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Outcome and Profile of Women and Men Presenting With Acute Coronary Syndromes: A Report From TIMI IIIB

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Objectives. **Women and men enrolled in the Thrombolysis in Myocardial Infarction (TIMI) IIIB trial of unstable angina and non–Q wave myocardial infarction (MI) were evaluated to determine gender differences in characteristics and outcome.**

Background. **Coronary heart disease is the leading cause of death for women and men. However, the characteristics and outcome of women compared with men with unstable angina and non–Q wave MI have not been extensively studied.**

Methods. **The characteristics, outcomes and proportion of 497 women and 976 men with unstable angina and non–Q wave MI at the time of enrollment were compared. When these proportions were noted to be significantly different, we compared them with the 7,731-patient TIMI IIIB Registry, which represents the nontrial, screened population with these syndromes at these centers.**

Results. **For both coronary syndromes, women were older, were less frequently white, had a higher incidence of diabetes and hypertension and were receiving more cardiac medications. The 42-day rate of death and MI in TIMI IIIB was similar for women and men (7.4% vs. 7.5%). Coronary angiography revealed less severe coronary artery disease for women than for men, with absence of critical obstructions in 25% versus 16% and mean ejection fractions 62 ± 12% versus 57 ± 13% for women versus men ($p < 0.01$). Medical management failed in women as often as in men, and rates of cardiac catheterization and percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery were similar for women and men in the conservative strategy arm as well as in the invasive strategy arm. Women in the TIMI IIIB trial had proportionately more unstable angina than did men. The proportion of unstable angina and non–Q wave MI for women was similar in the trial and Registry. However, proportionately more men in the trial had non–Q wave MI than men in the Registry.**

Conclusions. **1) Women with each acute coronary syndrome are older than men and have more comorbidity. 2) The outcome with unstable angina and non–Q wave MI is related to severity of illness and not gender. 3) Mortality associated with revascularization for unstable angina and non–Q wave MI was similar for women and men. 4) The proportion of women and men enrolled with each acute coronary syndrome is different. These rates reflect both the prevalence of disease and selection bias owing to trial eligibility criteria and other identified factors.**

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Coronary heart disease (CHD) is the leading cause of mortality and morbidity in the United States today in both women and men. At any given age, the prevalence of CHD is greater in men than in women. Nonetheless, many recent reports have concluded that women with CHD have a worse prognosis than men with this disease (1–4). Gillum (5), using data from the Centers for Disease Control and Prevention National Center for Health Statistics, recently reported that the age-adjusted death rates from ischemic heart disease decreased from 1980 to 1990 much more for men than for women. Several studies have reported that there is an unequal distribution in the use of resources between women and men, implying that the observed differences in outcome may in part relate to resource utilization. Women have been reported to undergo cardiac catheterization and consequently revascularization procedures less often than men (6–8). In addition, the results of revascularization procedures have been reported to be less favorable in women than in men (9–13).

More than 1.4 million patients are admitted to the hospital each year in the United States with a diagnosis of an acute coronary syndrome, either acute Q wave myocardial infarction

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Abbreviations and Acronyms

APTT	=	activated partial thromboplastin time
CABG	=	coronary artery bypass graft surgery
CAD	=	coronary artery disease
CHD	=	coronary heart disease
CI	=	confidence interval
MI	=	myocardial infarction
OR	=	odds ratio
PTCA	=	percutaneous transluminal coronary angioplasty
TIMI IIIB	=	Thrombolysis in Myocardial Infarction IIIB trial
t-PA	=	tissue-type plasminogen activator

(MI), non–Q wave MI or unstable angina. Although there are many reports on acute Q wave MI, the characteristics and outcome of women and men with unstable angina and non–Q wave MI have not been compared. This data base study examined the following questions: 1) Are there differences in the frequency with which women and men present with unstable angina and non–Q wave MI? 2) Is the higher mortality observed in women compared with men with Q wave MI (14) observed for the other acute coronary syndromes? 3) Are baseline characteristics of women and men with unstable angina and non–Q wave MI different? And 4) if so, might these differences explain any observed differences in outcome?

Methods

The Thrombolysis in Myocardial Infarction (TIMI) IIIB trial enrolled patients diagnosed with unstable, rest angina and non–Q wave MI. Enrolled were 1,425 men and women <76 years old with an episode of ischemic pain at rest lasting at least 5 min but not longer than 6 h and with objective evidence of ischemic heart disease (15). For a brief period, the trial's upper age limit was raised to 79 years for men and women. Forty-eight patients between 76 and 79 years old were enrolled. Patients were excluded if they had undergone previous coronary artery bypass graft surgery (CABG), had undergone percutaneous transluminal coronary angioplasty (PTCA) within 6 months, had experienced an MI within the preceding 21 days, were in cardiogenic shock, had a contraindication to thrombolytic therapy or heparin, were receiving oral anticoagulants or had left bundle branch block or a coexistent severe illness.

All enrolled patients received conventional medical therapy consisting of oxygen, bed rest and antianginal medications, including beta-adrenergic blocking agents, calcium antagonists, nitrates and heparin to maintain the activated partial thromboplastin time (APTT) at 1.5 to 2 times the patient's baseline value. Aspirin was to be started on day 2 at a dose of 325 mg/day.

Seven hundred twenty-nine patients were randomized to receive tissue-type plasminogen activator (t-PA) in a front-loaded, reduced dose regimen of heparin and aspirin, and 744 patients were to receive heparin and aspirin alone. Patients were also randomized to early invasive or early conservative strategy, resulting in 740 patients assigned to the early invasive strategy and 733 patients assigned to the early conservative strategy. Patients assigned to the early invasive strategy underwent cardiac catheterization and angiography at 18 to 48 h, followed by revascularization if anatomically suitable, whereas patients assigned to the early conservative strategy underwent cardiac catheterization and angiography only if spontaneous or provoked ischemia occurred.

To further evaluate our observation that women in the TIMI IIIB trial had proportionately more unstable angina than men, we compared the ratios of men and women with unstable angina and non–Q wave MI in the randomized trial to those from the nontrial screened population in the TIMI III Registry (16) at these centers.

Study end points. The primary end point for the t-PA and placebo comparison was "unsatisfactory outcome," defined as the occurrence of either death, nonfatal MI after randomization or failure of initial therapy measured at the 6-week visit (42 to 70 days) after randomization. Failure of initial therapy included rest angina with electrocardiographic (ECG) changes as previously described (15), silent ischemia on Holter monitoring, an early positive exercise treadmill test or a high risk thallium scan at hospital discharge and an early positive exercise treadmill test, unstable angina requiring rehospitalization or Canadian Cardiovascular Society class III or IV at the 6-week visit. Adverse events, major hemorrhage and stroke were also evaluated. The TIMI IIIB trial results have been previously reported (15).

Statistical considerations. The distribution of baseline characteristics and clinical course variables were compared by gender using the chi-square test for categoric data and the *t* test for continuous variables. Event rates were estimated using the Kaplan-Meier method (17), and comparisons among survival distributions were accomplished using the log-rank statistic (18).

The Mantel-Haenszel statistic (19) was used to perform statistical comparisons of binary attribute data by gender while controlling for study or patient group within the study. The Breslow-Day statistic (20) was used to test whether gender odds ratios are consistent among study or patient groups. Gender analyses for polychotomous data were performed using polychotomous logistic regression, with terms for gender, study and gender–study interaction included in the model.

Continuous variables were compared by gender and study using general linear models (21). Terms for interactions and main effects were included in each model. Comparisons of time to event variables between men and women, while adjusting for patient group, were performed using the Cox proportional hazards model (22), with terms for main effects (gender and study group) and interactions included in the model.

Because of the large numbers of statistical comparisons performed in TIMI IIIB, $p < 0.01$ was considered to provide some evidence for an association, and $p < 0.001$ to provide strong evidence of an association.

Information from TIMI IIIB was also compared to corre-

sponding information from the TIMI III Registry. The Registry is composed of two parts: an enumeration roster and a prospective study. The enumeration roster was used to identify all patients with unstable angina or non–Q wave MI entering 18 hospitals that also participated in TIMI IIIB and to collect selected information on these patients. The prospective study was performed on a subgroup of the enumeration roster patients. The purpose of this study was to collect more detailed information on the history and clinical course of unstable angina and non–Q wave MI in this subgroup. A process of direct adjustment was used to compare the Registry patients with the TIMI IIIB group. For each variable collected in the prospective study, the age-race-gender specific percentage (or mean) was calculated. These specific percentages or means were then combined into one summary measure using the method of direct adjustment. The details of this method have been presented previously (16).

Results

Patient group. *Baseline characteristics in TIMI IIIB.* Of the 1,473 patients enrolled in TIMI IIIB, 497 (34%) were women and 976 (66%) were men; 364 (37%) of 993 patients with unstable angina and 132 (28%) of 477 patients with non–Q wave MI were women. The male/female ratio was higher for those patients with non–Q wave MI (2.6) than for those with unstable angina (1.7) ($p = 0.001$). The male/female ratio for the 7,731 *screened* patients <76 years old in the TIMI III Registry at 18 hospitals that participated in both TIMI IIIB and the Registry (17) was similar for patients with non–Q wave MI (1.36) and unstable angina (1.63). The ratio of unstable angina to non–Q wave MI for women and men in the randomized trial, TIMI IIIB, was compared to the TIMI IIIB Registry. Only patients <76 years old are included because TIMI IIIB excluded patients over this age (see Methods section). The ratio of unstable angina to non–Q wave MI for women was the same in the trial (3.03) and registry (2.97), demonstrating that this ratio for women in the trial reflects the prevalence of each syndrome in hospitalized women. For men, however, there were significant differences in the ratio (1.96 vs. 3.55, respectively) ($p < 0.0001$), apparently due to larger numbers of men with non–Q wave MI in the TIMI IIIB trial. Overall, women were more often excluded than men from the trial owing to contraindications to thrombolytic therapy (odds ratio [OR] 1.17, 95% confidence interval [CI] 1.0 to 1.37, $p = 0.05$).

A p value for gender differences is shown to indicate the differing prevalence of the characteristic in women and men (Table 1). Women were older, were less frequently white, had a higher incidence of risk factors and were receiving more cardiac medications, but they had a lower incidence of previous MI. At the time of entry into TIMI IIIB, women experienced the same frequency and duration of ischemic episodes as men. Although women exhibited ST segment depression or ST segment elevation on the ECG as often as men did in TIMI IIIB, T wave inversion was significantly more common in women with unstable angina than in men with the same condition. Coronary disease, as evidenced by a previous MI or a significant stenosis on a previous angiogram, was less often observed in women in TIMI IIIB. There was a trend toward less aspirin use in women than in men in the 24 h before the ischemic event ($p = 0.028$).

Outcome of men versus women: non–Q wave MI and unstable angina. The overall rate of MI and death at 42 days was similar for women and men in TIMI IIIB. Although women with non–Q wave MI in TIMI IIIB had a higher event rate than men (9.8 vs. 7.5), this was not statistically different, despite the fact that women were significantly older. The 42-day event rate in patients with unstable angina was similar for the two groups (6.6% for women vs. 7.5% for men). In TIMI IIIB, an unsatisfactory outcome (death, MI or spontaneous or inducible ischemia) at the 6-week visit occurred in 54% of women and 54% of men assigned to receive t-PA. For women assigned to placebo, the event rate for unsatisfactory outcome was 53%, similar to the placebo event rate of 57% in men (p = NS). For the end point components making up an unsatisfactory outcome, spontaneous ischemia was the most frequent end point and was seen in 29% of women and 27% of men. Holter monitoring and treadmill exercise testing revealed abnormalities in a similar percentage of women and men. However, women were less likely to have a positive high risk exercise thallium scan (12.7% for women vs. 20.6% for men, $p < 0.001$). The outcome profiles for women and men with each syndrome in TIMI IIIB—unstable angina and non–Q wave MI—were similar, except for the lower likelihood of a positive high risk exercise thallium scan for women, as noted. The profiles and rates of unfavorable outcome were similar for women and men in each treatment group.

The failure of therapy profile in women with unstable angina and non–Q wave MI in TIMI IIIB was the same as that in men in both the early invasive and conservative strategy arms (Table 2). The components of failure of therapy were also similar in the two strategies and by gender (Table 2).

Predictors of outcome at 6 weeks for unstable angina and non–Q wave MI. A multivariate Cox regression model was used to test the association of 50 baseline variables with the end point of death or MI through 42 days. Gender did not relate to outcome for patients with either non–Q wave MI or unstable angina ($p = 0.767$ and $p = 0.463$, respectively) or for the combination (i.e., all TIMI IIIB patients). Increasing age was associated with death or MI for patients with non–Q wave MI ($p < 0.001$), and ST segment depression was prognostically important for both women and men with unstable angina (OR 2.03, 99% CI 1.09 to 3.80, $p = 0.004$). Similarly, the occurrence of an unsatisfactory outcome (death, nonfatal MI or spontaneous or inducible ischemia) was compared for women and men in each of three age groups: <55, 55 to 64 and >64 years old. Of the 493 patients <55 years old, an unsatisfactory outcome occurred in 47% (54 of 115) of women compared with 50% (188 of 378) of men; 51% (92 of 179) of women and 55% (181 of 329) of men 55 to 64 years old; and 59% (120 of 203) of women and 63% (170 of 269) of men >64 years of age.

Table 1. TIMI IIIB Patients: Comparison of Baseline Characteristics by Gender

	Men (N = 976)			Women (N = 497)			
	N	n	% (mean)	N	n	% (mean)	p Value*
Age (yr)							
<55	976	378	38.7	497	115	23.1	—
55–64	976	329	33.7	497	179	36.0	—
≥65	976	269	27.6	497	203	40.8	0.000
Mean	976	—	(57.6)	497	—	(61.2)	0.000
Race (white)	976	808	82.8	497	366	73.6	0.000
Past medical history							
History of smoking	976	73.1	74.9	497	284	57.1	0.000
Diabetes mellitus	527	62	11.8	255	52	20.4	0.001
Hypertension	965	338	35.0	492	277	56.3	0.000
Family history of CAD	929	365	39.3	483	207	42.9	0.195
History of angina	976	831	85.1	497	429	86.3	0.545
History of MI	976	444	45.5	497	153	30.8	0.000
Medications in previous week							
Nitrates	976	442	45.3	497	257	51.7	0.020
Beta-blockers	976	309	31.7	497	192	38.6	0.008
Calcium channel blockers	976	405	41.5	497	223	44.9	0.216
Aspirin <24 h before event	976	487	49.9	497	218	43.9	0.028
Heparin	976	137	14.0	497	85	17.1	0.120
Diuretic agents	976	114	11.7	497	128	25.8	0.000
ACE inhibitors	976	79	8.1	497	69	13.9	0.000
Presenting illness							
Number of episodes of pain in last 24 h	976	—	(3.1)	497	—	(3.1)	0.966
Length of qualifying episode of pain (h)	906	—	(1.9)	467	—	(2.0)	0.773
Time from pain to treatment (h)	967	—	(9.1)	483	—	(9.1)	0.918
Admission criteria							
ST segment elevation	975	102	10.5	497	49	9.9	0.719
ST segment depression	974	305	31.3	497	175	35.2	0.132
T wave changes	974	419	43.0	497	264	53.1	0.000
Previous angiogram with stenosis	974	349	35.8	497	134	27.0	0.001

*Value derived from chi-square or F test statistic comparing distributions among the two groups. ACE = angiotensin-converting enzyme; CAD = coronary artery disease; MI = myocardial infarction; N = total number of patients evaluated; n = number of patients with attribute.

Thus, the overall event rates rose consistently with age, but within the age groups no significant differences were observed in the rate of unsatisfactory outcome between women and men.

Incidence of stroke and hemorrhagic events. In TIMI IIIB, the incidence of intracranial hemorrhage in patients treated with a reduced dose of t-PA was 0.40% for women and 0.63% for men (p = NS). The overall rate of any type of stroke at 8 days was similar—0.8% for women and 0.6% for men—as were the two major spontaneous hemorrhagic event rates (1.8% vs. 1.3%).

Coronary angiographic findings in TIMI IIIB. Protocol design specified that all patients randomized to the early invasive strategy undergo cardiac catheterization. This was performed in 99% of women and 98% of men. The presence and extent of coronary artery disease (CAD), defined as ≥60% stenosis in one or more major arteries, was significantly different in women than in men. More women than men did not have a critical obstruction (25% vs. 16%), and women had multivessel CAD less often than men (37% vs. 47%) ($p < 0.005$ for CAD gender differences) (Table 3). The percent stenosis in the culprit artery and TIMI flow grade were similar for women and men. Preserved left ventricular systolic function, as measured by an ejection fraction >55% was more common in women than in men (74% vs. 56%, $p < 0.01$). The mean ejection fraction for women was 62 ± 12%, for men 57 ± 13% ($p < 0.01$). Patients assigned to the early conservative strategy were to undergo cardiac catheterization after the occurrence of an unsatisfactory outcome. Because of the similarity in the occurrence of unsatisfactory outcome in men and women, it is not surprising that a similar percentage (61% of women vs. 65% of men) assigned to the conservative strategy underwent cardiac catheterization (p = NS).

Revascularization procedures in men and women. There was a smaller percentage of women receiving CABG in TIMI IIIB (19% vs. 27%, $p < 0.001$), presumably because of the lower incidence of multivessel disease. Similar differences were observed in both the invasive strategy and conservative strategy. Overall, PTCA was performed equally in women and men (33% and 32%, respectively) both in the invasive and conservative strategies.

The most important *independent* predictors of the performance of revascularization in the invasive arm were race (with blacks undergoing revascularization less frequently), the pres-

Table 2. Failure of Therapy Profile at 6 Weeks for Men and Women by Strategy and Non–Q Wave Myocardial Infarction Status: TIMI IIIB

	Non–Q Wave MI				Unstable Angina				All Patients			
	Men		Women		Men		Women		Men		Women	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Invasive strategy												
Death	6	3.4	3	4.0	7	2.3	2	1.2	13	2.6	5	2.0
MI	8	4.5	2	2.7	19	6.1	9	5.2	27	5.5	11	4.4
Positive 6-week ETT	9	5.0	6	8.0	29	9.3	16	9.2	39	7.9	22	8.8
No end point	156	87.2	64	85.3	256	82.3	146	84.4	412	83.9	211	84.7
p value*				0.7				0.2				0.8
Conservative strategy												
Death	5	3.0	6	10.5	2	0.6	5	2.6	7	1.4	11	4.4
MI	8	4.8	2	3.5	21	6.6	11	5.8	29	6.0	13	5.2
Positive 6-week ETT	15	9.0	5	8.8	29	9.1	19	9.9	44	9.1	24	9.7
No end point	138	83.1	44	77.2	266	83.6	156	81.7	405	83.5	200	80.6
p value*				0.817				0.294				0.095

*Value obtained from a chi-square statistic comparing the distribution between the groups. ETT = exercise treadmill test; MI = myocardial infarction.

ence of ST segment depression and ST segment elevation and the number of diseased vessels (all $p < 0.01$). Independent predictors of revascularization in the conservative strategy included race, with blacks undergoing PTCA or CABG less frequently; history of angina; use of heparin at time of study entry; and presence of ST segment depression on the qualifying ECG (all $p < 0.002$). Gender, when forced into both of these analyses, did *not relate* to performance of revascularization when all other variables were taken into account.

For all patients undergoing PTCA by hospital discharge (invasive and conservative strategies, 150 women and 294 men), the occurrence of a complication—death, MI, stroke or CABG at 42 days after performance of PTCA—was similar for women and men (9.3% vs. 8.5%, $p = 0.77$) (23). For all patients in the conservative and invasive strategies, the mortality rate at 42 days for women undergoing CABG was 8.5% compared with 2.2% for men ($p = 0.05$). Because there were only seven deaths after CABG, results of multivariate analysis to assess the effect of age, body surface area and other variables are unreliable.

Discussion

Coronary heart disease is the leading cause of death of women in the United States, accounting for more than one-third of all deaths. Only recently has intense interest been focused on the diagnosis of and factors related to the outcome of women with this disease. Most clinical trials have enrolled primarily men, and the results have generally been extrapolated to women. Furthermore, observations made in the recent past suggest that such extrapolation of specific results found in men may not be appropriate (8,24,25).

Among the 1.4 million hospital admissions for acute coronary syndromes each year in the United States, unstable angina and non–Q wave MI are responsible for more than 750,000 admissions. The TIMI IIIB trial is the largest randomized trial

Table 3. TIMI IIIB Patients Who Had Invasive Strategy: Comparison of Angiographic Findings by Gender

	Men (N = 491)			Women (N = 249)			
	N	n	% (mean)	N	n	% (mean)	p Value*
Angiographic data							
No. vessels with stenosis ≥60%							
0	475	75	15.8	245	60	24.5	
1	475	178	37.5	245	94	38.4	
2	475	141	29.7	245	67	27.3	
3	475	81	17.1	245	24	9.8	0.005
Ejection fraction							
<35%	457	23	5.0	242	3	1.2	
35–55%	457	178	38.9	242	60	24.8	
>55%	457	256	56.0	242	179	74.0	0.000
Mean	457	—	(56.8)	242	—	(62.0)	0.000
Stenosis in culprit artery	324	—	(84.7)	157	—	(83.2)	0.253
Culprit lesion flow grade	308	—	(2.2)	148	—	(2.4)	0.047

*Values derived from a chi-square or F test statistic comparing distributions among the two groups. Abbreviations as in Table 1.

performed to date, enrolling both men and women with unstable angina and non–Q wave MI. The design of the trial focused on the management of patients with these syndromes and called for the same strategy to be used in men and women. Therefore, the outcomes observed in this trial for men and women are less likely to be related to possible treatment bias. In addition, the number of women enrolled in TIMI IIIB was large enough to allow for statistical comparison, which was not the case for most other investigations. Extensive clinical and angiographic data were collected.

At presentation, women were older and had more hypertension and diabetes. During the week before study enrollment, women were more often treated with nitrates, beta-blockers and calcium channel blockers than were men, and there was a trend ($p < 0.02$) for them to be treated less often with aspirin during this period. Lower rates of aspirin use in women were noted in the Survival and Ventricular Enlargement (7) and Determinants of Myocardial Infarction Onset Study (Muller J, personal communication, 1996). This may be the result of the mistaken concept that women do not derive benefit from aspirin. The meta-analysis on aspirin use for CHD (26) demonstrated clear benefit for women as well as men.

Outcomes for men and women in TIMI IIIB. The occurrence of major events—death or MI—was similar for men and women in TIMI IIIB. This was seen even though women less often had a previous MI, better left ventricular function and less extensive coronary disease, each of which should have correlated with a better outcome. The older age and greater prevalence of diabetes and hypertension among women may have counterbalanced the other more favorable characteristics. However, other pathophysiologic differences between men and women may help explain the similar outcome, despite less coronary disease and better ventricular function in women. In fact, the presence of other gender differences is suggested by the greater risk-adjusted rate of death for women with ST segment elevation and Q wave MI in other studies (2,16,27,28). These findings may result from gender differences in the balance of prothrombotic and antithrombotic forces (29–37). Less collateral blood flow has been reported for women (38), which could explain the finding in TIMI IIIB and other studies of more anginal symptoms and more antianginal medication use in women despite their less severe CAD. It would also explain the increased occurrence of certain complications of acute MI in women that may relate to more extensive transmurality of the infarction, such as cardiogenic shock and cardiac rupture (39–43).

For both women and men, the most important clinical variables predictive of outcome in TIMI IIIB were age and the presence of ST segment depression. Our results are similar to the Veterans Administration study on unstable angina (44) of men only, which identified similar variables as predictive of outcome. These clinical factors should prove useful in developing reasonable management strategies for physicians caring for patients of either gender with unstable angina and non–Q wave MI. Women with ST segment deviation have a greater likelihood of sustaining a MI or reinfarction or dying than those with no ECG changes or with T wave inversion. Furthermore, the success rate of PTCA was high, and there was a low complication rate in women. Therefore, a reasonable strategy for women as well as men is early cardiac catheterization and revascularization for those who have ST segment deviation on the ECG at presentation.

In TIMI IIIB, which used a reduced dose of t-PA, there was no difference in the rate of intracranial hemorrhage between men and women. This is in contrast to TIMI II (14), the International Tissue Plasminogen Activator/Streptokinase Mortality trial (45) and Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GUSTO) (27), which all reported increased bleeding complications in women treated with full-dose thrombolytic agents (46). Further investigation of weight- or size-adjusted doses of thrombolytic agents and adjunctive anticoagulant agents is needed.

Angiography and revascularization. It is interesting that one of four women who met strict criteria for rest angina and ECG changes or previous documented disease had no significant obstructive coronary disease. This is consistent with the finding that syndrome X and variant angina are more common in women than in men (47). The relative importance of fixed coronary stenoses, abnormalities in vasodilator reserve and abnormalities in coronary tone with or without vasospasm as the etiology of exertional and rest ischemia in women is the subject of current investigation.

The utilization of resources by women compared with men has been the focus of many recent reports (6–8,48–51). The TIMI IIIB protocol mandated coronary angiography in 50% of the patients assigned to that strategy. It revealed less extensive coronary disease in women, which is consistent with the findings of the Coronary Artery Surgery Study (CASS) of patients with chronic stable angina (52). Preserved left ventricular function was also seen more often in women in TIMI IIIB and is also consistent with a report from the Survival and Ventricular Enlargement (7) and CASS (52) trials.

In the early conservative strategy, coronary angiography and revascularization were required only if the therapy failed the patient. Women and men assigned to this strategy underwent cardiac catheterization at the same rates, reflecting that initial management failed women and men at similar rates and that there was no gender referral bias. The severity of the presenting illness and coronary anatomy, rather than gender, were the predictors of revascularization. Revascularization procedures were performed at similar rates for men and women in both the invasive and early conservative strategy arms. Coronary artery bypass graft surgery was less often performed in women, because they had less multivessel CAD and more often preserved left ventricular function compared with men.

Relation of men to women across the acute coronary syndromes. The comparison of unstable angina and non–Q wave MI between men and women could potentially offer insight into gender differences in the mode of presentation of patients hospitalized with CHD. There was a greater proportion of women with unstable angina (37%) than with non–Q

wave MI (28%) in the TIMI IIIB randomized trial. The similarly designed TIMI II trial for patients treated with thrombolytic agents for MI with ST segment elevation reported an even lower proportion of women (18%) (14). The GUSTO trial, which had no upper age limit, and an overview of large thrombolytic trials showed similar low percentages (24%) of women (27,53). Women are excluded from thrombolytic administration more often than men, and this is both due to older age and other factors independent of age (54–57). This was also reported in a population study from Minnesota, where women <75 years old received thrombolytic agents less often than did men (35% vs. 45%) ($p < 0.05$), including those with ST segment elevations and no obvious contraindication to thrombolysis (74% vs. 85%, $p = 0.09$) (56). A review of the TIMI III Registry confirmed that women were more often excluded from the randomized trial (TIMI IIIB) than men owing to contraindications to thrombolytic therapy. Recent comparisons in other thrombolytic trials with no upper age limit demonstrated that women comprised only 22% of the trial cohort, compared with 37% of the nontrial cohort (56). Nevertheless, a recent report from a study of the Glasgow population confirmed that women with cardiac events more often have nonspecific ST-T segment changes and probable MI, and men more often have definite Q wave MI (57). These and our data strongly suggest that the proportion of women enrolled with different acute coronary syndromes (i.e., MI with ST segment elevation, non–Q wave MI and unstable angina) reflects both the differential rates of each syndrome in men and women *and* selection factors affecting enrollment in clinical trials that require thrombolytic eligibility. The TIMI III Registry more accurately represents the true proportion of male and female patients with unstable angina and non–Q wave MI hospitalized for these syndromes. Lower overall proportions of women enrolled in TIMI IIIB compared with the TIMI III Registry (16) are explained by these selection factors, an upper age limit and ineligibility to receive a thrombolytic agent. However, the greater proportion of women with unstable angina compared with non–Q wave MI in the trial, compared with those age <76 years old in the Registry, is not readily explained. The similar ratio of unstable angina to non–Q wave MI for women in the trial compared with the Registry, but the lower ratio of unstable angina to non–Q wave MI for men in the trial compared with the Registry, may indicate that a disproportionate number of men with non–Q wave MI were enrolled, not that women with non–Q wave MI were excluded.

Conclusions. The TIMI IIIB trial is the largest study to date to examine the differences and similarities between women and men with unstable angina and non–Q wave MI. We conclude that 1) the proportion of women and men enrolled with each of the two acute coronary syndromes—unstable angina and non–Q wave MI—differed, which appears to reflect disproportionate enrollment of men with non–Q wave MI; 2) women with each acute coronary syndrome are significantly older than men and have more comorbidity; 3) the outcome of women with unstable angina and non–Q wave MI is similar to that of men and is related to the severity of illness rather than to gender itself; and 4) women undergoing revascularization for unstable angina and non–Q wave MI have a mortality rate similar to that of men.

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