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Gender Disparities in the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes

Large-Scale Observations From the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative

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OBJECTIVES We hypothesized that significant disparities in gender exist in the management of patients with non–ST-segment elevation (NSTE) acute coronary syndromes (ACS).

BACKGROUND Gender-related differences in the diagnosis and treatment of ACS have important healthcare implications. No large-scale examination of these disparities has been completed since the publication of the revised American College of Cardiology/American Heart Association guidelines for management of patients with NSTE ACS.

METHODS Using data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative, we examined differences of gender in treatment and outcomes among patients with NSTE ACS.

RESULTS Women (41% of 35,875 patients) were older (median age 73 vs. 65 years) and more often had diabetes and hypertension. Women were less likely to receive acute heparin, angiotensin-converting enzyme inhibitors, and glycoprotein IIb/IIIa inhibitors and less commonly received aspirin, angiotensin-converting enzyme inhibitors, and statins at discharge. The use of cardiac catheterization and revascularization was higher in men, but among patients with significant coronary disease, percutaneous revascularization was performed in a similar proportion of women and men. Women were at higher risk for unadjusted in-hospital death (5.6% vs. 4.3%), reinfarction (4.0% vs. 3.5%), heart failure (12.1% vs. 8.8%), stroke (1.1% vs. 0.8%), and red blood cell transfusion (17.2% vs. 13.2%), but after adjustment, only transfusion was higher in women.

CONCLUSIONS Despite presenting with higher risk characteristics and having higher in-hospital risk, women with NSTE ACS are treated less aggressively than men. (J Am Coll Cardiol 2005;45: 832–7) © 2005 by the American College of Cardiology Foundation

Cardiovascular disease, primarily coronary heart disease, is the leading cause of death for women. In 2001, women comprised 53.6% (n = 498,863) of all deaths from cardiovascular disease (1). Although advances in the diagnosis and treatment of acute coronary syndromes (ACS) have resulted in a decrease in coronary heart disease mortality during the course of the last decade among men, the death rate among women continues to increase, and more women than men have died of cardiovascular disease in every year since 1984 (1). Furthermore, women have higher rates of recurrent myocardial infarction (MI) and age-adjusted mortality after their first MI (2). Thirty-eight percent of women who have

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Abbreviations and Acronyms

ACC	= American College of Cardiology
ACS	= acute coronary syndromes
AHA	= American Heart Association
CRUSADE	= Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines
GP	= glycoprotein
MI	= myocardial infarction
NSTE	= non–ST-segment elevation

an MI die within one year compared with 25% of men. Within six years of an MI, 35% of women will have another MI, sudden cardiac death will claim the lives of 6%, and 46% will be disabled with heart failure (1).

Most of the literature regarding the diagnosis and management of coronary heart disease and ACS is supported by studies performed in predominantly male populations. Although several recent studies raised concerns about differing responses to some therapies among male and female subgroups (3–5), other studies have challenged these findings (6–8), and for most therapies, the weight of evidence supports use in both women and men (9).

The American College of Cardiology (ACC) and the American Heart Association (AHA) recently published updated guidelines for the management of patients with unstable angina and non–ST-segment elevation (NSTE) MI, the two conditions that collectively make up NSTE ACS (9). The recommendations contained in the guidelines are "gender-neutral," but no large-scale assessment of gender disparity has been undertaken since their release. We hypothesized that, despite widely disseminated guidelines for the treatment of these patients, gender differences would still exist.

The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative is designed to track adherence to guidelines, provide feedback about performance, and develop quality-improvement tools to improve adherence to guidelines recommendations. In this analysis, we used the CRUSADE data to perform the first large-scale, practice-based examination of gender disparities in the diagnosis and treatment of patients with NSTE ACS. Data from the CRUSADE initiative revealed that women are treated very differently than men, and we suggest reasons and potential solutions for these differences.

METHODS

Patient population. Data from 40,912 patients presenting with NSTE ACS at 391 U.S. hospitals participating in the CRUSADE initiative between March 31, 2000, and December 31, 2002, were available at the time of this analysis. Specifics of the CRUSADE initiative's educational efforts and quality-improvement goals have been described elsewhere (10). Briefly, the CRUSADE initiative collects demographic, diagnostic, treatment, and in-hospital outcome data on patients who meet the diagnostic criteria of high-risk NSTE ACS (ischemic symptoms at rest lasting for at least 10 min within 24 h before presentation and high-risk features, including ST-segment depression ≥0.5 mm, transient ST-segment elevation 0.5 to 1.0 mm [lasting for <10 min], and/or positive cardiac markers [elevated troponin I or T and/or creatine kinase-myocardial band > upper limit of normal for the local laboratory assay]). Treatment patterns and compliance with the ACC/AHA guidelines are collected by each site and aggregated in a central database. Individual site performance on selected quality indicators in NSTE ACS care, national norms, and the 10th and 90th percentiles are provided rapidly to individual sites to quantify their performance and to facilitate their quality-improvement efforts.

Statistical methods. The goal of our analysis was to explore the relations of gender, the use of guideline-recommended in-hospital care, and in-hospital clinical outcomes. Patients excluded from this analysis included those who were transferred to another hospital, which resulted in incomplete information on baseline and discharge therapy use and in-hospital outcomes (3,210 men and 1,827 women), and patients with missing gender status (n = 66). In determining the frequency of use of each guidelines-recommended medication, only patients without documented contraindications to a given medication were considered eligible to receive that medication and were included in the denominator (10). Our final analysis population included 35,875 individuals.

Patient characteristics, care patterns, and outcomes were compared between men and women. We reported medians (25th, 75th percentiles) for continuous variables and frequencies for categorical variables. Wilcoxon rank-sum and chi-square tests were used to evaluate gender differences in continuous and categorical variables, respectively.

In examining the relationships between a patient's gender and care patterns and outcomes, we adjusted for variables collected in the CRUSADE registry as described previously (11). These variables included baseline patient clinical risk factors, including age, body mass index, race, family history of coronary artery disease, hypertension, diabetes, smoking status, hypercholesterolemia, previous MI, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous congestive heart failure, previous stroke, renal insufficiency, ST-segment depression, transient ST-segment elevation, positive cardiac markers, signs of congestive heart failure, heart rate, systolic blood pressure, and insurance status, as well as for provider and hospital characteristics (physician specialty; total number of hospital beds; region of the country; presence of cardiac catheterization, coronary intervention, and bypass surgery facilities; and type of hospital—academic or nonacademic). Generalized estimating equation models were used to adjust for

Table 1. Baseline Clinical Characteristics

Variable	Overall (N = 35,875)	Male (n = 21,323)	Female (n = 14,552)
Age (yrs)	68.0 (56.0, 78.0)	65.0 (54.0, 76.0)	73.0 (61.0, 82.0)
Body mass index (kg/m^2)	27.6 (24.3, 31.7)	27.8 (24.8, 31.5)	27.3 (23.4, 32.1)
Family history of coronary artery disease (%)	37.0	38.4	34.9
History of hypertension (%)	69.7	66.2	74.8
Diabetes (%)	32.6	30.6	35.6
Insulin-dependent diabetes mellitus (%)	12.1	10.3	14.7
Non–insulin-dependent diabetes mellitus (%)	21.7	21.3	22.2
Current/recent smoker (%)	27.9	32.0	21.8
Hypercholesterolemia (%)	47.1	48.8	44.5
Previous myocardial infarction (%)	32.0	34.0	29.2
Previous percutaneous coronary intervention (%)	22.4	24.5	19.3
Previous coronary artery bypass grafting (%)	21.0	24.7	15.6
Previous congestive heart failure (%)	19.0	16.2	23.2
Previous stroke (%)	11.0	10.0	12.6
Renal insufficiency (%)	13.9	13.8	14.0
Presenting characteristics			
ST-segment depression (%)	41.4	40.4	42.9
Transient ST-segment elevation (%)	10.5	11.1	9.5
Positive cardiac marker (%)	86.6	87.7	84.8
Signs of congestive heart failure (%)	22.7	19.8	26.9

Age and body mass index are presented as median (25th, 75th percentile).

correlations among clustered responses (e.g., within-hospital correlations because patients within a single hospital are more likely to be similar) (12). For all tests, differences were considered significant at $p < 0.05$. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics. Among the 35,875 patients included in our analysis, 14,552 (41%) were women. Women were significantly older than men and smoked less often, had hyperlipidemia, or had a family history of coronary artery disease but more often had diabetes and hypertension (Table 1). Fewer women had a history of MI, percutaneous coronary intervention, or coronary artery bypass grafting. More women presented with a history of congestive heart failure and with active signs of congestive heart failure on presentation. Women were less likely to be cardiac marker-positive or to have transient ST-segment elevation but more often had ST-segment depression at presentation, although these differences were small.

Treatment patterns. Women were less likely to have an electrocardiogram (ECG) performed within 10 min of hospitalization presentation (25.2% vs. 29.3% for men) and were less commonly cared for by a cardiologist during the inpatient hospitalization (53.4% vs. 63.4% for men).

Treatment disparities were present for women with both acute (within 24 h) and discharge medications (Table 2). After adjustment, women were less likely to receive acute heparin and acute angiotensin-converting enzyme inhibitors. In addition, regardless of troponin results, women were less often treated acutely with glycoprotein (GP) IIb/IIIa inhibitors. Similar treatment patterns existed for discharge medication use, as women were significantly less likely to receive aspirin, angiotensin-converting enzyme inhibitors, and statins compared with men (Table 2).

Table 3 shows differences in the use of procedures. Men more frequently underwent diagnostic catheterization, whereas women were more likely to undergo stress testing. Revascularization procedures were performed less frequently in women. However, the likelihood of percutaneous coronary intervention was similar among men and women who underwent diagnostic catheterization (adjusted odds ratio 0.97; 95% confidence interval 0.91 to 1.03) and among those who were found to have significant coronary disease (>70% obstruction in one, two, or three major epicardial coronary vessels) during catheterization (adjusted odds ratio 1.04; 95% confidence interval 0.98 to 1.12).

Clinical outcomes. The frequencies of unadjusted adverse outcomes were higher in women compared with men (Table 4). However, after adjustment, only the risk of red blood cell transfusion was higher in women.

DISCUSSION

Using the CRUSADE data, we are able to provide the first large-scale, contemporary examination of the diagnosis and treatment of patients with NSTE ACS across the U.S. since the revision of the ACC/AHA guidelines for the management of patients with NSTE ACS. Despite the widespread, multidisciplinary dissemination of this evidence-based consensus document, most accepted treatments remain underused in this high-risk patient population. In our study, we found that although women with NSTE ACS are at higher risk for unadjusted adverse clinical outcomes during hospitalization, they less often received guidelines-recommended therapy than men. Several differences were noted in both

Table 2. Use of Medical Treatment by Gender With Odds Ratios for Use in Women Relative to Men

Variable	Male (n = 21,323)	Female (n = 14,552)	Unadjusted OR	Adjusted* OR (95% CI)
Treatment within 24 h				
Aspirin	91.6%	89.6%	0.83	0.93 (0.86–1.01)
Heparin, any	84.0%	80.0%	0.80	0.91 (0.86–0.97)
Unfractionated heparin	54.8%	48.5%	0.81	0.91 (0.87–0.95)
Low molecular weight heparin	35.9%	37.7%	1.07	1.03 (0.98–1.08)
Glycoprotein IIb/IIIa inhibitor, any	38.6%	28.7%	0.68	0.86 (0.81–0.92)
Troponin-positive	39.9%	30.5%	0.69	0.87 (0.81–0.92)
Troponin-negative	29.0%	19.4%	0.68	0.81 (0.71–0.93)
Beta-blocker	77.7%	75.8%	0.94	1.01 (0.95–1.06)
Angiotensin-converting enzyme inhibitor	42.2%	42.4%	1.03	0.95 (0.90–0.99)
Clopidogrel	41.0%	35.6%	0.82	0.97 (0.92–1.01)
Discharge medications				
Aspirin	90.4%	87.5%	0.79	0.91 (0.85–0.98)
Beta-blocker	82.7%	80.5%	0.89	0.94 (0.88–1.00)
Angiotensin-converting enzyme inhibitor	55.5%	55.3%	1.01	0.93 (0.88–0.98)
Statin	63.4%	55.9%	0.77	0.92 (0.88–0.98)
Clopidogrel	53.2%	48.0%	0.84	1.01 (0.96–1.06)

*Reference is male; variables in model listed in methods.
CI = confidence interval; OR = odds ratio.

diagnostic and treatment measures. Time to ECG was longer for women than for men, women were less likely to be cared for by a cardiologist, and invasive diagnostic measures and treatments were less frequently used in women. Moreover, even when invasive diagnostic and therapeutic interventions were used, women waited longer to receive them. Both acute and discharge guidelines-recommended medical therapies were consistently applied less often to female patients. These patterns of relative underuse in women were similar whether considering older, more established therapies, such as aspirin and heparin, or newer, perhaps more controversial ones, such as clopidogrel. In addition, GP IIb/IIIa inhibitors were used less often in the acute setting, even when only troponin-positive women and men were considered.

Treatment disparities demonstrated in this analysis are similar to those in previous studies that found women to be less aggressively diagnosed and treated than men (13–15). In one of the largest studies to date, the National Registry of Myocardial Infarction-1 investigators found that similar patterns existed among ST-segment elevation patients with MI (2). Using a database of 354,435 patients at 1,234 U.S. hospitals, important gender-related differences in treatment were observed. Accepted pharmacologic interventions, such as aspirin, beta-blockers, and heparin, were used less frequently in women, and thrombolytic therapy was administered, on average, 14 min later in women than men. Women also were less likely to receive invasive procedures, such as cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass grafting, and insignificant disease on catheterization more often was noted in women compared with men (11.5% vs. 6.0%, $p < 0.0001$). Our analyses, which reveal similar rates of percutaneous coronary intervention use among women and men after accounting for use of diagnostic angiography and extent of coronary disease, suggest that observed gender-related differences in the use of revascularization procedures stem primarily from disparities in the use of angiography and/or the extent of disease rather than in the use of revascularization itself. Thus, the literature has clearly documented gender disparities in the management of ACS, and our findings of a continued trend for women to less often receive guidelines-recommended treatment, despite the clear gender-neutrality of the ACC/AHA guidelines, are concerning, particularly given women's higher overall risk.

Table 3. Use of In-Hospital Procedures by Gender With Odds Ratios for Use in Women Relative to Men

Variable	Male (n = 21,323)	Female (n = 14,552)	Unadjusted OR	Adjusted* OR (95% CI)
Noninvasive stress testing	11.7%	13.2%	1.10	1.07 (1.00–1.14)
Diagnostic catheterization	71.1%	60.1%	0.70	0.86 (0.82–0.91)
Catheterization ≤24 h of arrival	48.7%	42.1%	0.69	0.87 (0.82–0.92)
Arrival to catheterization (h)†	22.6 (7.2, 45.9)	26.5 (12.4, 53.9)	1.16	1.08 (1.02–1.14)
Percutaneous coronary intervention (PCI)	40.4%	31.4%	0.73	0.91 (0.86–0.96)
PCI ≤24 h of arrival	51.9%	44.3%	0.64	0.85 (0.79–0.91)
Arrival to PCI, (h)†	21.0 (4.7, 44.2)	25.2 (9.0, 52.8)	1.17	1.06 (0.99–1.19)
Coronary artery bypass grafting	14.0%	9.0%	0.62	0.59 (0.54–0.64)

*Variables in the model are same as in Table 2. Data are presented as percentages except arrival to catheterization and arrival to percutaneous coronary intervention = median (25th, 75th percentile). †For continuous variables, data presented are unadjusted or adjusted estimate and 95% CI for adjusted estimate.
Abbreviations as in Table 2.

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Table 4. In-Hospital Clinical Outcomes by Gender With Odds Ratios for Clinical Outcomes in Women Relative to Men

Outcome	Male (n = 21,323)	Female (n = 14,552)	Unadjusted OR	Adjusted* OR (95% CI)
Death	4.3%	5.6%	1.27	1.01 (0.90–1.13)
Death or myocardial infarction	7.1%	8.6%	1.17	1.02 (0.93–1.11)
Postadmission myocardial infarction	3.5%	4.0%	1.12	1.08 (0.97–1.20)
Cardiogenic shock	2.7%	3.1%	1.10	1.01 (0.87–1.18)
Congestive heart failure	8.8%	12.1%	1.35	1.07 (0.99–1.17)
Stroke	0.8%	1.1%	1.37	1.13 (0.88–1.44)
Red blood cell transfusion	13.2%	17.2%	1.37	1.17 (1.09–1.25)

*Variables in the model same as Tables 2 and 3.
Abbreviations as in Table 2

The undertreatment of female patients with NSTE ACS is likely multifactorial. One possible explanation might be diagnostic uncertainty when physicians are presented with female patients. The uncertainties caused by a lower age-adjusted frequency of coronary artery disease among women presenting with symptoms of possible ACS and delays in symptom recognition in women might translate to delays in ECG acquisition and undertreatment. However, these factors cannot explain the management deficits we observed, because to be included in the CRUSADE initiative, patients had to have been diagnosed with high-risk NSTE ACS and therefore should have received similar consideration.

In our study, women with NSTE ACS more often were admitted to the care of a noncardiologist. This might explain the lower use of newer, perhaps more aggressive cardiologist-specific therapies, such as clopidogrel and GP IIb/IIIa inhibitors in women, as well as the lower use of invasive therapies. However, it does not adequately explain the less frequent use of older, more established therapies such as aspirin and heparin. Women in the CRUSADE initiative also were less likely to present with positive troponin levels and were more likely to present with ST-segment depression. Although these differences in presentation may affect choice of therapy or intervention, our analyses suggest that it is unlikely that these differences alone drove the observed disparities.

As would be expected, women were older, and many had high-risk baseline features. Although such features contribute to increased risk and thus portend greater absolute treatment benefits, these characteristics often are associated with undertreatment, in part because of the lack of clinical trials evidence in these groups and in part because of fear of complications. The "do-no-harm" adage may actually preclude clinicians from actively treating these patients without the understanding that such undertreatment might be the more harmful choice. One perceived obstacle in treating older women might be related to an increased incidence of bleeding, which was reflected by an increased rate of red blood cell transfusion in our study.

Despite the clear underuse of recommended therapies in women, adjusted in-hospital outcomes were not different between men and women. Gan et al. (16) noted a similar pattern of less aggressive treatment without a concomitant effect on early mortality in patients with acute MI. This pattern likely reflects both the influence of a greater prevalence of high-risk comorbidities in women than in men and the influence of unmeasured selection biases in the use of therapies that make comparisons of the effect of therapies in observational datasets challenging. Only when all patients receive appropriate, similar treatment strategies will we be able to confidently answer the question of their effect on outcome.

Study limitations. The results from the CRUSADE initiative represent the largest examination of gender differences in NSTE ACS treatment to date. Given the large number of patients in the CRUSADE database, many of the differences noted in this study are relatively small but statistically significant. The clinical significance of these differences should be considered when interpreting our results. Additionally, patients transferred to other care facilities were excluded from our analysis because current privacy regulations, which prohibit the collection of anonymous data after interhospital transfer. Although this situation represents a significant number of patients (3,210 men [13%] and 1,827 women [11%]), the proportion of men and women in these groups is similar and therefore cannot account for differences in treatment, and differences in cardiac catheterization rates in particular.

Conclusions. Women make up more than 40% of patients presenting with high-risk NSTE ACS in the CRUSADE initiative. The risk for in-hospital complications, including death, is 15% to 20% higher for women compared with men, in part because of greater comorbidities. Despite women being at greater risk, we found that guidelines-recommended medical and interventional strategies are used significantly less frequently in women than in men. These pervasive and continuing gender disparities represent a significant opportunity for quality improvement in the care of patients with NSTE ACS. Barriers that contribute to treatment disparities in women and the influence of other clinical characteristics on differences in treatment patterns and outcomes among women and men require further investigation.

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