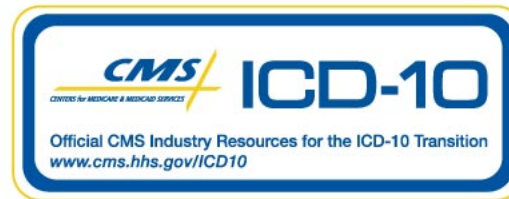


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From Acute Coronary Syndromes**

Sonia S. Anand, Chang Chun Xie, Shamir Mehta, Maria Grazia Franzosi, Campbell Joyner, Susan Chrolavicius, Keith A.A. Fox, Salim Yusuf, for the CURE Investigators

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Differences in the Management and Prognosis of Women and Men Who Suffer From Acute Coronary Syndromes

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OBJECTIVES	The purpose of this research was to determine if sex and gender differences in the management of acute coronary syndromes (ACS) are associated with differences in prognosis after ACS.
BACKGROUND	Previous investigators have reported sex/gender differences in the management of patients with ACS, but the impact of these differences on prognosis is unclear.
METHODS	We analyzed data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which enrolled 4,836 women and 7,726 men with ACS. Patients were classified into risk strata using the Thrombolysis In Myocardial Infarction (TIMI) score.
RESULTS	Women underwent fewer invasive procedures including angiography, angioplasty, and coronary artery bypass graft (CABG) surgery (47.6% vs. 60.5%; $p = 0.0001$) compared to men. No significant differences in cardiovascular death, myocardial infarction (MI), or stroke were observed (9.8% vs. 10.9%; $p = 0.04$), although women were more likely than men to develop refractory ischemia and to be rehospitalized for chest pain during follow-up (16.6% vs. 13.9%; $p = 0.0001$). These differences were particularly evident among TIMI high-risk women. A significant interaction between TIMI risk and gender for the outcome of refractory angina and rehospitalization for angina was present.
CONCLUSIONS	Compared to men, high-risk women with ACS undergo less coronary angiography, angioplasty, and CABG surgery, and while they do not have higher incidence cardiovascular death, recurrent MI, or stroke, they suffer an increased rate of refractory ischemia and rehospitalization. All high-risk women and men with ACS should receive optimal medical management, and be considered for coronary angiography with possible revascularization if their coronary anatomy warrants it. (J Am Coll Cardiol 2005;46:1845–51) © 2005 by the American College of Cardiology Foundation

Coronary heart disease is the single leading cause of death and is a significant cause of morbidity among women in North America (1). Acute coronary syndromes (ACS) represent a continuum of acute myocardial ischemia and

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include acute transmural myocardial infarction (MI) with ST-segment elevation, MI without ST-segment elevation (NSTEMI), and unstable angina (UA). On its own, NSTEMI/UA is a significant cause of morbidity and mortality and is associated with a 10% to 15% rate of death or MI at one year (2); NSTEMI/UA accounts for more

than 1.5 million hospitalizations annually in the U.S., and nearly 50% of these admissions occur among women (1).

Over the past decade, investigators have reported on sex/gender differences among patients with ACS (3–7). This research is fuelled by beliefs that biological differences influence the pathogenesis of coronary artery disease (CAD) and the response to medical therapies (sex differences), as well as a perception that women's access to medical therapy and cardiac procedures such as cardiac catheterization, angioplasty, and bypass surgery is inappropriately restricted (gender differences) (3,8,9). Prior investigators have reported that women with ACS receive fewer invasive cardiac procedures compared to men, although it remains unclear if this affects their prognosis after ACS. To address this issue, we compared the management of ACS patients among women and men to determine if sex/gender differences were associated with prognosis after ACS in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which enrolled 4,836 women and 7,726 men (10).

METHODS

We conducted a post-hoc analysis of data from the CURE trial. Details of the CURE trial have been reported previously (10). Briefly, the trial enrolled men and women who

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Abbreviations and Acronyms

ACS	= acute coronary syndrome
CABG	= coronary artery bypass graft
CAD	= coronary artery disease
CURE	= Clopidogrel in Unstable Angina to Prevent Recurrent Events
MI	= myocardial infarction
NSTEMI	= non-ST-segment elevation myocardial infarction
PTCA	= percutaneous transluminal coronary angioplasty
TIMI	= Thrombolysis In Myocardial Infarction
UA	= unstable angina

presented within 24 h of symptoms onset with ACS, including UA and NSTEMI as previously described (10). Patients with contraindications to antithrombotic/antiplatelet therapy, who were at high risk of bleeding, who had severe heart failure (class IV), who had an ongoing long-term need for oral anticoagulants, and who had percutaneous transluminal coronary angioplasty (PTCA)/stent, or coronary artery bypass graft (CABG) within three months before randomization were excluded. Patients were recruited between December 1998 and September 2000 from 482 centers in 28 countries. The protocol was approved by the institutional review board of each hospital, and all patients provided written informed consent.

Clinical outcomes. All primary and secondary efficacy and safety outcomes for the trial were adjudicated by an independent panel of clinicians who were blinded to the treatment allocation. Cardiovascular death was defined as any death for which there was no clearly documented nonvascular cause. Myocardial infarction was defined as the presence of at least two of the following: ischemic chest pain; elevation of the serum levels of cardiac markers or enzymes (troponin, creatine kinase, creatine kinase-MB isoenzyme, or other cardiac enzymes) to at least twice the upper limit of the normal, or three times the upper limit of normal within 48 h after percutaneous coronary intervention; and electrocardiographic (ECG) changes compatible with infarction. Stroke was defined as a new focal neurologic deficit of vascular origin lasting more than 24 h. Refractory angina was defined using stringent criteria, specifically a patient must have severe anginal chest pain in the hospital lasting more than 5 min associated with new ECG changes while the patient was receiving optimal medical therapy leading to an additional intervention such as thrombolytic therapy, cardiac catheterization, the insertion of an intra-aortic balloon pump, coronary revascularization, or transfer to a referral hospital for an invasive procedure by midnight of the next calendar day. Refractory ischemia after hospital discharge was defined by rehospitalization for UA lasting for at least 24 h and associated with ischemic ECG changes (10). Invasive cardiac procedures including coronary angiography, PTCA, and CABG since randomization were also recorded. Angiographers recorded which vessels were sig-

nificantly diseased, and the corresponding percent stenoses. Stenoses in significantly sized branches defined as >2 mm in diameter were recorded under the major vessel from which they originated. Significant CAD was defined as triple-vessel disease (defined as $>50\%$ stenosis in the proximal or mid/distal left anterior descending, circumflex, and right coronary artery) or left main stenosis $>50\%$. Follow-up assessments occurred at discharge, at 1 month, and then every 3 months for a maximum of 12 months or a minimum of 3 months (mean 9 months).

Statistical considerations. Baseline characteristics, medical and coronary interventions, and clinical outcomes were compared between women and men. For comparisons of continuous variables, linear regression was used, and for comparisons of categorical values, logistic regression was used. Patients were stratified by risk status using the previously validated Thrombolysis In Myocardial Infarction (TIMI) risk score, which includes clinical, ECG criteria, and biochemical factors (11). Multivariable models were constructed to determine the predictive value of gender and procedure use on clinical outcomes, with gender, TIMI score, and the interaction between gender \times TIMI score used as independent variables. Comparisons between women and men were adjusted for differences in baseline factors, which influence clinical outcomes including age, diabetes, smoking status, history of cardiovascular disease, cardiac enzyme/troponin abnormality, geographic region (because intervention rates vary significantly by region) (12), and treatment allocation (i.e., clopidogrel vs. placebo). To avoid spurious findings in the face of multiple statistical comparisons, statistical significance was declared when p values were <0.01 .

RESULTS

Baseline characteristics. A total of 12,562 patients were enrolled in the trial: 4,836 women and 7,726 men. Women were older, and had higher age-adjusted rates of diabetes, hypertension, and elevated cholesterol compared to men. Men were more likely to be smokers, and have a prior history of MI, peripheral arterial disease, and stroke compared to women. The average time from symptom onset to presentation was similar, although women were more likely to have an abnormal ECG at presentation, and men were more likely to have abnormal cardiac enzymes. Approximately 15% of women and men were classified as "high-risk" by the TIMI score (Table 1).

Medical treatments received. At hospital presentation, no differences in the use of aspirin, statins, or beta-blockers between women and men were observed, although women were more likely to be taking angiotensin-converting enzyme inhibitors, and 7% of women were taking hormone replacement therapy. During the initial hospitalization, the use of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitor medications increased significantly among all patients. However, during the hospitaliza-

Table 1. Baseline Characteristics*

	Women	Men	Significance
Number	4,836	7,726	
Age, yrs (SD)	66.5 (10.7)	62.7 (11.4)	0.0001
BMI, kg/m ² (SD)	27.6 (4.5)	27.3 (3.9)	0.0001
Diabetes (%)	24.6	20.9	0.0001
Hypertension (%)	68.8	53.0	0.0001
Current or former smoker (%)	37.4	76.4	0.0001
Hypercholesterolemia (%)	48.7	44.3	0.0001
History of MI (%)	23.9	36.9	0.0001
History of PAD (%)	5.8	9.0	0.0001
History of stroke (%)	3.0	4.1	0.0008
Prior PTCA with or without stent (%)	7.2	11.5	0.0001
Prior CABG surgery (%)	6.8	13.3	0.0001
Other evidence of CAD including chronic stable angina (%)	46.2	43.8	0.01
History of any CVD† (%)	59.0	63.7	0.0001
Time from symptoms onset to hospital presentation (h)	14.0	14.2	0.17
Abnormal ECG at presentation‡ (%)	95.3	92.8	0.0001
Cardiac enzyme or troponin abnormality (%)	18.8	29.3	0.0001
Congestive heart failure on admission (%)	1.2	1.3	0.43
Length of initial hospitalization (days)	10.7	10.1	0.0001
TIMI risk score (mean = 1.77)—low§	26.2	26.0	0.77
TIMI risk score (mean = 3.49)—moderate§	58.3	58.0	0.74
TIMI risk score (mean = 5.22)—high§	15.5	16.0	0.43

*Age-adjusted mean and proportions using linear or logistic regression; †defined as prior MI, PTCA, CABG, other CAD, stroke, or PAD; ‡defined as significant ST-segment abnormality (depression ≥ 1 mm, elevation ≤ 1 mm, transient ST-segment elevation > 2 mm) or T-wave inversion; §not age-adjusted as age is included in the definition of the Thrombolysis In Myocardial Infarction (TIMI) score.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CVD = cardiovascular disease; MI = myocardial infarction; PAD = peripheral arterial disease; PTCA = percutaneous transluminal coronary angioplasty.

tion and at the time of discharge, women were less likely to be treated with beta-blockers compared to men (Table 2). This difference persisted throughout the follow-up period (data not shown).

Invasive procedures. Coronary angiography was performed among significantly fewer women compared to men during the initial hospitalization (adjusted rates: 25.4% vs. 29.5%; $p = 0.0001$), and over the course of the nine months of follow-up (14.0% vs. 16.0%, $p = 0.006$) (Table 3). Among those who had angiography, women were more likely to have normal coronary vessels (26.7% vs. 13.2%, $p = 0.0001$), and less likely to have significant CAD (34.9% vs. 44.7%, $p = 0.00001$) compared to men. Subsequently,

significantly fewer women underwent PTCA or CABG surgery, although among women and men who were identified as having significant CAD on angiography, the proportion of patients who underwent PCTA or CABG was similar (69.2% vs. 72.7%, $p = 0.10$) (Table 3). No difference in the incidence of cardiovascular death, recurrent MI, or stroke was observed at 30 days (4.4% vs. 4.9%, $p = 0.23$) or at the end of follow-up (approximately 9 months) (9.7% vs. 11.1%, $p = 0.04$) between women and men. However, compared to men, significantly more women had refractory ischemia during the index hospitalization and were rehospitalized for UA during the course of follow-up (16.6% vs. 13.9%, $p = 0.0002$) (Table 3).

Table 2. Medication Use

	Presentation	In-Hospital	Discharge
Aspirin (%)			
Women	65.8	99.7	95.7
Men	66.6	99.8	95.6
HMG-CoA reductase inhibitor (%)			
Women	25.3	45.8	48.2
Men	25.4	47.3	50.0
Beta-blocker (%)			
Women	58.1	77.0†	68.4*
Men	59.1	79.6	73.1
ACE inhibitor (%)			
Women	41.3†	50.3	46.5
Men	37.8	51.2	47.8

Adjusted for age, diabetes, hypertension, smoking status, hypercholesterolemia, prior myocardial infarction, prior history of cardiovascular disease. Women versus men: * $p < 0.001$, † $p < 0.01$.

ACE = angiotensin-converting enzyme.

Table 3. Procedures and Clinical Outcomes

	Women	Men	Significance
n	4,836	7,726	
Angiography (overall) (%)	39.4	45.5	p = 0.0001
In-hospital (%)	25.4	29.5	p = 0.0001
Out of hospital (%)	14.0	16.0	p = 0.006
No diseased vessels (%)	499 (26.7)	480 (13.2)	p = 0.00001
Significant coronary artery disease by angiography (triple-vessel disease or left main >50%) (%)	652 (34.9)	1,621 (44.7)	p = 0.00001
Angioplasty or CABG (%)	29.8	40.4	p = 0.0001
Angioplasty or CABG among patients with significant coronary artery disease (%)	451/652 (69.2%)	1,178/1,621 (72.7%)	p = 0.10
CV death, MI, stroke at 30 days (%)*	4.4	4.9	p = 0.23
CV death, MI, stroke at end of follow-up (%)*	9.7	11.1	p = 0.04
Refractory angina or rehospitalization for angina (%)*	16.6	13.9	p = 0.0002
CVD, MI, stroke, refractory angina, or rehospitalization (%)*	23.6	22.5	p = 0.19

*Adjusted for: age, diabetes, smoker, history of any cardiovascular (CV) disease, cardiac enzyme/troponin abnormality, region, and treatment allocation. Use of 50% cut-off for stenosis as definition for "diseased." *Triple-vessel disease \geq 50% stenosis in proximal or mid-/distal left anterior descending coronary artery, circumflex, right coronary artery, excluding left main >50%. Region = North America, South America/Mexico, Western Europe, Eastern Europe, Australia/New Zealand, South Africa.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CVD = cardiovascular disease; MI = myocardial infarction; PAD = peripheral arterial disease; PTCA = percutaneous transluminal coronary angioplasty.

Risk stratification. Patients were stratified into low-, intermediate-, and high-risk categories using the previously validated TIMI risk score. As expected, with increasing risk, the rate of cardiovascular death, MI, stroke, and refractory

coronary ischemia increased significantly among all patients; surprisingly, however, the rate of coronary angiography did not differ. Across all risk strata, angiography rates were significantly lower among women compared to men.

Table 4. Gender Differences in Invasive Procedures and Clinical Outcomes by TIMI Risk

	TIMI Low	TIMI Intermediate	TIMI High	Significance Women vs. Men
Angiography				
Women	538/1,268 (42.4%)	1,042/2,818 (37.0%)	286/750 (38.1%)	p < 0.001 within each risk strata
Men	987/2,008 (49.2%)	2,074/4,479 (46.3%)	564/1,239 (45.5%)	
Significant coronary artery disease on angiography				
Women	95/538 (17.6)	383/1,042 (36.7)	174/286 (60.8)	p < 0.00001 in low and intermediate strata, p = 0.68 in high stratum
Men	289/987 (29.2)	997/2,074 (48.1)	335/564 (59.4)	
PTCA or CABG among those with significant coronary disease				
Women	73/95 (76.8)	265/383 (69.2)	113/174 (64.9)	p _{low} = 0.31; p _{mod} = 0.17; p = 0.97
Men	235/289 (81.3)	725/997 (72.7)	218/335 (65.1)	
Refractory (in-hospital) or rehospitalization for chest pain (adjusted for treatment allocation, region)				
Women	148/1,268 (11.7%)	463/2,818 (16.4%)	179/750 (23.9%)	p = 0.73 for low, p = 0.02 for intermediate, p < 0.0001 for high-risk stratum, p interaction = 0.0001
Men	231/2,008 (11.5%)	679/4,479 (15.2%)	189/1,239 (15.3%)	
CV death, MI, stroke by end of follow-up (adjusted for treatment allocation, region)				
Women	55/1,268 (4.3%)	288/2,818 (10.2%)	146/750 (19.5%)	p = 0.11 for low-, p = 0.35 for intermediate-, p = 0.40 for high-risk
Men	107/2,008 (5.3%)	486/4,479 (10.8%)	219/1,239 (17.8%)	
CV death, MI, stroke or refractory ischemia (adjusted for treatment allocation, region)				
Women	193/1,268 (15.2%)	681/2,818 (24.2%)	273/750 (36.4%)	p = 0.54 for low-, p = 0.24 for intermediate-, p = 0.0009 for high-risk
Men	322/2,006 (16.0%)	1,056/4,479 (23.6%)	360/1,239 (29.1%)	

CABG = coronary artery bypass graft surgery; CV = cardiovascular; MI = myocardial infarction; mod = moderate; PTCA = percutaneous transluminal coronary angioplasty; TIMI = Thrombolysis In Myocardial Infarction.

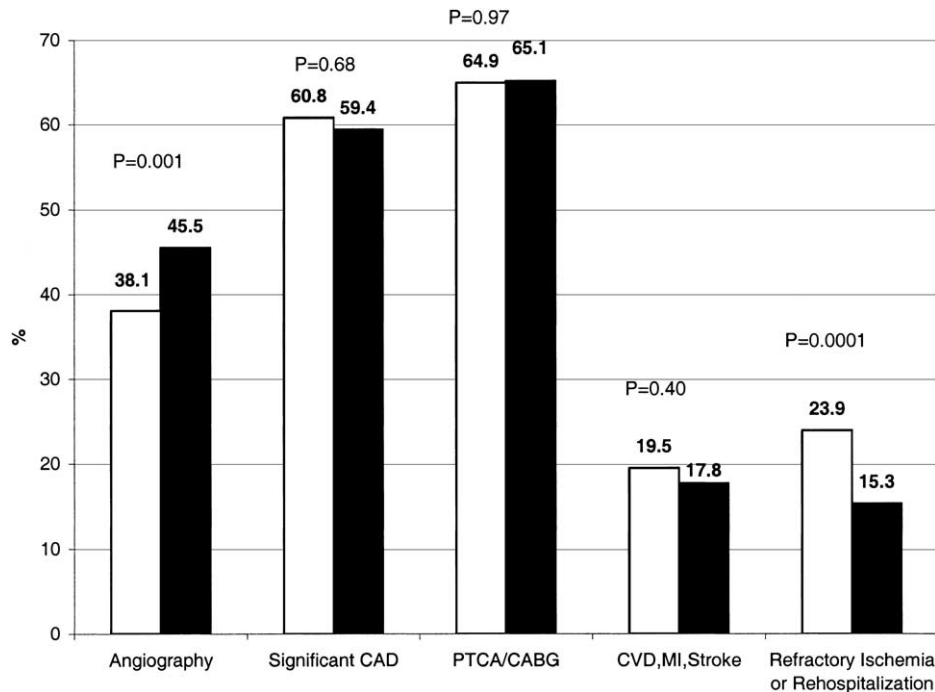


Figure 1. High-risk acute coronary syndrome patients. **Open bars** = women; **solid bars** = men. Significant coronary artery disease (CAD) by angiography indicates triple-vessel disease or left main disease. * $p < 0.005$. CABG = coronary artery bypass graft surgery; CVD = cardiovascular disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Among low- and moderate-risk patients, women were less likely to have significant CAD on angiography compared to men, whereas among high-risk patients, women had a similar proportion of “significant” coronary disease compared to men (60.8% vs. 59.4%; $p = 0.68$), and the rates of PTCA or CABG surgery among those with significant CAD were similar (64.9% vs. 65.1%; $p = 0.97$) (Table 4). The incidence of cardiovascular death, MI, stroke was not increased among high-risk women compared to men (19.5% vs. 17.8%; $p = 0.40$), but the incidence of refractory angina

and rehospitalization for chest pain during follow-up was significantly higher (23.9% vs. 15.3%; $p = 0.0001$) (Fig. 1, Table 4). A significant interaction between the TIMI risk strata and gender for the outcome of refractory angina and rehospitalization was present ($p_{\text{interaction}} = 0.0001$) (Fig. 2).

DISCUSSION

Our findings demonstrate that, after ACS, women are less likely to undergo angiography, PTCA, and CABG compared to men, and while they have no differences in cardiovascular death, MI, or stroke, they do suffer an increased rate of refractory angina and rehospitalization for UA. This is especially true among high-risk women.

Our study is consistent with the results of previous investigators who have reported that, compared with men, women with NSTEMI/UA are generally older, have more comorbidities at the time of presentation, and undergo fewer coronary interventions (13–15). However, the lower rate of invasive cardiac procedures has not been convincingly linked to differences in prognosis after the acute coronary episode, nor has it been linked to any systematic biases (5,7,13–15). Explanations for the differences in the rates of coronary invasive procedures between women and men are multiple, and include differences in the presentation of ACS (e.g., reporting of typical versus atypical symptoms) (3), patient preferences to undergo invasive cardiac procedures (8,16–18), and physician practices in the referral of women for cardiac catheterization (8).

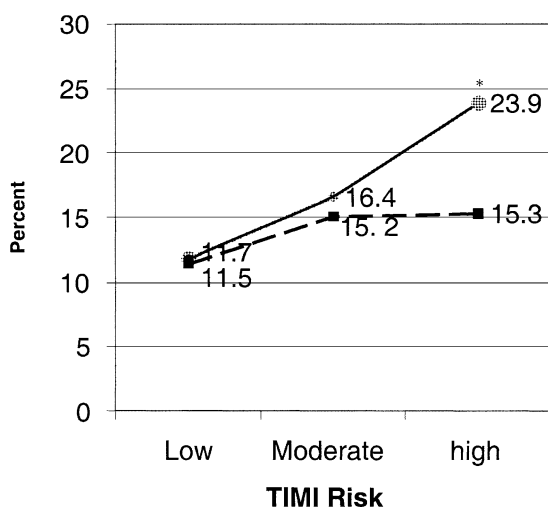


Figure 2. Refractory ischemia and rehospitalization by gender and Thrombolysis In Myocardial Infarction (TIMI) risk. Adjusted for treatment allocation and region. **Solid line** = women; **dashed line** = men. *Note: p for interaction between TIMI risk and gender = 0.001.

Our analysis differs from previous reports because it includes the largest number of women enrolled into an ACS clinical trial to date ($n = 4,836$); it includes patients from a broad representation of countries (e.g., North and South America, and Europe), and it examines procedure use and prognosis according to the TIMI risk score. Surprisingly in the CURE trial cohort, the decision to perform angiography was *not* linked to the risk status of patients, and in all risk groups women were less likely to have angiography. Among women who did undergo angiography, those in the low- or moderate-risk TIMI categories were less likely to have significant CAD, whereas women in the high-risk stratum had a similar proportion of significant CAD compared to men. The lower angiography rates among high-risk women likely “underidentified” women with significant CAD who required coronary revascularization, and this difference in angiography may be particularly important to address given that high-risk women suffered a significantly higher incidence of refractory angina and rehospitalization for ACS over the long-term compared to men (Fig. 2). However, it is not clear from existing clinical trials whether an early invasive strategy is as beneficial in reducing hard clinical outcomes such as death and MI among women as it is among men.

Recently, subgroup analyses of the Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC)-2 ($n = 749$ women) (13) and Randomized Intervention Trial of unstable Angina (RITA)-3 ($n = 648$ women) (14) randomized clinical trials reported worsened outcomes among women who underwent invasive management of ACS, which has raised doubt as to whether the management approach toward women and men should be similar. The results from these trials conflict with the more recent Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial report ($n = 757$ women) in which women appeared to benefit as much as men from an early invasive strategy (32% risk reduction in death and MI; $p = 0.02$), especially women with elevated troponin T levels at baseline (15). This is supported by the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines Quality Improvement Initiative (CRUSADE) prospective registry of 17,926 ACS patients from 248 U.S. hospitals in which women who were 14% less likely to receive early invasive management after ACS had a significantly higher in-hospital mortality (no early invasive vs. early invasive: 8.9% vs. 4.7%) (19). Whether the differences observed across studies reflect differences in the clinical characteristics of women, differences in health system approaches to the treatment of men and women with ACS, retrospective methodology, or the unreliable nature of subgroup analyses remains unclear. Despite the fact that our trial included the largest number of women enrolled into an ACS trial to date ($n = 4,836$), an examination of the reasons for sex/gender differences is limited because detailed

information regarding presentation, symptoms, center characteristics (i.e., cath lab facilities), changes in risk factors and medication use over time, referral patterns, and patient preferences was not collected. The only way to definitively determine if differences in early intervention rates between women and men with NSTEMI/UA, including those at high risk, are associated with differences in their long-term prognosis, especially hard outcomes such as cardiovascular death, MI, and stroke, is to randomize women to different intervention strategies and collect long-term follow-up data.

The medical management of men and women with ACS appears to be equivalent as the use of aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors increased significantly during the initial hospitalization among all patients in our trial, although significantly fewer women were prescribed beta-blockers at the time of discharge compared to men. This may be appropriate given that fewer women had suffered from a previous MI. More women were taking angiotensin-converting enzyme inhibitors at the time of admission, which is likely due to the greater proportion of women with diabetes, who were on angiotensin-converting enzyme inhibitors for renal protection. In the CURE trial, the risk reduction with clopidogrel was not significantly heterogeneous between women compared to men. This is consistent with data for a number of other pharmacologic treatments that indicate that antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering therapies clearly reduce the risk of future vascular events by approximately a quarter in both women and men (20). Therefore, as the incidence of cardiovascular death, MI, and stroke was between three to four times greater among high-risk patients compared to low-risk patients in our trial, it appears especially important that all high-risk patients—men *and* women—receive optimal medical management, and are considered for coronary angiography with possible revascularization when their coronary anatomy warrants it (15,20,21).

Conclusions. Compared to men, high-risk women with ACS undergo less coronary angiography, angioplasty, and CABG surgery, and while they do not have higher incidence CV death, recurrent MI, or stroke, they suffer an increased rate of refractory ischemia and rehospitalization. All high-risk women and men with ACS should receive optimal medical management, and be considered for coronary angiography with possible revascularization if their coronary anatomy warrants it.

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