive patients who presented with an acute coronary syndrome, including myocardial infarction with ST elevation, infarction with no ST elevation, and unstable angina. Electrocardiographic criteria included persistent or transient ST elevation or depression of more than 0.5 mm or definite T-wave inversion of more than 1 mm. An infarction was considered to have occurred at the time of enrollment if the level of creatine kinase MB isoenzyme was above normal (and at least 3 percent of the total creatine kinase level) at base line or eight hours after enrollment. If the creatine kinase MB level was elevated 16 hours after enrollment, and if no symptoms occurred between enrollment and the 16th hour, we considered the patient to have had an infarction at enrollment. If the creatine kinase MB level had not been measured, then the total creatine kinase level had to be more than twice the upper limit of the normal range at base line or 8 or 16 hours after enrollment.

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Thrombolytic therapy with either streptokinase or an accelerated infusion of alteplase was administered at the discretion of the attending physician. Patients were randomly assigned to receive three to five days of hirudin or heparin. Demographic and medical data were collected for all enrolled patients during hospitalization and for up to 30 days of follow-up.

The decision to perform coronary angiography was based on clinical factors. The primary end point of the study was a composite of death or nonfatal infarction within 30 days after enrollment. The analysis of sex differences in outcomes was a prospective substudy.

Statistical Analysis

We compared the base-line characteristics and clinical outcomes of women with those of men. We used adjusted base-line models to determine whether the differences between the sexes in certain base-line characteristics persisted after adjustment for other base-line characteristics. We adjusted for age, hypertension, diabetes, smoking status, hyperlipidemia, previous infarction, previous angina, previous heart failure, cerebrovascular disease, previous bypass surgery, previous angioplasty, peripheral vascular disease, heart rate, and systolic blood pressure. Statistical testing was performed with the use of the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Multivariable logistic-regression techniques were used to determine whether women were more likely than men not to have ST elevation (that is, to have myocardial infarction without ST elevation or to have unstable angina). Similarly, we created logistic models to determine whether women in this stratum were more likely than men to present with unstable angina.

We created multivariable logistic-regression models to determine, after adjusting for base-line differences, the effect of sex on the rates of death at 30 days, death or infarction (or reinfarction) at 30 days, and moderate or severe bleeding. We tested interactions between sex and acute coronary syndrome (infarction with ST elevation, infarction with no ST elevation, or unstable angina) to determine whether the effect of sex on outcome was similar in the three groups. We imputed missing base-line characteristics for all patients, using a method for the simultaneous imputation and transformation of predictor variables that is based on the concepts of maximal generalized variance and canonical variables.²⁵ We tested predictors in each model using the Wald chi-square test. We also present results as odds ratios and 95 percent confidence intervals.

RESULTS

Base-Line Characteristics

A total of 12,142 patients were enrolled in the trial: 8480 men (69.8 percent) and 3662 women (30.2 percent). Of these patients, 3693 (30.4 percent) were enrolled in U.S. centers (2441 men and 1252 women) and 8449 (69.6 percent) were enrolled outside the United States (6039 men and 2410 women). Overall, the women were older than the men and were more likely to have hypertension, diabetes, elevated total cholesterol levels, and a history of angina, congestive heart failure, and cerebrovascular disease (Table 1). They were less likely ever to have smoked and less likely to have a history of peripheral vascular disease, myocardial infarction, angioplasty, or bypass surgery. These differences in the base-line characteristics, except for cerebrovascular disease, persisted after adjustment for the other base-line characteristics. At presentation, the women had higher systolic blood pressures and higher heart rates than the men and were in higher Killip classes.

Relation of Sex to Type of Coronary Syndrome at Presentation

Of the 12,142 patients in the study, 4131 presented with ST elevation at enrollment, and 8011 had infarction with no ST elevation or unstable angina with no ST elevation. Significantly fewer women than men presented with ST elevation (27.2 percent vs. 37.0 percent, $P < 0.001$). Similarly, of the 8009 patients with no ST elevation for whom data were complete, only 36.6 percent of the women (974 of 2664) had infarction, as compared with 47.6 percent of the men (2544 of 5345, $P < 0.001$). For 2 of the 8011 patients with no ST elevation (1 man and 1 woman), we were unable to determine the status of myocardial infarction at enrollment, so these patients were excluded from the analysis.

The base-line characteristics of patients who presented with ST elevation on electrocardiography differed from those of patients with no ST elevation. Characteristics that were associated with an increased likelihood of the absence of ST elevation were previous infarction, previous bypass surgery, previous angina, hyperlipidemia, family history of myocardial infarction, previous congestive heart failure, previous cerebrovascular disease, higher systolic blood pressure, lower diastolic blood pressure, and greater height. In contrast, diabetes, treatment at a center in the United States, white race, higher Killip class at base line, and current smoking were associated with an increased likelihood of ST elevation. After adjustment for the base-line differences, female sex remained a significant predictor of the absence of ST elevation at presentation (chi-square = 38.24; $P < 0.001$; odds ratio, 1.50; 95 percent confidence interval, 1.32 to 1.71).

Among patients with no ST elevation, the following were associated with an increased likelihood of presenting with unstable angina: previous bypass surgery, previous angioplasty, previous angina, previous congestive heart failure, and higher systolic blood pressure. Current smoking, race, white race, U.S. center, greater age, greater heart rate, greater weight, and higher diastolic blood pressure were associated with a decreased likelihood of unstable angina at presentation. After adjustment for these differences, women were still significantly more likely than men to present with unstable angina (chi-square = 47.76; $P < 0.001$; odds ratio, 1.51; 95 percent confidence interval, 1.34 to 1.69).

Angiographic Characteristics

Coronary angiography was performed in 1941 women (53.0 percent) and 5025 men (59.3 percent, $P < 0.001$). Among the 4638 men and 1768 women for whom angiographic data were available (92.0 percent of the patients who underwent angiography), women in all subgroups were significantly more likely than men to have no severe stenosis (Table 2).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	MYOCARDIAL INFARCTION WITH ST ELEVATION			MYOCARDIAL INFARCTION WITH NO ST ELEVATION			UNSTABLE ANGINA		
	MEN	WOMEN	P VALUE	MEN	WOMEN	P VALUE	MEN	WOMEN	P VALUE
	(N=3134)	(N=997)		(N=2544)	(N=974)		(N=2801)	(N=1690)	
Age — yr			<0.001			<0.001			<0.001
Median	61	69		64	71		64	68	
25th and 75th percentiles	51, 69	62, 76		55, 72	63, 77		54, 71	60, 75	
Black race — %	2.6	3.4	0.17	2.0	4.0	0.001	3.1	4.0	0.13
Hypertension — %	36	54	<0.001	41	59	<0.001	45	57	<0.001
Diabetes — %	14	22	<0.001	17	22	<0.001	17	23	<0.001
Current or former smoker — %	76	46	<0.001	76	40	<0.001	74	38	<0.001
Elevated total cholesterol — %	34	43	<0.001	38	45	0.001	39	47	<0.001
Prior myocardial infarction — %	18	13	0.001	31	24	<0.001	38	27	<0.001
Prior angina — %	46	53	<0.001	68	72	0.08	82	82	0.54
Prior congestive heart failure — %	2.4	4.0	0.005	4.6	9.5	<0.001	6.1	10.2	<0.001
Cerebrovascular disease — %	1.6	2.0	0.42	2.4	4.9	<0.001	2.9	3.4	0.35
Prior bypass surgery — %	5.4	3.5	0.02	11.2	6.5	<0.001	16.6	9.2	<0.001
Prior angioplasty — %	5.8	5.2	0.51	6.8	4.8	0.03	14.4	11.8	0.01
Peripheral vascular disease — %	7.3	6.2	0.26	9.0	6.7	0.03	9.4	7.9	0.09
Heart rate —beats/min			0.008			<0.001			<0.001
Median	74	76		73	80		71	76	
25th and 75th percentiles	63, 85	65, 86		63, 85	68, 90		62, 83	67, 86	
Systolic blood pressure — mm Hg			0.03			<0.001			<0.001
Median	130	132		133	140		138	140	
25th and 75th percentiles	115, 146	115, 150		120, 150	120, 155		120, 150	125, 160	
Killip class — no. (%)			<0.001			<0.001			<0.001
1 (no heart failure)	2793 (89.1)	821 (82.3)		2168 (85.2)	764 (78.4)		2497 (89.1)	1456 (86.2)	
2 (heart failure)	290 (9.3)	140 (14.0)		288 (11.3)	174 (17.9)		239 (8.5)	184 (10.9)	
3 (pulmonary edema)	26 (0.8)	17 (1.7)		41 (1.6)	23 (2.4)		19 (0.7)	24 (1.4)	
4 (cardiogenic shock)	13 (0.4)	9 (0.9)		7 (0.3)	4 (0.4)		1 (0.04)	3 (0.2)	
Unknown	12 (0.4)	10 (1.0)		40 (1.6)	9 (0.9)		45 (1.6)	23 (1.4)	

*Because of rounding, not all percentages total 100. For two patients (one man and one woman) without ST elevation, it was unknown whether they had myocardial infarction at enrollment; these patients have been excluded.

TABLE 2. SEVERITY OF CORONARY ARTERY DISEASE AMONG WOMEN AS COMPARED WITH MEN ACCORDING TO CORONARY SYNDROME AND SEX.*

SEVERITY OF DISEASE	MYOCARDIAL INFARCTION WITH ST ELEVATION			MYOCARDIAL INFARCTION WITH NO ST ELEVATION			UNSTABLE ANGINA		
	MEN	WOMEN	P VALUE	MEN	WOMEN	P VALUE	MEN	WOMEN	P VALUE
	(N=1759)	(N=492)		(N=1299)	(N=450)		(N=1580)	(N=826)	
	no. (%)			no. (%)			no. (%)		
No. of diseased vessels			0.07			0.001			<0.001
0	119 (6.8)	50 (10.2)†		55 (4.2)	41 (9.1)‡		220 (13.9)	252 (30.5)§	
1	820 (46.6)	226 (45.9)		409 (31.5)	147 (32.7)		464 (29.4)	217 (26.3)	
2	469 (26.7)	130 (26.4)		406 (31.3)	130 (28.9)		430 (27.2)	169 (20.5)	
3	351 (20.0)	86 (17.5)		429 (33.0)	132 (29.3)		466 (29.5)	188 (22.8)	

*Because of rounding, not all percentages total 100. Data are shown for the 4638 men and 1768 women for whom angiographic data were available.

†P=0.02 for the comparison with one, two, or three diseased vessels.

‡P=0.001 for the comparison with one, two, or three diseased vessels.

§P<0.001 for the comparison with one, two, or three diseased vessels.

TABLE 3. COMPLICATIONS DURING HOSPITALIZATION.*

COMPLICATION	MYOCARDIAL INFARCTION WITH ST ELEVATION		MYOCARDIAL INFARCTION WITH NO ST ELEVATION		UNSTABLE ANGINA	
	MEN (N=3134)	WOMEN (N=997)	MEN (N=2544)	WOMEN (N=974)	MEN (N=2801)	WOMEN (N=1690)
	percent					
Any bleeding	30	40	25	28	21	24
Moderate or severe bleeding	7.3	15.9	8.1	13.1	8.0	10.9
Any stroke	0.8	1.8	0.9	0.9	0.8	0.5
Hemorrhagic stroke	0.4	0.7	0.1	0.1	<0.1	0.1
Worst Killip class						
1	73	63	72	61	82	77
2	19	25	20	25	15	17
3	4.1	5.9	3.7	7.9	1.9	3.4
4	3.9	6.9	4.0	6.3	1.1	2.0
Acute mitral regurgitation	0.6	1.6	0.7	1.5	0.2	0.2
Sustained hypotension	7.3	11.9	5.1	6.7	1.9	2.7
Atrioventricular block	5.4	7.4	1.7	3.0	1.0	2.0
Sustained ventricular tachycardia	4.3	4.2	1.8	2.4	0.9	0.8
Ventricular fibrillation	4.6	4.6	2.4	2.2	1.2	0.4
Asystole	2.3	3.8	1.8	2.3	0.9	0.8
Electromechanical dissociation	1.3	2.9	1.1	1.7	0.5	0.3
Atrial fibrillation or flutter	8.6	11.0	7.0	10.2	6.0	5.0
Pulmonary edema	6.0	8.5	6.1	11.3	2.4	3.3

*Because of rounding, not all percentages total 100. For two patients (one man and one woman) without ST elevation, it was unknown whether they had myocardial infarction at enrollment; these patients have been excluded.

Complications during Hospitalization

Table 3 shows the complications that occurred during hospitalization. Women were in higher Killip classes than men ($P<0.001$), and they had higher rates of bleeding (29.2 percent vs. 25.6 percent, $P<0.001$). In a model containing only sex, type of acute coronary syndrome, and the interaction between the two terms, female sex was associated with an increased risk of moderate or severe bleeding ($P<0.001$). There was a significant interaction between sex and the type of acute coronary syndrome ($P=0.002$). Women in all three groups had a significantly higher risk of moderate or severe bleeding than men, especially in the group of patients who had infarction with ST elevation (infarction with ST elevation: odds ratio, 2.41; 95 percent confidence interval, 1.94 to 2.99; $P<0.001$; infarction with no ST elevation: odds ratio, 1.72; 95 percent confidence interval, 1.36 to 2.18; $P<0.001$; and unstable angina: odds ratio, 1.42; 95 percent confidence interval, 1.15 to 1.74; $P=0.001$). These differences remained significant after the exclusion of patients who underwent invasive procedures.

In addition, we constructed a model for moderate or severe bleeding, adjusting for the base-line predictors identified by Berkowitz et al.²⁶ We adjusted

for black race, age, weight, pulse, diastolic blood pressure, previous angina, hypertension, anterior location of infarct, current smoking, treatment (desirudin [the current name for hirudin] vs. heparin), Killip class, U.S. center, and the interaction between Killip class and U.S. center. We included treatment at a U.S. center as a variable because it was a significant predictor of moderate or severe bleeding in the GUSTO I trial, possibly because revascularization procedures are used more frequently in the United States than in other countries. However, because the study did not record when bleeding occurred relative to the procedure, this relation could not be verified.

After adjustment for these base-line differences, female sex remained a significant predictor of moderate or severe bleeding ($P=0.04$), with a trend toward significance for the interaction between sex and the type of acute coronary syndrome ($P=0.11$). After adjustment, female sex was associated with moderate or severe bleeding only in the group of patients who had infarction with ST elevation (odds ratio, 1.43; 95 percent confidence interval, 1.12 to 1.83; $P=0.004$). The adjusted rates of moderate or severe bleeding were similar among women and men who had infarction with no ST elevation (odds ratio, 1.04; 95 percent confidence interval, 0.80 to 1.37; $P=0.32$)

or unstable angina (odds ratio, 1.05; 95 percent confidence interval, 0.83 to 1.33; $P=0.43$).

Despite these findings, the rates of stroke did not differ significantly between men and women (0.83 percent vs. 1.0 percent for any stroke and 0.2 percent vs. 0.3 percent for hemorrhagic stroke). Likewise, after stratification according to the type of coronary syndrome, the rates of hemorrhagic stroke were not significantly higher among women than among men, although the small number of hemorrhagic strokes in this population (26) meant that the test had little power to detect significant differences. Rates of hemorrhagic stroke were significantly higher among women with ST elevation than among women in the other two groups.

Outcome in Relation to Sex and Strata

Women had a significantly higher mortality rate at 30 days than did men (6.0 percent vs. 4.0 percent, $P<0.001$) and similar rates of reinfarction (6.2 percent vs. 5.6 percent, $P=0.19$). After adjustment for the base-line differences, the overall rates of death or reinfarction at 30 days were similar for women and men ($P=0.47$). However, when the interaction between sex and the type of coronary syndrome was added to the model, it was significant ($P=0.001$). There was a nonsignificant trend toward a higher risk of death or reinfarction among women as compared with men only in the group with ST elevation (odds ratio, 1.27; 95 percent confidence interval, 0.98 to 1.63; $P=0.07$). The adjusted risk of death or reinfarction at 30 days for women who had infarction with no ST elevation was similar to that for men (odds ratio, 0.93; 95 percent confidence interval, 0.72 to 1.21; $P=0.61$). In the group with unstable angina, female sex was associated with an independent protective effect (odds ratio for death or infarction, 0.65; 95 percent confidence interval, 0.49 to 0.87; $P=0.003$).

DISCUSSION

Multiple studies¹⁻²³ have shown that women with acute ischemic syndromes tend to be older than men with such syndromes and are more likely to have a history of hypertension, diabetes, angina, and congestive heart failure. They are less likely to be smokers and less likely to have had a prior infarction. Our study confirms these findings.

In our trial, the proportion of women with ST elevation was significantly lower than that of men, whereas the proportion of women with unstable angina was significantly higher than that of men. Even after adjustment for base-line differences, women were significantly less likely to present with the syndrome associated with occlusive thrombus — that is, with infarction with ST elevation.

Results from other clinical trials parallel these findings. Trials that examined thrombolytic therapy

in patients who had acute infarction with ST elevation consistently enrolled a smaller percentage of women than did trials that included patients with other acute ischemic syndromes. Only 18 to 25 percent of the patients in these studies were women,¹²⁻¹⁶ percentages remarkably lower than the 34 percent enrolled in the Thrombolysis in Myocardial Infarction (TIMI) III study of patients who presented with unstable angina or non-Q-wave myocardial infarction. In that trial, the ratio of men to women with a non-Q-wave infarction was significantly greater than the ratio of men to women with unstable angina (2.6 vs. 1.7, $P=0.001$). Also consistent with our findings, the Multicenter Investigation of the Limitation of Infarct Size reported that women were more likely than men to have non-Q-wave infarction (46 percent vs. 35 percent, $P<0.05$).¹⁸ The TIMI III investigators cautioned, however, that the sex ratios in clinical trials may be biased, with women more often excluded because of ineligibility for thrombolytic therapy.¹¹

Population-based studies and studies based on hospital registries have reported that the incidence of a first acute infarction is significantly higher among men than among women^{27,28} but that the incidence of angina is greater among women.²⁹ Among patients with a definite infarction, men are significantly more likely than women to have a Q-wave infarction.²³

Studies of sex-based differences among hospitalized patients with acute coronary syndromes consistently demonstrate that among patients who present with symptoms suggestive of cardiac ischemia, myocardial infarction develops in a larger percentage of men than women.^{1,4,29} However, the results of studies reporting the relative ratios of Q-wave to non-Q-wave infarction among men and women who were hospitalized for acute myocardial infarction have not been as uniform.^{2,5,8,9,17,20,29} Differences in study design most likely account for the variability in results; some studies included patients within a specific age range, or performed age-adjusted analyses.^{8,20,22} The results of these investigations suggest that sex-based differences in presentation are significant only among younger patients and are no longer present after adjustment for age.^{8,9,20} The Myocardial Infarction Triage and Intervention registry, however, demonstrated that among patients who were hospitalized for suspected acute infarction, women had confirmed infarction less often, independent of age.¹ These results parallel our findings.

Differences between the sexes in coronary syndromes may relate to differences in thrombotic and fibrinolytic activity³⁰⁻³³ or differences in the extent and severity of coronary disease and the presence of collateral blood flow.^{11,34,35} Our findings of higher rates of clinically insignificant coronary artery disease among women confirm prior reports^{11,34}; 30.5 percent of women with unstable angina did not have

clinically significant stenosis, as compared with 13.9 percent of men. However, the conclusions we can draw are limited, because coronary angiography was not performed in all patients and because it was performed less often in women. The Coronary Artery Surgery Study reported that women had higher rates of angina than men, even when the patients were stratified according to the number of diseased vessels.³⁶

The women in our study were more likely than the men to have congestive heart failure during hospitalization, as was also found in many previous studies.^{1,4,9,13-15,21} This finding may relate to the fact that a higher percentage of women have heart failure or a history of heart failure at presentation, and it may also reflect diastolic dysfunction in women.¹¹

The primary limitation of fibrinolytic therapy is the associated risk of bleeding, including hemorrhagic stroke. Clinical trials examining the efficacy of various thrombolytic regimens have shown that women are at greater risk for bleeding, although the overall benefit is similar to that for men.^{12-15,26,37} We found that the rate of moderate or severe bleeding was higher among women, regardless of the type of coronary syndrome at presentation. There was no difference between men and women in the response to treatment with hirudin or heparin. In a model adjusted for significant base-line predictors, female sex was associated with moderate or severe bleeding only in the group with ST elevation. The fixed dose of heparin that was widely used (a 5000-U bolus, followed by an intravenous infusion of 1000 U per hour) is probably too high for women with low body weight. Weight-adjusted regimens for low-body-weight patients are now used more widely.^{38,39}

We found that the crude rates of ischemic events, including death and nonfatal infarction, at 30 days were significantly higher for women than men. However, the relative outcomes for women as compared with men differed depending on the type of coronary syndrome at presentation. After adjustment for differences in base-line variables, the 30-day event rate among women with infarction and ST elevation was only marginally higher than that among men; the rate among women who had infarction with no ST elevation was the same as that among men, and women with unstable angina had fewer events than men.

Previous studies have also reported that women with acute myocardial infarction have higher in-hospital and short-term mortality rates than do men.^{1-5,7,8,12-18,21} Studies of women and men with unstable angina or infarction without ST elevation, however, have demonstrated similar outcomes, despite the fact that the women were older and had more coexisting conditions than the men.¹¹ After adjustment for such differences, many studies^{1-5,8,12,14-16} have concluded that sex is not an independent predictor of mortality after acute myocardial infarction. However, some studies have reported a higher risk of death among women

that was independent of base-line variables.^{7,9,13,16,17,22} The variability in results probably reflects the mixed populations studied, with differing percentages of patients with non-Q-wave and Q-wave infarction. We compared sex-based differences in outcome for each acute coronary syndrome, a design that enabled us to determine the outcome in a well-defined population.

Because differences between men and women in the risk of death and nonfatal infarction were evident in patients with unstable angina and infarction with ST elevation and were independent of base-line variables, other factors are likely to have influenced the prognosis. Differences in underlying anatomy or pathophysiology^{11,30-35} or in the rates of referral for diagnostic testing and revascularization^{2,34} may influence outcome; we found that women had lower rates of coronary angiography and were less likely to have clinically significant coronary artery stenosis. The latter finding may explain the better outcome for women with unstable angina, but it did not seem to affect the outcomes for women with myocardial infarction. Perhaps reduced collateral blood flow in women³⁵ accounts for the higher rate of complications when total coronary occlusion (infarction with ST elevation) occurs. It would also explain the finding of a higher rate of angina with less extensive coronary disease among women. Further research is needed to determine which factors account for the significant differences in outcome.

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REFERENCES

1. Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction: results from the Myocardial Infarction Triage and Intervention Registry. *Arch Intern Med* 1992;152:972-6.
2. Chiriboga DE, Yarzebski J, Goldberg RJ, et al. A community-wide perspective of gender differences and temporal trends in the use of diagnostic and revascularization procedures for acute myocardial infarction. *Am J Cardiol* 1993;71:268-73.
3. Fiebach NH, Viscogli CM, Horwitz RI. Differences between women and men in survival after myocardial infarction: biology or methodology? *JAMA* 1990;263:1092-6.
4. Robinson K, Conroy RM, Mulcahy R, Hickey N. Risk factors and in-hospital course of first episode of myocardial infarction or acute coronary insufficiency in women. *J Am Coll Cardiol* 1988;11:932-6.
5. Kostis JB, Wilson AC, O'Dowd K, et al. Sex differences in the management and long-term outcome of acute myocardial infarction: a statewide study. *Circulation* 1994;90:1715-30.
6. Clarke KW, Gray D, Keating NA, Hampton JR. Do women with acute myocardial infarction receive the same treatment as men? *BMJ* 1994;309:563-6.
7. He J, Klag MJ, Whelton PK, Zhao Y, Weng X. Short- and long-term prognosis after acute myocardial infarction in Chinese men and women. *Am J Epidemiol* 1994;139:693-703.
8. Ditttrich H, Gilpin E, Nicod P, Cali G, Henning H, Ross J Jr. Acute myocardial infarction in women: influence of gender on mortality and prognostic variables. *Am J Cardiol* 1988;62:1-7.
9. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1524 women after myocardial infarction: comparison with 4315 men. *Circulation* 1991;83:484-91.

10. Behar S, Gottlieb S, Hod H, et al. Influence of gender in the therapeutic management of patients with acute myocardial infarction in Israel. *Am J Cardiol* 1994;73:438-43.
11. Hochman JS, McCabe CH, Stone PH, et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. *J Am Coll Cardiol* 1997;30:141-8.
12. Stone GW, Grines CL, Browne KF, et al. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 1995;75:987-92.
13. Weaver WD, White HD, Wilcox RG, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. *JAMA* 1996;275:777-82.
14. Lincoff AM, Califf RM, Ellis SG, et al. Thrombolytic therapy for women with myocardial infarction: is there a gender gap? *J Am Coll Cardiol* 1993;22:1780-7.
15. White HD, Barbash GI, Modan M, et al. After correcting for worse baseline characteristics, women treated with thrombolytic therapy for acute myocardial infarction have the same mortality and morbidity as men except for a higher incidence of hemorrhagic stroke. *Circulation* 1993;88:2097-103.
16. Becker RC, Terrin M, Ross R, et al. Comparison of clinical outcomes for women and men after acute myocardial infarction. *Ann Intern Med* 1994;120:638-45.
17. Kober L, Torp-Pedersen C, Ottesen M, Rasmussen S, Lessing M, Skagen K. Influence of gender on short- and long-term mortality after acute myocardial infarction. *Am J Cardiol* 1996;77:1052-6.
18. Tofler GH, Stone PH, Muller JE, et al. Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. *J Am Coll Cardiol* 1987;9:473-82.
19. Vacek JL, Rosamond TL, Kramer PH, et al. Sex-related differences in patients undergoing direct angioplasty for acute myocardial infarction. *Am Heart J* 1993;126:521-5.
20. Demirovic J, Blackburn H, McGovern PG, Luepker R, Sprafka JM, Gilbertson D. Sex differences in early mortality after acute myocardial infarction (the Minnesota Heart Survey). *Am J Cardiol* 1995;75:1096-101.
21. Puletti M, Sunseri L, Curione M, Erba SM, Borgia C. Acute myocardial infarction: sex related differences in prognosis. *Am Heart J* 1984;108:63-6.
22. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women. *Am J Cardiol* 1996;78:9-14.
23. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985-1991: presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. *Circulation* 1996;93:1981-92.
24. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;335:775-82.
25. Harrell FE Jr. Transcan: S function for transformation and imputation using canonical variates. 1996. (See <http://lib.stat.cmu.edu>.) (See NAPS document no. 05526 for 12 pages, c/o microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.)
26. Berkowitz SD, Granger CB, Pieper KS, et al. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation* 1997;95:2508-16.
27. Weinblatt E, Shapiro S, Frank CW. Prognosis of women with newly diagnosed coronary heart disease — a comparison with course of disease among men. *Am J Public Health* 1973;63:577-93.
28. Murabito JM, Evans JC, Larson MG, Levy D. Prognosis after the onset of coronary heart disease: an investigation of differences in outcome between the sexes according to initial coronary disease presentation. *Circulation* 1993;88:2548-55.
29. Cunningham MA, Lee TH, Cook EF, et al. The effect of gender on the probability of myocardial infarction among emergency department patients with acute chest pain: a report from the Multicenter Chest Pain Study Group. *J Gen Intern Med* 1989;4:392-8.
30. Conlan MG, Folsom AR, Finch A, et al. Associations of factor VIII and von Willebrand factor with age, race, sex, and risk factors for atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *Thromb Haemost* 1993;70:380-5.
31. Tracy RP, Bovill EG, Fried LP, et al. The distribution of coagulation factors VII and VIII and fibrinogen in adults over 65 years: results from the Cardiovascular Health Study. *Ann Epidemiol* 1992;2:509-19.
32. Stegner M, Pentek M. Fibrinolytic response to venous occlusion in healthy subjects: relationship to age, gender, body weight, blood lipids and insulin. *Thromb Res* 1993;69:81-92. [Erratum, *Thromb Res* 1993;72:173.]
33. Cucuianu M, Lanczek M, Roman S. Plasminogen activator inhibitor (PAI) in obese men and obese women. *Rom J Intern Med* 1993;31:183-92.
34. Krumholz HM, Douglas PS, Lauer MS, Pasternak RC. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? *Ann Intern Med* 1992;116:785-90.
35. Johansson S, Bergstrand R, Schlossman D, Selin K, Vedin A, Wilhelmsson C. Sex differences in cardioangiographic findings after myocardial infarction. *Eur Heart J* 1984;5:374-81.
36. Davis KB, Chaitman B, Ryan T, Bittner V, Kennedy JW. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS Registry study: Coronary Artery Surgery Study. *J Am Coll Cardiol* 1995;25:1000-9.
37. Malacrida R, Genoni M, Maggioni AP, et al. A comparison of the early outcome of acute myocardial infarction in women and men. *N Engl J Med* 1998;338:8-14.
38. Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Clinical practice guideline number 10. Rockville, Md.: Agency for Health Care Policy and Research, 1994. (AHCPR publication no. 94-0602.)
39. Hochman JS, Wali AU, Gavrilu D, Sim MJ, Malhotra S, Palazzo AM. An improved regimen for heparin use in acute coronary syndromes. *Am Heart J* (in press).