

Sex Differences in Medical Care and Early Death After Acute Myocardial Infarction

Hani Jneid, MD; Gregg C. Fonarow, MD; Christopher P. Cannon, MD; Adrian F. Hernandez, MD; Igor F. Palacios, MD; Andrew O. Marea, MD; Quinn Wells, MD; Biykem Bozkurt, MD; Kenneth A. LaBresh, MD; Li Liang, PhD; Yuling Hong, MD, PhD; L. Kristin Newby, MD, MHS; Gerald Fletcher, MD; Eric Peterson, MD, MPH; Laura Wexler, MD; for the Get With the Guidelines Steering Committee and Investigators

Background—Women receive less evidence-based medical care than men and have higher rates of death after acute myocardial infarction (AMI). It is unclear whether efforts undertaken to improve AMI care have mitigated these sex disparities in the current era.

Methods and Results—Using the Get With the Guidelines—Coronary Artery Disease database, we examined sex differences in care processes and in-hospital death among 78 254 patients with AMI in 420 US hospitals from 2001 to 2006. Women were older, had more comorbidities, less often presented with ST-elevation myocardial infarction (STEMI), and had higher unadjusted in-hospital death (8.2% versus 5.7%; $P < 0.0001$) than men. After multivariable adjustment, sex differences in in-hospital mortality rates were no longer observed in the overall AMI cohort (adjusted odds ratio [OR]=1.04; 95% CI, 0.99 to 1.10) but persisted among STEMI patients (10.2% versus 5.5%; $P < 0.0001$; adjusted OR=1.12; 95% CI, 1.02 to 1.23). Compared with men, women were less likely to receive early aspirin treatment (adjusted OR=0.86; 95% CI, 0.81 to 0.90), early β -blocker treatment (adjusted OR=0.90; 95% CI, 0.86 to 0.93), reperfusion therapy (adjusted OR=0.75; 95% CI, 0.70 to 0.80), or timely reperfusion (door-to-needle time ≤ 30 minutes: adjusted OR=0.78; 95% CI, 0.65 to 0.92; door-to-balloon time ≤ 90 minutes: adjusted OR=0.87; 95% CI, 0.79 to 0.95). Women also experienced lower use of cardiac catheterization and revascularization procedures after AMI.

Conclusions—Overall, no sex differences in in-hospital mortality rates after AMI were observed after multivariable adjustment. However, women with STEMI had higher adjusted mortality rates than men. The underuse of evidence-based treatments and delayed reperfusion among women represent potential opportunities for reducing sex disparities in care and outcome after AMI. (*Circulation*. 2008;118:000-000.)

Key Words: myocardial infarction ■ percutaneous coronary intervention ■ reperfusion ■ revascularization ■ sex

Despite advances in cardiovascular therapeutics and research and the associated decline in cardiovascular death, cardiovascular disease remains the leading cause of death in the United States.¹ Death from acute myocardial infarction (AMI) in the United States remains particularly elevated among women. In 2004, AMI claimed the lives of nearly 74 000 women in the United States.¹ Multiple reports have also shown increased early death among women presenting with AMI compared with their male counterparts.^{2,3} In addition, women receive less medical and invasive treatments after AMI compared with men.^{4–8}

However, many of the aforementioned reports are currently outdated, and each examined only limited aspects of medical

care and outcome among men and women presenting with AMI. Whether the sex disparities in care processes and death after AMI are still present in the current era and the extent to which differences in baseline risk account for any existing mortality rate gap remain a matter of constant debate and have important clinical implications.

Therefore, we conducted a comprehensive analysis of the association of sex with medical care and early death after AMI using a large contemporary national database. More specifically, we systematically compared the use of early medical treatments, reperfusion strategies, and invasive procedures, as well as the timeliness of mechanical and pharmacological reperfusion, and in-hospital death between men and

Received April 30, 2008; accepted September 17, 2008.

From the Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Tex (H.J., B.B.); University of California at Los Angeles Medical Center (G.C.F.); Thrombolysis in Myocardial Infarction Group and Brigham and Women's Hospital, Boston, Mass (C.P.C.); Duke Clinical Research Institute and Duke University Medical Center, Durham, NC (L.L., L.K.N., A.F.H., E.P.); Massachusetts General Hospital, Boston, Mass (H.J., I.F.P., A.O.M., Q.W.); MassPro, Inc, Waltham, Mass (K.A.L.); American Heart Association National Center, Dallas, Tex (Y.H.); Mayo Clinic, Jacksonville, Fla (G.F.); and University of Cincinnati College of Medicine, Cincinnati, Ohio (L.W.).

Guest Editor for this article was Richard F. Gillam, MD, MS.

Correspondence to Hani Jneid, MD, Division of Cardiology, Michael E. DeBakey VA Medical Center and Baylor College of Medicine, 2002 Holcombe Blvd, Houston, TX 77030. E-mail jneid@bcm.tmc.edu

© 2008 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.108.789800

women hospitalized with AMI. We also separately examined sex disparities in in-hospital mortality rates in the ST-elevation myocardial infarction (STEMI) subgroup.

Methods

Data Source and Study Sample

The primary data source was Get With the Guidelines—Coronary Artery Disease (GWTG-CAD), a registry and performance-improvement initiative undertaken by the American Heart Association to enhance guidelines adherence among patients hospitalized with CAD. The overall GWTG program objectives were described previously.^{9–11} The database includes teaching and nonteaching, rural and urban, large and small hospitals from all census regions of the United States. Hospitals were required to submit data from consecutive patients. Data were collected by participating hospitals without financial compensation and entered by highly trained personnel. Admission staff, medical staff, or both recorded race/ethnicity, usually as patients were registered. Case finding was predominantly based on clinical identification of patients with these diagnoses in most hospitals, frequently with additional confirmation by retrospective *International Classification of Diseases, Ninth Revision* coding. Data quality reports were generated regularly to summarize quality problems and provide feedback to the individual sites.

At the time of the analysis, the GWTG-CAD database included 84 900 patients admitted directly to non-national health service hospitals with AMI. Of those, we excluded patients on renal dialysis ($n=1853$; or 2.2% of the overall population), patients enrolling in clinical trials ($n=115$; 0.1%), patients with missing or invalid arrival dates or times ($n=3682$; 4.3%), patients with prolonged length of stay >30 days ($n=789$; 0.9%), and those with missing sex variable data ($n=207$; 0.2%). Exclusions were based on the fact that these small subgroups were usually not representative of real-world AMI patients and that meaningful analyses were not feasible in the absence of the aforementioned variable data.

The final study population included 78 254 patients hospitalized with AMI in 420 hospitals throughout the United States between January 2001 and April 2006. Patients discharged to other medical facilities were excluded from the analyses of in-hospital death and invasive procedures ($n=7804$ patients). Measures of the timeliness of reperfusion were available and reported in 10 480 patients with STEMI. Reperfusion measures were applicable to and analyzed only in the STEMI cohort ($n=25 353$). In-hospital death rates were equally available in 99.5% of all AMI and STEMI patients (70 105 and 23 015 patients, respectively).

Data Collection and Measures

Sex (female versus male) was the primary independent variable. The primary study outcome was in-hospital death. Secondary outcomes included clinical performance measures (early medical therapies, acute reperfusion therapies, timeliness of reperfusion parameters) and invasive procedures.

Guidelines-recommended early medical therapies included the following: aspirin use within 24 hours of arrival in AMI patients with no contraindication to the medication ($n=70 360$) and β -blocker use within 24 hours of arrival in AMI patients with no contraindication to the medication ($n=64 681$). Patients who died, left against medical advice, or were discharged within 24 hours of arrival were excluded from these analyses. Acute reperfusion therapies were analyzed in the reperfusion-eligible STEMI subpopulation and included the following: primary percutaneous coronary intervention (PCI), fibrinolytic therapy, and any reperfusion. Timeliness of reperfusion parameters included the proportion of STEMI patients who received fibrinolytic therapy within the American College of Cardiology/American Heart Association guidelines-recommended 30-minute door-to-needle (DTN) time and the proportion of STEMI patients who received primary PCI within the American College of Cardiology/American Heart Association guidelines-recommended 90-minute door-to-balloon (DTB) time. DTN was defined as the time

from hospital arrival to initiation of fibrinolytic therapy, and DTB time was defined as the time from hospital arrival to first balloon inflation. Invasive procedures included cardiac catheterization, PCI, coronary artery bypass graft surgery (CABG), and overall revascularization. The STEMI subpopulation included 25 353 patients defined by the presence of initial ECG findings showing diagnostic ST-segment elevation or left bundle-branch block.

Statistical Analysis

For the descriptive analyses, patients' sociodemographic and medical history variables, baseline clinical characteristics, clinical performance measures, invasive procedures, and in-hospital mortality rates were compared between women and men. Percentages and mean \pm SD values were reported to describe the distribution of categorical and continuous variables, respectively. Medians and interquartile ranges (25th to 75th) were reported for DTB and DTN times. Categorical and continuous variables were compared with the use of the χ^2 and Wilcoxon rank sum tests, respectively. Multivariable logistic regression analyses, with the use of the generalized estimating equations method¹² to adjust for clustering within hospitals, were performed to determine whether sex was independently associated with each measure and outcome. The regression model adjusted for the following covariates: age, race, body mass index (BMI), insurance type, systolic blood pressure, cardiac diagnosis, initial ECG with diagnostic ST-segment elevation or left bundle-branch block, diabetes, hypertension, hyperlipidemia, heart failure, previous myocardial infarction (MI), peripheral vascular disease, renal insufficiency, stroke, chronic obstructive pulmonary disease, and adult history of smoking. Odds ratios (ORs) with their 95% CIs were reported for women versus men for each measure and outcome. A probability value of <0.05 was considered statistically significant for all tests. All analyses were performed by the Duke Clinical Research Institute (Durham, NC) with the use of the Statistical Analysis System (SAS) software version 8.2 (SAS Institute, Cary, NC).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Patient Characteristics

The study population included 78 254 patients with AMI, of whom 39% ($n=30 698$) were women. In the overall AMI cohort, women were older, less likely to be white, and more likely to have Medicare or Medicaid insurance and had lower BMI (Table 1). Women presenting with AMI had more comorbidities, except for hyperlipidemia, smoking history, and a prior MI history, which were more common among men. Women were also less likely to present with STEMI (28.2% versus 35.1%; $P<0.0001$) and had higher systolic blood pressure and ejection fraction on admission.

Clinical Performance Measures

Women presenting with AMI were less likely than their male counterparts to receive aspirin and β -blockers within 24 hours of arrival (91.0% versus 93.3% and 84.7% versus 87.2%; each with $P<0.0001$) (Table 2). Overall, 67% of patients in the STEMI subpopulation received acute reperfusion therapy (primary PCI or fibrinolytic therapy), with lower rates observed among STEMI women (56.3% versus 73.0%; $P<0.0001$). Compared with men, women with STEMI were less likely to receive fibrinolytic therapy alone, primary PCI, or the combination of fibrinolytic therapy and PCI (5.1% versus 6.2%, 47.3% versus 61.1%, and 3.9% versus 5.8%, respectively; $P<0.0001$). Women presenting with STEMI

Table 1. Baseline Characteristics

Description	Overall (n=78 254), % (n)	Men (n=47 556), % (n)	Women (n=30 698), % (n)	P
Sociodemographic characteristics				
Age, mean±SD, y	67.8±14.7	64.7±14.1	72.6±14.2	<0.0001
Race				<0.0001
White	74.7 (58 465)	75.1 (35 700)	74.1 (22 756)	
Black	6.9 (5420)	6.1 (2922)	8.1 (2498)	
Asian	4.1 (3209)	4.1 (1926)	4.2 (1283)	
Hispanic	6.4 (4992)	6.7 (3190)	5.9 (1802)	
American Indian	0.2 (140)	0.2 (78)	0.2 (62)	
Other	1.6 (1229)	1.7 (813)	1.4 (416)	
BMI, mean±SD, kg/m ²	28.1±6.5 (69 405)	28.4±5.9 (42 584)	27.8±7.3 (26 821)	<0.0001
Health insurance				<0.0001
Medicare	49.7 (38 884)	43.2 (20 526)	59.8 (18 358)	
Medicaid	6.0 (4698)	4.5 (2121)	8.4 (2577)	
Other source	36.9 (28 886)	43.7 (20 792)	26.4 (8094)	
No insurance/UTD	7.4 (5786)	8.7 (4117)	5.4 (1669)	
Medical history				
Angina	9.7 (7588)	10.0 (4776)	9.2 (2812)	<0.0001
Atrial fibrillation	8.3 (6497)	7.2 (3437)	10.0 (3060)	<0.0001
Chronic obstructive pulmonary disease	12.9 (10 122)	11.8 (5628)	14.6 (4494)	<0.0001
Diabetes	29.9 (23 355)	28.0 (13 300)	32.8 (10 055)	<0.0001
Heart failure	15.6 (12 197)	12.8 (6071)	20.0 (6126)	<0.0001
Hypertension	61.7 (48 255)	57.7 (27 438)	67.8 (20 817)	<0.0001
Hyperlipidemia	34.9 (27 307)	36.1 (17 171)	33.0 (10 136)	<0.0001
No regular exercise	10.3 (8070)	10.0 (4731)	10.9 (3339)	0.0002
Previous MI	20.0 (15 683)	21.2 (10 062)	18.3 (5621)	<0.0001
Peripheral vascular disease	8.2 (6434)	8.0 (3798)	8.6 (2636)	0.01
Renal insufficiency	10.0 (7827)	9.5 (4497)	10.9 (3330)	<0.0001
Stroke	8.2 (6377)	6.9 (3302)	10.0 (3075)	<0.0001
Adult history of smoking	28.4 (22 207)	32.8 (15 586)	21.6 (6621)	<0.0001
Clinical characteristics				
STEMI diagnosis	32.4 (25 353)	35.1 (16 694)	28.2 (8659)	<0.0001
Diastolic BP, mean±SD, mm Hg	68±14 (68 273)	69±13 (41 689)	66±14 (26 584)	<0.0001
Systolic BP, mean±SD, mm Hg	124±22 (68 414)	123±22 (41 775)	126±24 (26 639)	<0.0001
Total cholesterol, mean±SD, mg/dL	175±48 (49 766)	173±47 (31 271)	180±49 (18 495)	<0.0001
Ejection fraction, mean±SD, %	47±15 (52 375)	47±14 (32 240)	48±15 (20 135)	<0.0001

UTD indicates unable to determine; BP, blood pressure.

were also less likely to achieve timely DTN (28.3% versus 35.2%; $P=0.0005$) and timely DTB (39.0% versus 44.8%; $P<0.0001$). Median DTN and DTB times for women versus men were 47 versus 39 minutes and 103 versus 95 minutes, respectively, each with $P<0.0001$ (Table 2).

The sex disparities in the aforementioned clinical performance measures persisted after multivariable adjustment and remained highly statistically significantly different (Table 3).

Invasive Procedures

Compared with men, women with AMI were less likely to undergo a cardiac catheterization procedure during their index hospitalization (45.6% versus 56.2%; $P<0.0001$), PCI (36.1% versus 52.3%; $P<0.0001$), CABG (5.4% versus

9.2%; $P<0.0001$), and any revascularization (40.9% versus 60.2%; $P<0.0001$) (Table 2). These sex differences in invasive procedures persisted after multivariable adjustment (Table 3).

In-Hospital Mortality Rates

Women had higher unadjusted in-hospital mortality rates in the overall AMI cohort (8.2% versus 5.7%; $P<0.0001$) and STEMI subpopulation (10.2% versus 5.5%; $P<0.0001$) (Figure). After multivariable adjustment, women had significantly higher in-hospital mortality rates than men in the STEMI subpopulation (adjusted OR=1.12; 95% CI, 1.02 to 1.23; $P=0.015$), but the difference was no longer observed in the overall AMI cohort (adjusted OR=1.04; 95% CI, 0.99 to 1.10; $P=0.1$).

Table 2. Sex-Based Differences in Clinical Performance Measures and Invasive Procedures

Measure/Treatment	Overall (n=78 254), % (n)	Men (n=47 556), % (n)	Women (n=30 698), % (n)	P
Early medical therapy				
Aspirin within <24 h	92.4 (65 018)	93.3 (40 332)	91.0 (24 686)	<0.0001
β-Blockers within <24 h	86.2 (55 777)	87.2 (34 653)	84.7 (21 124)	<0.0001
Invasive procedures				
Cardiac catheterization	52.1 (40 745)	56.2 (26 733)	45.6 (14 012)	<0.0001
PCI	45.9 (32 323)	52.3 (22 253)	36.1 (10 070)	<0.0001
CABG	7.7 (5394)	9.2 (3893)	5.4 (1501)	<0.0001
Revascularization	52.6 (37 023)	60.2 (25 614)	40.9 (11 409)	<0.0001
Timeliness of reperfusion*				
DTN time, median (25th–75th), min	40.0 (25.0–70.0)	39.0 (24.0–66.0)	47.0 (27.0–83.0)	<0.0001
DTB time, median (25th–75th), min	97.0 (70.0–140.0)	95.0 (69.0–135.0)	103.0 (74.0–154.0)	<0.0001
DTN ≤30 minutes, % (n)	33.2 (933)	35.2 (711)	28.3 (222)	0.0005
DTB ≤90 minutes, % (n)	43.2 (3316)	44.8 (2510)	39.0 (806)	<0.0001
Acute reperfusion*				
Any reperfusion therapy	67.3 (17 058)	73.0 (12 184)	56.3 (4874)	<0.0001
Reperfusion therapies				<0.0001
Primary PCI	56.4 (14 292)	61.1 (10 196)	47.3 (4096)	
Fibrinolytic therapy	5.8 (1467)	6.2 (1028)	5.1 (439)	
Fibrinolytic therapy+PCI	5.1 (1299)	5.8 (960)	3.9 (339)	

*STEMI subpopulation.

To examine the attributable effects of treatments and clinical performance measures in closing the residual sex gap in death rates among STEMI patients, we further excluded STEMI patients who died (n=475) or left against medical advice (n=34) in the initial 24 hours of hospitalization from the analyses (52% were women), reasoning that these patients did not have time to receive therapies. After these patients were excluded, the adjusted in-hospital mortality rate was no longer different between women and men presenting with STEMI (1.02; 95% CI, 0.91 to 1.15; $P=0.7$), indicating that the residual sex differences in adjusted in-hospital mortality rates were accounted for by excess very early deaths (in the initial 24 hours) among women with STEMI.

During the initial 24 hours of hospitalization, women with STEMI were more than twice as likely to die or leave against medical advice compared with men (3.4% versus 1.6%; $P<0.0001$). Among those STEMI patients who died or left against medical advice in the initial 24 hours, women were older than men (78.4 ± 13.8 versus 68.2 ± 15.5 years; $P<0.0001$) and more frequently had hypertension and heart failure but had lower BMI and less often smoked (data not shown). Women in this STEMI subgroup were also less likely to undergo cardiac catheterization (26.7% versus 35.8%; $P=0.03$), primary PCI (19.2% versus 29.6%; $P=0.002$), revascularization (21.1% versus 33.3%; $P=0.002$), or any reperfusion therapy (26.7% versus 41.6%; $P=0.0004$). No significant differences in DTN and DTB times were observed in this STEMI subgroup (women versus men: 55 versus 49 minutes, and 110 versus 107 minutes, respectively), although these latter analyses are underpowered.

Discussion

The present study demonstrates that women presenting with AMI had adjusted in-hospital death rates similar to those of men but were less likely to receive early medical treatments, acute reperfusion therapies, timely pharmacological and mechanical reperfusion, and invasive procedures. Women presenting with AMI were older and had overall higher baseline risk profile than men, which explained their higher unadjusted in-hospital mortality rates. On the other hand, women presenting with STEMI had higher adjusted in-hospital mortality rates than men. The residual sex-based disparity in adjusted in-hospital mortality rates after STEMI was accounted for by an excess of very early deaths (in the initial 24 hours of hospitalization) among STEMI women, who appeared to receive less invasive procedures and revascularization during this time period. After multivariable adjustment, persistent sex disparities after AMI were observed in all clinical performance measures and invasive procedures.

Similar to prior reports, our contemporary analysis confirms the higher unadjusted early death of women hospitalized with AMI compared with men^{2,3,13,14} and demonstrates that the mortality rate gap is even larger in the higher-risk STEMI subpopulation. As reported previously, women are older, have more comorbidities than men when presenting with AMI,^{3,7} and are less likely to present with STEMI.³ Multiple studies have shown the increased death among women to be related to their higher baseline risk.^{2,15,16} The third International Study of Infarct Survival (ISIS-3) previously demonstrated, in a cohort of 36 080 AMI patients eligible for fibrinolytic therapy, that adjustment for baseline characteristics narrowed but did not completely eliminate the

Table 3. Adjusted ORs* for Clinical Performance Measures, Invasive Procedures, and In-Hospital Death

Measure/Treatment/Outcome	n	Adjusted OR (95% CI) (Women vs Men)	P
Early medical therapy			
Aspirin within 24 h	70 360	0.86 (0.81–0.90)	<0.0001
β-Blocker within 24 h	64 681	0.90 (0.86–0.93)	<0.0001
Invasive procedures			
Cardiac catheterization	74 769	0.91 (0.88–0.94)	<0.0001
PCI	67 477	0.78 (0.74–0.81)	<0.0001
CABG	67 477	0.60 (0.55–0.65)	<0.0001
Revascularization	67 477	0.68 (0.65–0.71)	<0.0001
Acute reperfusion and timeliness of reperfusion†			
DTN ≤30 min	2807	0.78 (0.65–0.92)	0.004
DTB ≤90 min	7673	0.87 (0.79–0.95)	0.004
Reperfusion therapy	24 742	0.75 (0.70–0.80)	<0.0001
Primary PCI	24 742	0.83 (0.78–0.87)	<0.0001
Fibrinolytic therapy	24 742	0.87 (0.81–0.93)	<0.0001
In-hospital death			
Overall AMI cohort	70 105	1.04 (0.99–1.10)	0.1
STEMI subpopulation	23 015	1.12 (1.02–1.23)	0.015

*ORs, which are for women vs men, were adjusted for age, race, BMI, insurance type, systolic blood pressure, cardiac diagnosis, initial ECG with diagnostic ST-segment elevation or left bundle-branch block, diabetes, hypertension, hyperlipidemia, heart failure, previous MI, peripheral vascular disease, renal insufficiency, stroke, chronic obstructive pulmonary disease, and adult history of smoking. The generalized estimation equations approach was also employed to adjust for clustering within hospitals.

†STEMI subpopulation.

early mortality rate gap (women versus men: adjusted OR=1.14; 95% CI, 1.05 to 1.23).¹⁶ Women hospitalized for AMI have also been shown to receive less aggressive medical and invasive treatments.^{4–8} Although some have found that

the treatment differences are small and do not affect early death,¹⁷ others have attributed the sex gap in death after AMI to these treatment inequalities.^{5,8} Thus, the extent to which mortality rate differences between men and women are related to discrepancies in baseline risk versus treatment bias remains a matter of constant debate. The controversy in the literature stems largely from differences in the studied populations and from methodological variations, including differences in definitions and adjustment analyses.

In the present study, the mortality rate gap was no longer observed after a comprehensive multivariable adjustment, which lends support to the notion that sex by itself, in the current era, does not independently predict early death after AMI among hospitalized patients. The mortality rate gap, however, persisted among STEMI patients and was possibly accounted for by a higher rate of very early deaths (in the initial 24 hours of hospitalization) among women. In 1 report paralleling our findings, the largest sex disparity in death rates after AMI occurred in the early hospitalization period, namely, during the initial 5 days of hospitalization.¹⁴ Another study demonstrated increased case fatality after AMI in the initial 24 hours of hospitalization but did not find sex differences in case fatality during this time period.¹⁸ Both of these reports included overall AMI patients and did not examine STEMI patients in particular.^{14,18} In our analysis, women who sustained very early deaths in our STEMI subpopulation were older, had slightly different risk profiles, and underwent revascularization and reperfusion less frequently than men. Whether the excess very early death among STEMI women was related to treatment differences or to sicker patients dying before receiving adequate therapies was difficult to discern. It is likely, though, that both were important contributing factors. Regardless, women presenting with STEMI appear to be at high risk of dying in the initial 24 hours and to represent a subgroup of patients in whom prompt and aggressive therapies are warranted. It is important to note

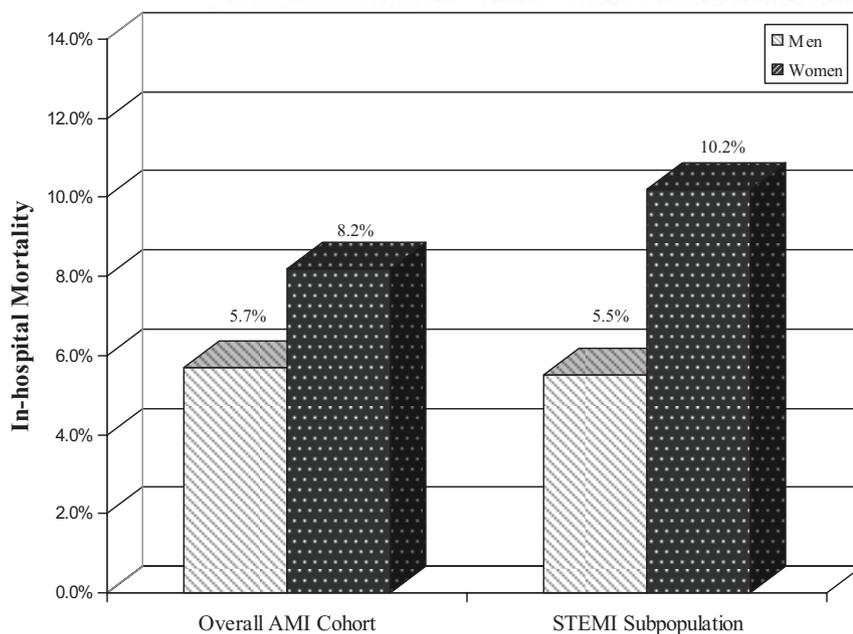


Figure. In-hospital mortality rates among hospitalized women and men in the overall AMI cohort and in the STEMI subpopulation.

that these post hoc findings are exploratory in nature and need confirmation in larger analyses.

Of note, our data included hospitalized AMI patients only and did not account for out-of-hospital deaths. Evidence suggests that AMI women are more likely to survive and reach the hospital compared with their male counterparts.^{15,19} One report even contends that the higher probability among women of surviving to reach the hospital counterbalances their subsequent excess death.¹⁵ Therefore, it is conceivable that such a selection bias might have enriched hospitals with higher-risk AMI women and explained our observed sex differences in risk profiles and mortality rates.

In addition to providing a contemporary glimpse at sex disparities in early death after AMI, a distinct advantage of our study is that it confirms the existence of concomitant disparities in clinical performance measures using a systematic review of multiple care processes. Complementing a wealth of prior studies,^{4–8} we have described consistently lower use of early medical treatments and timely reperfusion among hospitalized women presenting with AMI. This highlights the persisting opportunities to improve healthcare among these patients. This is especially important given that the described treatment biases can be more readily rectified in the controlled hospital setting, in contradistinction to the more challenging task of altering primary and secondary prevention therapies in the out-of-hospital setting. Besides differences in baseline risk, other modifiable factors and contributing etiologies may further explain the observed discrepancies in treatments and outcome after AMI between women and men. These factors are worth examining in future analyses and may include, but are not limited to, race, adherence to guidelines-recommended treatments, delayed hospital presentation, and delayed AMI diagnosis among women.

We were unable to fully ascertain appropriateness of revascularization in our analysis given the lack of angiographic data. Younger women, for example, are known to have higher incidence of coronary in situ thrombosis, smaller vessels, and more vasospastic disease.²⁰ Therefore, one may argue that the lower PCI use among women may reflect appropriate physicians' decisions. The lower use of CABG can also be ascribed to differences in surgical suitability, and physicians' reticence to administer fibrinolytics to women may be attributed to their higher proclivity to suffer intracranial hemorrhage and other complications.^{21,22} On the other hand, many of the treatments and measures examined in our analysis are proven therapies^{13,23} and accepted clinical performance measures²⁴ for both women and men after AMI. Disparities in the use of early aspirin and β -blocker therapies, which were recorded only in patients with no contraindication to these medications, and the disparities in DTB and DTN times are hard to attribute to anything but inappropriate treatment biases. Evidence also suggests that patients' preferences in dictating treatments, which were not captured in our data, usually account only for a very small fraction of the sex differences in care processes.²⁵ Overall, the persistence and magnitude of sex disparities after multivariable adjustment and their existence across several clinical perfor-

mance measures indicate the presence of inappropriate sex-based treatment biases after AMI in the contemporary era. It is also noteworthy to emphasize that overall rates of use of most treatments and measures were less than ideal among both women and men, suggesting that there is room for improving overall care for all AMI patients.

Overall, our analysis has several strengths, including the following: its inclusion of a community-based contemporary patient population, inclusive of all regions of the United States; its comprehensive evaluation of multiple processes of care and clinical data; and the robustness and consistency of our findings. The GWTG database utilized carefully defined data entries, standardized diagnostic criteria, and regular quality assessment. The GWTG database included patients with confirmed AMI diagnosis at discharge. This is an important distinction from other registries that enroll patients with suspected AMI at presentation, many of whom are determined to be misdiagnosed. Consent procedures and eligibility for specific treatments were not required for enrollment in the GWTG program, which minimizes bias and increases our study generalizability. On the other hand, our study has several limitations. The GWTG hospitals are self-selected and may not be fully representative of national care patterns and clinical outcomes. We had no data on predischARGE and postdischarge mortality and morbidity. Moreover, eligibility for treatment was based on documentation in the medical record and was thus dependent on the accuracy of this documentation. Finally, there might be other measured or unmeasured confounding variables that, had they been adjusted for, would have modified the relationship between sex and in-hospital mortality rates.

In conclusion, women presenting with AMI had higher unadjusted in-hospital mortality rates than men. After adjustment for baseline risk and clinical characteristics, sex-based differences in early death after AMI were no longer observed overall but remained apparent in the STEMI subpopulation and were possibly accounted for primarily by excess death among women in the initial 24 hours of hospitalization. Evidence of lower use of guidelines-based treatments and delayed reperfusion among women compared with men highlights the existing opportunities to improve the provision of healthcare among women hospitalized with AMI. Special attention should be given to those at highest risk, especially women with STEMI during their early hospitalization period.

Sources of Funding

This publication is supported by a grant from the Council on Clinical Cardiology of the American Heart Association. The GWTG-CAD program is funded in part by the Merck/Schering-Plough partnership. Data collection and management was performed by Outcome, Inc (Cambridge, Mass). The analysis of registry data was performed at Duke Clinical Research Institute (Durham, NC), which also receives funding from the American Heart Association. The sponsor was not involved in the management, analysis, or interpretation of data or the preparation of the manuscript.

Disclosures

Dr Jneid is a member of the Council on Clinical Cardiology of the American Heart Association and has received a database research seed grant from the Council on Clinical Cardiology. Dr Fonarow reported that he has received research grants from GlaxoSmithKline, Medtronic, and Pfizer (all significant). He has also received honoraria in the past 2 years from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Merck, Novartis, Pfizer, Sanofi-Aventis, and Schering-Plough (all significant). He is or has been a consultant for GlaxoSmithKline, Medtronic, and Merck (significant); and for AstraZeneca, Boston Scientific, Pfizer, Sanofi-Aventis, and Schering-Plough (modest). Dr Fonarow serves as Chair of the American Heart Association's Get With the Guidelines Steering Committee. Dr Cannon receives research grant support from the following companies: Accumetrics, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Sanofi-Aventis, and Schering Plough. Dr LaBresh has a modest consulting relationship with Wyeth. Dr Newby has received research grant support within the past 2 years from Schering-Plough, Inverness Medical, Bristol-Myers Squibb, Medicare, Adolor, and BG Medicine and has received consulting honoraria from Biosite, Roche Diagnostics, AstraZeneca, Novartis, Proctor and Gamble, CV Therapeutics, and Scios. Dr Hernandez has received research funding from the American Heart Association's Pharmaceutical Roundtable Grant, Scios, Medtronic, Novartis, and GlaxoSmithKline, as well as honoraria from Novartis. Dr Hong is the Director, Epidemiology and Research Services at the American Heart Association National Center. Dr Peterson has received research grant support and/or consulting fees from Bristol-Myers Squibb, Merck, Sanofi-Aventis, and Schering-Plough. He is the Associate Director of the Duke Clinical Research Institute, which also receives funding from the American Heart Association. Detailed disclosures for Dr Peterson can be found at: <http://www.dcri.duke.edu/research/coi.jsp>.

References

- Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e25–e146.
- Vaccarino V, Krumholz HM, Berkman LF, Horwitz RI. Sex differences in mortality after myocardial infarction: is there evidence for an increased risk for women? *Circulation*. 1995;91:1861–1871.
- Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ, Califf RM; Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIB Investigators. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med*. 1999;341:226–232.
- Barron HV, Bowlby LJ, Breen T, Rogers WJ, Canto JG, Zhang Y, Tiefenbrunn AJ, Weaver WD. Use of reperfusion therapy for acute myocardial infarction in the United States: data from the National Registry of Myocardial Infarction 2. *Circulation*. 1998;97:1150–1156.
- Barakat K, Wilkinson P, Suliman A, Ranjadayalan K, Timmis A. Acute myocardial infarction in women: contribution of treatment variables to adverse outcome. *Am Heart J*. 2000;140:740–746.
- Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med*. 2005;353:671–682.
- Jneid H, Thacker HL. Coronary artery disease in women: different, often undertreated. *Cleve Clin J Med*. 2001;68:441–448.
- Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation*. 2007;115:833–839.
- LaBresh KA, Ellrodt AG, Gliklich R, Liljestrand J, Peto R. Get With the Guidelines for cardiovascular secondary prevention: pilot results. *Arch Intern Med*. 2004;164:203–209.
- LaBresh KA, Gliklich R, Liljestrand J, Peto R, Ellrodt AG. Using "Get With the Guidelines" to improve cardiovascular secondary prevention. *Jt Comm J Qual Saf*. 2003;29:539–550.
- Hong Y, Labresh KA. Overview of the American Heart Association "Get With the Guidelines" programs: coronary heart disease, stroke, and heart failure. *Crit Pathw Cardiol*. 2006;5:179–186.
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130.
- Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110:e82–e292.
- Simon T, Mary-Krause M, Cambou JP, Hanania G, Gueret P, Lablanche JM, Blanchard D, Genes N, Danchin N. Impact of age and gender on in-hospital and late mortality after acute myocardial infarction: increased early risk in younger women: results from the French nation-wide USIC registries. *Eur Heart J*. 2006;27:1282–1288.
- MacIntyre K, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, Finlayson A, Redpath A, Gilmour H, McMurray JJ. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol*. 2001;38:729–735.
- Malacrida R, Genoni M, Maggioni AP, Spataro V, Parish S, Palmer A, Collins R, Moccetti T; The Third International Study of Infarct Survival Collaborative Group. A comparison of the early outcome of acute myocardial infarction in women and men. *N Engl J Med*. 1998;338:8–14.
- Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. *N Engl J Med*. 2000;343:8–15.
- Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol*. 1997;146:483–494.
- Pell JP, Sirel J, Marsden AK, Cobbe SM. Sex differences in outcome following community-based cardiopulmonary arrest. *Eur Heart J*. 2000;21:239–244.
- Anderson RD, Pepine CJ. Gender differences in the treatment for acute myocardial infarction: bias or biology? *Circulation*. 2007;115:823–826.
- Berkowitz SD, Granger CB, Pieper KS, Lee KL, Gore JM, Simoons M, Armstrong PW, Topol EJ, Califf RM; The Global Utilization of Tissue Plasminogen activator for Occluded coronary arteries (GUSTO) I Investigators. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation*. 1997;95:2508–2516.
- Weaver WD, White HD, Wilcox RG, Aylward PE, Morris D, Guerci A, Ohman EM, Barbash GI, Bत्रीu A, Sadowski Z, Topol EJ, Califf RM; GUSTO-I Investigators. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. *JAMA*. 1996;275:777–782.
- Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons; endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation*. 2007;116:e148–e304.
- Krumholz HM, Anderson JL, Brooks NH, Fesmire FM, Lambrew CT, Landrum MB, Weaver WD, Whyte J, Bonow RO, Bennett SJ, Burke G, Eagle KA, Linderbaum J, Masoudi FA, Normand SL, Pina IL, Radford MJ, Rumsfeld JS, Ritchie JL, Spertus JA. ACC/AHA clinical performance measures for adults with ST-elevation and non-ST-elevation

myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures on ST-Elevation and Non-ST-Elevation Myocardial Infarction). *Circulation*. 2006;113:732–761.

25. Rathore SS, Ordin DL, Krumholz HM. Race and sex differences in the refusal of cardiac catheterization among elderly patients hospitalized with acute myocardial infarction. *Am Heart J*. 2002;144:1052–1056.

CLINICAL PERSPECTIVE

Women receive less evidence-based medical care than men and had higher rates of death after acute myocardial infarction (AMI). It is unclear whether efforts undertaken to improve AMI care have mitigated these sex disparities in the current era. We therefore examined sex differences in care processes and in-hospital death among 78 254 patients with AMI from the Get With the Guidelines–Coronary Artery Disease database in 420 US hospitals from 2001 to 2006. Women were older, had more comorbidities, less often presented with ST-elevation myocardial infarction, and had higher unadjusted in-hospital mortality rates (8.2% versus 5.7%; $P<0.0001$) than men. After adjustment for baseline risk and clinical characteristics, sex-based differences in rates of death early after AMI were no longer observed overall but remained apparent in the ST-elevation myocardial infarction subpopulation (10.2% versus 5.5%; $P<0.0001$; adjusted odds ratio=1.12; 95% CI, 1.02 to 1.23) and were possibly accounted for by excess death among women in the initial 24 hours of hospitalization. Compared with men, women were also less likely to receive early aspirin and β -blocker treatments or reperfusion therapy or to achieve timely reperfusion. Women also experienced lower use of cardiac catheterization and revascularization procedures after AMI. This report confirms the notion that women still sustain higher adjusted mortality rates after ST-elevation myocardial infarction compared with men. Evidence of lower use of guidelines-based treatments and delayed reperfusion highlights the existing opportunities to improve the provision of healthcare among women hospitalized with AMI. Special attention should be given to those at highest risk, especially women with ST-elevation myocardial infarction during their early hospitalization period.



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Sex Differences in Medical Care and Early Death After Acute Myocardial Infarction

Hani Jneid, Gregg C. Fonarow, Christopher P. Cannon, Adrian F. Hernandez, Igor F. Palacios, Andrew O. Maree, Quinn Wells, Biykem Bozkurt, Kenneth A. LaBresh, Li Liang, Yuling Hong, L. Kristin Newby, Gerald Fletcher, Eric Peterson and Laura Wexler
for the Get With the Guidelines Steering Committee and Investigators

Circulation. published online December 8, 2008;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2008 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circ.ahajournals.org/content/early/2008/12/08/CIRCULATIONAHA.108.789800.citation>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>