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# Sex Differences in Mortality Following Acute Coronary Syndromes

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**C**ARDIOVASCULAR DISEASE IS THE leading cause of death in both men and women, accounting for one-third of all deaths.<sup>1</sup> Although several studies have shown an improvement of prognosis in women over time,<sup>2</sup> overall outcomes remain worse for women compared with men,<sup>3</sup> providing a strong rationale for focusing on the study of sex-based differences in the outcome of acute coronary syndromes (ACS). Previous analyses of sex-based differences following ACS have reported conflicting results, even after adjustment for demographics and clinical characteristics.<sup>4-17</sup> In a large systematic review comparing short-term mortality between women and men, Vaccarino et al<sup>3</sup> concluded that after adjustment for differences in age and baseline prognostic factors, some but not all of the excess mortality was explained.

**Context** Conflicting information exists about whether sex differences modulate short-term mortality following acute coronary syndromes (ACS).

**Objectives** To investigate the relationship between sex and 30-day mortality in ACS, and to determine whether this relationship was modified by clinical syndrome or coronary anatomy using a large database across the spectrum of ACS and adjusting for potentially confounding clinical covariates.

**Design, Setting, and Participants** A convenience sample of patients pooled from 11 independent, international, randomized ACS clinical trials between 1993 and 2006 whose databases are maintained at the Duke Clinical Research Institute, Durham, North Carolina. Of 136 247 patients, 38 048 (28%) were women; 102 004 (26% women) with ST-segment elevation myocardial infarction (STEMI), 14 466 (29% women) with non-STEMI (NSTEMI), and 19 777 (40% women) with unstable angina.

**Main Outcome Measure** Thirty-day mortality following ACS.

**Results** Thirty-day mortality was 9.6% in women and 5.3% in men (odds ratio [OR], 1.91; 95% confidence interval [CI], 1.83-2.00). After multivariable adjustment, mortality was not significantly different between women and men (adjusted OR, 1.06; 95% CI, 0.99-1.15). A significant sex by type of ACS interaction was demonstrated ( $P < .001$ ). In STEMI, 30-day mortality was higher among women (adjusted OR, 1.15; 95% CI, 1.06-1.24), whereas in NSTEMI (adjusted OR, 0.77; 95% CI, 0.63-0.95) and unstable angina, mortality was lower among women (adjusted OR, 0.55; 95% CI, 0.43-0.70). In a cohort of 35 128 patients with angiographic data, women more often had nonobstructive (15% vs 8%) and less often had 2-vessel (25% vs 28%) and 3-vessel (23% vs 26%) coronary disease, regardless of ACS type. After additional adjustment for angiographic disease severity, 30-day mortality among women was not significantly different than men, regardless of ACS type. The relationship between sex and 30-day mortality was similar across the levels of angiographic disease severity ( $P$  for interaction = .70).

**Conclusions** Sex-based differences existed in 30-day mortality among patients with ACS and vary depending on clinical presentation. However, these differences appear to be largely explained by clinical differences at presentation and severity of angiographically documented disease.

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Several studies have offered novel approaches to understanding sex-based differences following ACS.<sup>14,18-21</sup> A large cohort analysis from the National Registry of Myocardial Infarction demonstrated a higher risk of early death for younger but not older women.<sup>14</sup> A prior analysis from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO IIb)<sup>22</sup> found that women and men have outcomes that differ according to the type of ACS.

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Compared with men, women had lower rates of adverse events in unstable angina, although no significant difference was observed in ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI). However, due to the limited sample size, the relationship between mortality and sex could not be evaluated in these subgroups.<sup>22</sup> In addition to clinical differences between women and men, many studies have noted sex-based differences in angiographic severity in ACS.<sup>8,21-24</sup> However, the relationships between angiographic severity in women and men across the spectrum of ACS and implications for mortality have not been fully explored.

Our study evaluated the relationships among sex, presenting clinical classification, angiographic disease burden, and 30-day mortality following ACS using a large, pooled clinical trials database spanning the full spectrum of ACS.

## METHODS

### Patient Population and Outcome Measures

Patients were pooled from a convenience sample of 11 independent, international, randomized ACS clinical trials between 1993 and 2006 whose databases are maintained at the Duke Clinical Research Institute, Durham, North Carolina, and who were available in existing merged data sets before our analysis (TABLE 1). The methods of each individual trial have been previously reported along with definitions for each clinical syndrome.<sup>25-35</sup> For our analysis, demographic information, clinical characteristics, angiographic data, and 30-day mortality were used as recorded in the database for each clinical trial. The number of patients enrolled in each trial, type of ACS evaluated, and randomized interventions within each trial are shown in Table 1.

Obstructive coronary disease was defined as more than 50% stenosis in the left main, proximal, or mid-distal left

anterior descending, circumflex, or right coronary artery. Patients were evaluated by number of coexistent obstructive coronary arteries (0, 1, 2, or 3) involved. Race/ethnicity of each patient was noted by a check mark on the case report form selected by the investigator.

The primary end point of our study was all-cause mortality within 30 days of enrollment.

### Statistical Analysis

All analyses were performed in 4 populations: all patients with ACS and 3 subgroups, which included patients with STEMI, NSTEMI, and unstable angina. Baseline characteristics are described for each group and subgroup reporting percentiles for discrete variables and medians (interquartile ranges) for continuous factors.

Multivariable logistic regression models were used to evaluate the relationship between sex and 30-day mortality, while controlling for important

**Table 1.** Summary of Trials Used in the Study

Source	No./Total No. (%) of Patients Enrolled		Type of ACS Evaluated	Intervention
	Women	Men		
GUSTO I, <sup>25</sup> 1993	10 315/40 968 (25.2)	30 653/40 968 (74.8)	STEMI	Streptokinase and subcutaneous heparin, streptokinase and intravenous heparin, accelerated tissue plasminogen activator and intravenous heparin, or a combination of streptokinase plus tissue plasminogen activator with intravenous heparin
GUSTO IIb, <sup>26</sup> 1996	3661/12 140 (30.2)	8479/12 140 (69.8)	STEMI, NSTEMI, unstable angina	Heparin; hirudin
GUSTO III, <sup>27</sup> 1997	4124/15 059 (27.4)	10 935/15 059 (72.6)	STEMI	Tissue plasminogen activator; reteplase
ASSENT II, <sup>28</sup> 1999	3930/17 004 (23.1)	13 074/17 004 (76.9)	STEMI	Tissue plasminogen activator; tenecteplase
ASSENT III, <sup>29</sup> 2001	1438/6116 (23.5)	4678/6116 (76.5)	STEMI	Full-dose tenecteplase and heparin; full-dose tenecteplase and enoxaparin; half-dose tenecteplase and abciximab
ASSENT III+, <sup>30</sup> 2003	378/1639 (23.1)	1261/1639 (76.9)	STEMI	Full-dose tenecteplase and heparin; full-dose tenecteplase and enoxaparin
HERO 2, <sup>31</sup> 2001	4850/17 087 (28.4)	12 237/17 087 (71.6)	STEMI	Bivalirudin; heparin; streptokinase
PURSUIT, <sup>32</sup> 2000	3857/10 947 (35.2)	7090/10 947 (64.8)	NSTEMI, unstable angina	Placebo; low-dose eptifibatide; high-dose eptifibatide
PARAGON A, <sup>33</sup> 1998	776/2262 (34.3)	1486/2262 (65.7)	NSTEMI, unstable angina	Low-dose lamifiban with and without heparin; high-dose lamifiban with and without heparin
PARAGON B, <sup>34</sup> 2000	1789/5225 (34.2)	3436/5225 (65.8)	NSTEMI, unstable angina	Lamifiban; heparin
GUSTO IV, <sup>35</sup> 2001	2930/7800 (37.6)	4870/7800 (62.4)	NSTEMI, unstable angina	Heparin; 24-h abciximab; 48-h abciximab
Total	<b>38 048/136 247 (27.9)</b>	<b>98 199/136 247 (72.1)</b>		

Abbreviations: ACS, acute coronary syndromes; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

clinical characteristics. Extensive work has been performed to identify clinical risk factors in 30-day mortality models developed from the GUSTO-I<sup>36</sup> (patients with STEMI) and PURSUIT<sup>37</sup> (patients with NSTEMI and/or unstable angina) databases. Variables that were predictive in either patient group were included in our analysis whenever possible, based on available data. These included age, heart rate, systolic blood pressure, weight, height, race, Killip class (class I indicates no evidence of heart failure by physical examination; class II, findings consistent with mild to moderate heart failure [ $S_3$ , lung rales less than one-half way up the posterior lung fields, or jugular venous distension]; class III, overt pulmonary edema; or class IV, cardiogenic shock), age  $\times$  Killip class, current smoking, former smoking, history of diabetes, history of congestive heart failure, history of myocardial infarction (MI), history of coronary artery bypass graft (CABG) surgery, history of percutaneous coronary intervention, and history of hypertension. Due to extensive missing data, we were unable to consider a history of peripheral vascular disease or stroke. To ensure that these were not a source of confounding, we conducted sensitivity analyses on the patients for whom these data were available. We observed no change in the sex effect depending on whether these covariates were included. Naturally continuous variables, such as age, were analyzed as continuous variables and were not categorized or modified. The continuous variables were checked for linear association with mortality and splines were used to account for non-linearity whenever appropriate. Due to missing data on various covariates, the fully adjusted models in the overall cohort had 115 389 patients and the cohort with angiographic data had 32 599 patients. The variables with the most missing data (>1% missing) were height, heart rate, blood pressure, and Killip class. Analysis was conducted on complete cases.

Our data consisted of multiple trials that were conducted at different times.

We conducted sensitivity analyses to account for potential differences over time or between trials. We fit the adjusted analysis in the overall cohort including trial as a categorical covariate and observed no difference in the sex effect. Similarly, we observed no difference in the sex effect when date of patient randomization was included in the model to account for time. We also fit the adjusted models, conditional on ACS category, and observed no changes in the sex effect. In these models, there were no interactions between sex and trial or sex and randomization date; therefore, we were confident in our aggregate analysis over trials.

Our primary goal was to assess the sex effect within the subgroups of ACS (STEMI, NSTEMI, or unstable angina), although we also presented results for the overall cohort. We obtained estimates of the sex effect, conditional on ACS category, from a multivariable logistic regression model using all patient data (all ACS). This was performed by including the interaction between sex and ACS (STEMI, NSTEMI, or unstable angina). To evaluate whether differences in coronary anatomy between women and men may explain any difference in mortality, we also fit models adjusted for angiographic disease severity. Thus, we obtained odds ratios (ORs) of women vs men conditional on the ACS category and both adjusted and unadjusted for disease severity. To evaluate if sex has a different association with mortality based on angiographic disease severity, interaction between sex and angiographic disease severity was assessed. We estimated the sex effect conditional on angiographic disease severity by including the interaction between sex and angiographic disease severity. This provided ORs of women vs men conditional on disease severity. This final analysis was conducted for all ACS and repeated in the subgroups of patients with STEMI, NSTEMI, and unstable angina.

Our goal was to assess the adjusted effect of sex. Unadjusted analyses have been reported previously and were in-

cluded for the purpose of comparison. The unadjusted frequency of 30-day mortality is presented as well as the unadjusted ORs with 95% confidence intervals (CIs). Our primary analyses consisted of tests for a sex effect in ACS categories, tests for interaction between sex and ACS, and tests for interaction between sex and angiographic disease severity in adjusted models. We used the Bonferroni correction to adjust for multiple comparisons in our primary analyses. The Bonferroni-adjusted threshold for statistical significance was  $P \leq .005$ . SAS version 8.2 (SAS Institute Inc, Cary, North Carolina) was used for all statistical analyses.

Each participating center obtained approval from its local ethics board before patient enrollment. Our analysis was performed as part of an institutional review board–approved subanalyses of the Duke Clinical Research Institute clinical trials database.

## RESULTS

### Patient Characteristics

Of the 136 247 patients with ACS in this analysis, 38 048 (28%) were women. There were 102 004 patients with STEMI (26% women), 14 466 with NSTEMI (29% women), and 19 777 with unstable angina (40% women). Baseline characteristics for women and men are shown in TABLE 2. Approximately, 40% of women and men were enrolled from North America (United States and Canada). Women were older and had a higher prevalence of hypertension, hyperlipidemia, diabetes, and heart failure. Men were more likely to be smokers and had a higher prevalence of prior MI and prior CABG surgery. These differences were consistent across the entire spectrum of ACS. Patients with NSTEMI or unstable angina had a higher prevalence of risk factors and previous cardiac disease than those patients with STEMI.

### Angiographic Disease Severity

Among the 35 128 patients who had catheterizations (26% of the overall population), 9399 (27%) were women.

Among patients who had catheterization, 20 352 presented with STEMI (24% women), 6743 with NSTEMI (26% women), and 8033 with unstable angina (35% women). Angiographic disease severity among those patients selected for angiography differed by sex across the spectrum of ACS (FIGURE 1). Overall, women who underwent catheterization were more likely to have nonobstructive disease and less likely to have multivessel disease compared with men. The difference in nonobstructive coronary disease prevalence was most notable in the NSTEMI and unstable angina groups in which women had a 2-fold higher prevalence of nonobstructive disease than men. More than 25% of all women with unstable angina who underwent coronary angiography in these clinical

trials had no obstructive coronary disease. The prevalence of single-vessel disease differed according to type of ACS; women were more likely to have single-vessel disease in STEMI; however, no difference was found with NSTEMI or unstable angina. Left main disease was more frequent among men compared with women in the overall cohort (5.9%; 95% CI, 5.6%-6.2% vs 4.7%; 95% CI, 4.3%-5.1%), STEMI (4.0%; 95% CI, 3.7%-4.3% vs 3.0%; 95% CI, 2.6%-3.5%), NSTEMI (9.0%; 95% CI, 8.2%-9.8% vs 7.3%; 95% CI, 6.0%-8.5%), and unstable angina (8.7%; 95% CI, 7.9%-9.5% vs 6.0%; 95% CI, 5.1%-6.8%) populations.

### 30-Day Mortality

Women had a significantly higher unadjusted 30-day mortality compared

with men (OR, 1.91; 95% CI, 1.83-2.00) (FIGURE 2). After multivariable adjustment for clinical characteristics, no significant difference was observed in 30-day mortality between women and men (OR, 1.06; 95% CI, 0.99-1.15). A significant interaction existed between sex and ACS type ( $P < .001$ ). Among patients with STEMI, 30-day mortality was significantly higher among women compared with men; however, it was markedly attenuated after adjustment (unadjusted OR, 2.29; 95% CI, 2.18-2.40; adjusted OR, 1.15; 95% CI, 1.06-1.24). In contrast, the unadjusted risk in NSTEMI was significantly greater in women compared with men, but after adjustment 30-day mortality was lower in women (unadjusted OR, 1.50; 95% CI, 1.28-1.75; adjusted OR, 0.77; 95%

**Table 2.** Baseline Characteristics of Women and Men Presenting With Any ACS, STEMI, NSTEMI, or Unstable Angina

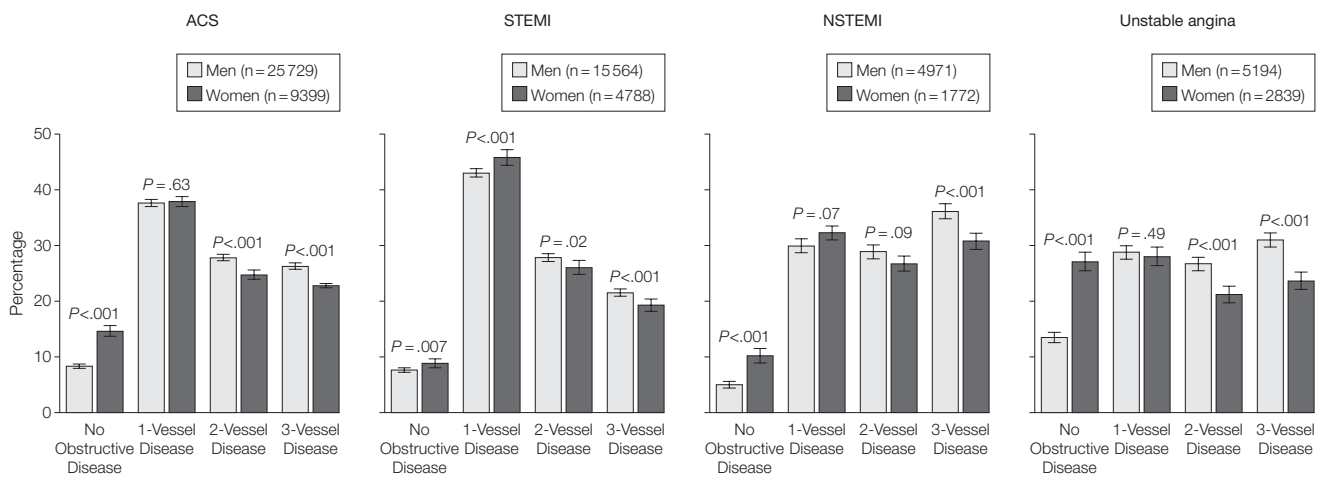
Characteristics	No. (%) of Patients							
	Any ACS		STEMI		NSTEMI		Unstable Angina	
	Women (n = 38 048)	Men (n = 98 199)	Women (n = 26 032)	Men (n = 75 972)	Women (n = 4159)	Men (n = 10 307)	Women (n = 7857)	Men (n = 11 920)
<b>Demographics</b>								
Age, median (IQR), y	68 (60-75)	60 (51-69)	68 (60-75)	60 (50-68)	69 (61-76)	63 (54-71)	67 (59-74)	64 (54-71)
White race	30 083 (92)	77 215 (92)	19 162 (93)	56 644 (92)	3819 (92)	9557 (93)	7102 (90)	11 014 (93)
BMI, median (IQR)	26.6 (24-30)	26.6 (24-29)	26.5 (24-30)	26.5 (24-29)	27.0 (24-30)	26.9 (25-30)	27 (24-30)	27 (24-29)
Smoker	9845 (26)	38 482 (40)	7728 (30)	31 523 (42)	870 (21)	3647 (36)	1247 (16)	3312 (28)
<b>Geographic region</b>								
North America	14 874 (40)	36 760 (38)	11 128 (44)	29 811 (41)	1510 (36)	3568 (35)	2236 (29)	3381 (28)
Western Europe	11 702 (31)	33 774 (35)	6938 (27)	23 438 (32)	1635 (39)	4631 (45)	3129 (40)	5705 (48)
Eastern Europe	6576 (18)	12 140 (13)	4192 (17)	9516 (13)	643 (16)	1040 (10)	1741 (22)	1584 (13)
Other <sup>a</sup>	4184 (11)	13 028 (14)	3062 (12)	10 710 (14)	371 (9)	1068 (10)	751 (10)	1250 (11)
<b>Clinical history</b>								
Hypertension	21 738 (57)	37 719 (39)	14 167 (55)	27 323 (36)	2632 (63)	4618 (45)	4939 (63)	5778 (49)
Diabetes	8496 (22)	14 229 (15)	5442 (21)	10 052 (13)	1107 (27)	1923 (19)	1947 (25)	2254 (19)
Hyperlipidemia	12 181 (39)	25 926 (33)	7095 (36)	17 356 (31)	1780 (43)	3944 (39)	3306 (43)	4626 (40)
Prior MI	6783 (18)	20 641 (21)	3625 (14)	12 936 (17)	1042 (25)	3302 (32)	2116 (27)	4403 (37)
Prior CABG surgery	1471 (4)	6009 (6)	564 (2)	3025 (4)	260 (6)	1220 (12)	647 (8)	1764 (15)
Heart failure	2391 (6)	3180 (3)	997 (4)	1455 (2)	533 (13)	759 (7)	861 (11)	966 (8)
<b>Clinical presentation</b>								
Heart rate, median (IQR), beats/min	75.0 (64-87)	73.0 (62-85)	75.0 (64-88)	74.0 (62-85)	76.0 (68-88)	72.0 (64-84)	76.0 (68-88)	72.0 (64-84)
Systolic BP, median (IQR), mm Hg	132.0 (117-150)	130.0 (118-150)	130.0 (115-150)	130.0 (116-148)	138.0 (120-152)	130.0 (120-150)	140.0 (120-155)	134.0 (120-150)
<b>Killip class score<sup>b</sup></b>								
I	28 567 (82)	80 564 (87)	20 771 (81)	65 199 (87)	2864 (82)	7569 (88)	4932 (90)	7796 (92)
II	5120 (15)	10 201 (11)	4126 (16)	8677 (12)	521 (15)	892 (10)	473 (9)	632 (7)
III-IV	1050 (3)	1619 (2)	880 (2)	1399 (1)	99 (3)	144 (2)	71 (1)	79 (1)

Abbreviations: ACS, acute coronary syndromes; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CABG, coronary artery bypass graft; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; STEMI, ST-segment elevation MI.

<sup>a</sup>Includes Latin America, Australia, New Zealand, Israel, South Africa, Asia, and Arab region.

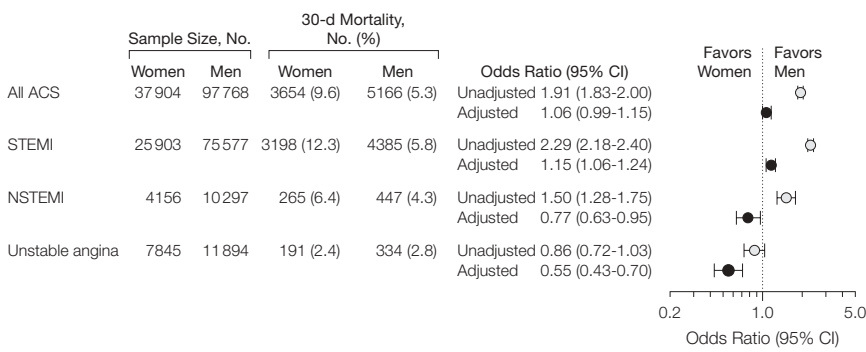
<sup>b</sup>See the "Methods" section for definition of Killip class scores.

**Figure 1.** Angiographic Data in Women and Men Presenting With ACS, STEMI, NSTEMI, or Unstable Angina



ACS indicates acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI. Error bars indicate 95% confidence intervals.

**Figure 2.** Unadjusted and Multivariable-Adjusted 30-Day Mortality Models in Women vs Men Across the Spectrum of ACS in the Overall Cohort (n=136,247)



ACS indicates acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI; CI, confidence interval. Odds ratios of women vs men (and 95% CIs) obtained through logistic regression include age, Killip class, age × Killip class, heart rate, systolic blood pressure, weight, height, history of congestive heart failure, history of myocardial infarction, history of coronary artery bypass graft surgery, history of diabetes, history of percutaneous coronary intervention, history of hypertension, current smoking status, and former smoking status, along with type of ACS. Unadjusted and adjusted STEMI, NSTEMI, and unstable Angina include ACS × sex interaction to obtain the sex effect conditional on ACS categories. Adjusted STEMI and adjusted unstable Angina were statistically significant in overall 30-day mortality between women and men under the Bonferroni-adjusted significance level of  $P = .005$  ( $= .05/10$ ).

CI, 0.63-0.95). In unstable Angina, women and men had similar unadjusted risk; however, after adjustment, women had a significantly lower 30-day mortality than men (unadjusted OR, 0.86; 95% CI, 0.72-1.03; adjusted OR, 0.55; 95% CI, 0.43-0.70).

The relationship between angiographic disease and sex-specific mortality across the spectrum of ACS is shown in FIGURE 3. Among those patients who underwent cardiac

catheterization (n=35,128), we observed no significant interaction between sex and severity of disease on 30-day mortality ( $P$  for interaction = .70); the more severe the angiographic disease, the worse the prognosis regardless of sex (eTable, available at <http://www.jama.com>). When angiographic severity was included in the 30-day mortality models containing comorbidities and sex, there were no longer any statistically signifi-

cant associations between sex and mortality, suggesting that in this subset of patients selected for catheterization, the mortality difference originally observed may have been related to the difference in disease severity among women and men (Figure 3).

The relationship between sex and age as well as sex and diabetes was evaluated to assess whether a different 30-day mortality risk existed in women compared with men. Overall, no significant interaction was detected between sex and age ( $P = .68$ ) or between sex and diabetes ( $P = .12$ ).

**COMMENT**

The association between sex and mortality among patients with cardiovascular disease has been a major topic of study during the past several decades. Despite the increased attention, this relationship is poorly understood. Some studies demonstrate increased rates of mortality among women, some indicate no difference, and other studies show lower rates of mortality for women compared with men.<sup>3-12,15,16</sup> By pooling high-quality clinical and angiographic data from 11 clinical trials, we enhanced our ability to evaluate relationships among sex, clinical characteristics, disease presentation, coronary anatomy, and all-cause mortality following ACS.

In the resulting large patient population, 30-day mortality was higher for women than men; however, much of this difference was attenuated following adjustment for baseline differences between women and men at the time of presentation. In addition to those clinical parameters included in the adjusted model, differences in a number of variables were identified that could affect the relationship between mortality and sex. These included additional comorbidities, disease presentation, and coronary anatomy.

Consistent with previous findings,<sup>3,22,38,39</sup> we found that women as a group were older with more comorbidities than men, including hypertension, hyperlipidemia, diabetes, and heart failure. In contrast, men were more likely to be smokers and to have a history of MI or CABG surgery. Furthermore, these differences in risk burden were present and similar across all forms of ACS. In particular, the median age of women was similar across the 3 major categories of ACS, although differences between men and women were less in unstable angina than in STEMI.

The reduction in the magnitude of differences in outcomes after multivariable adjustment is consistent with older age and worse baseline risk factors for women than men. In unadjusted analyses, we found almost a 2-fold increased risk for 30-day mortality in women compared with men (OR, 1.91; 95% CI, 1.83-2.00). A subset of covariates (age, smoking, hypertension, heart rate, and height) had the largest effect in attenuating the crude association. When we fit an adjusted model with only these covariates, we get similar results to the fully adjusted model (OR, 1.05; 95% CI, 0.98-1.13). This suggests that the crude differences in mortality are largely explained by these differences at presentation. Previous analyses demonstrated that certain risk factors, such as age and diabetes, confer a different mortality risk in women compared with men.<sup>13,14,18-20,40</sup> Data from US National

**Figure 3.** Unadjusted and Multivariable-Adjusted Plus Angiographic Disease Severity 30-Day Mortality Models in Women vs Men Across the Spectrum of ACS in Patients With Angiographic Data (n=35 128)



ACS indicates acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI; CI, confidence interval. Odds ratios of women vs men (and 95% CIs) obtained through logistic regression include age, Killip class, age  $\times$  Killip class, heart rate, systolic blood pressure, weight, height, history of congestive heart failure, history of myocardial infarction, history of coronary artery bypass graft surgery, history of diabetes, history of percutaneous coronary intervention, history of hypertension, current smoking status, and former smoking status, along with type of ACS and angiographic disease severity. Unadjusted and adjusted STEMI, NSTEMI, and unstable angina include ACS  $\times$  sex interaction to obtain the sex effect conditional on ACS categories. There was no significant differences in overall 30-day mortality between women and men under the Bonferroni-adjusted significance level of  $P = .005$  ( $= .05/10$ ).

Registry of Myocardial Infarction found an increased short-term mortality risk for young women compared with young men, with no mortality difference in the older population.<sup>14</sup> However, in our analysis, no significant interaction was detected between sex and age ( $P = .68$ ) in the overall population. Other studies have found that diabetes is associated with a greater mortality risk among women than men.<sup>18,19</sup> However, in our study, the differences in mortality between patients with and without diabetes were similar for women and men across the spectrum of ACS, and no significant interaction was detected between sex and diabetes ( $P = .12$ ). It is plausible that once coronary disease is manifested the influence of various risk factors is similar among men and women. Alternatively, differences in inclusion criteria, study design, or end points analyzed may partially explain the differences between studies.

Perhaps the most striking findings in our analyses relate to the examination of mortality according to type of ACS. We found a significant interaction between sex and type of ACS ( $P < .001$ ), such that 30-day mortality risk among women was modestly

higher than men only for those patients presenting with STEMI. In patients with NSTEMI and unstable angina, women had a lower adjusted 30-day mortality risk than men. In fact, the strongest finding after full adjustment was lower risk among women with unstable angina. These results are in part consistent with prior studies that noted decreased risk of adverse events following unstable angina among women vs men.<sup>4,22</sup> In our study, we extended these findings to evaluate the relationship between type of MI and mortality by sex, demonstrating that women with STEMI have modestly higher mortality than men with STEMI. The effect of adjustment in NSTEMI resulted in a qualitative difference in the association, going from excess risk to a trend toward lower risk. Thus, there is a gradient of differential risk between the sexes in relationship to clinical syndrome. Although many sex-specific studies lump all patients with ACS together and we present these data for purposes of comparability, our study indicates that STEMI, NSTEMI, and unstable angina should not be combined, but evaluated separately.

One of the key features of our study was the availability of angiographic data. Women and men who present with ACS have sex-based differences in angiographic disease burden. The relationship between burden of disease and mortality is complex with some studies suggesting worse outcomes in single-vessel coronary disease, perhaps due to less collateral circulation and myocardial preconditioning.<sup>41-45</sup> However, the relationship between overall burden of coronary disease and mortality is well established.<sup>46</sup> Similar to previous studies,<sup>8,21-24</sup> we observed lower rates of clinically significant coronary stenosis in women compared with men. This finding was consistent across the spectrum of ACS. The apparently paradoxical worse prognosis of women in STEMI, yet better prognosis in unstable angina, may represent the complex spectrum of this disease.

Regardless of ACS type, there were no significant differences in 30-day mortality for women and men, after adjusting for clinical covariates and angiographic disease severity and accounting for multiple comparisons (Figure 3). Although sex-based difference in outcome may not be completely explained by women's lesser burden of angiographic disease, coronary anatomy may partially explain the difference in mortality in those patients with unstable angina, as the adjusted OR for the sex effect was attenuated after the inclusion of angiographic disease severity. Furthermore, our study was unable to detect a significant interaction between sex and angiographic disease severity with respect to 30-day mortality, suggesting a similar effect of anatomy on mortality between women and men.

Several potential explanations for sex-related differences in mortality following ACS are offered. Consistent with prior studies and clinical experience, our results indicate that women and men who present with ACS are a heterogeneous group. Studies of low-risk patients have consistently found either no significant difference in the mortality rate between women and men

or a lower rate among women.<sup>4,5,12,47</sup> In contrast, studies of women at higher risk note similar or increased risk compared with men.<sup>6,9,16</sup> We compared 30-day mortality stratified by type of ACS, a design that enabled us to more precisely define the risk in each clinical population independently; therefore, to more appropriately determine the outcome by category of risk. Although our data set cannot address a possible contribution from differential effectiveness or safety of therapies, our findings indicate that careful attention to clinical syndrome, clinical characteristics, and coronary anatomy are essential to ascertaining and understanding sex-related differences.

The modest differences in risk after adjustment argue against differences in pathophysiology of ACS by sex. However, there may be subtle differences according to type of ACS and by sex. Whereas STEMI is more likely to be caused by acute plaque rupture, NSTEMI and unstable angina often originate from a moderate coronary stenosis.<sup>48,49</sup> It is possible that intrinsic differences in angiogenesis and collateralization between women and men<sup>22,42</sup> play a role, such that a sudden coronary occlusion puts women at greater risk in the setting of STEMI creating more transmural infarctions associated with higher complications. Conversely, in syndromes like NSTEMI and unstable angina without epicardial occlusion, women's lesser angiographic disease burden is associated with a better prognosis. Sex-based differences in the culprit lesion of acute MI also exist.<sup>50-52</sup> Plaque rupture is more common in men; however, plaque erosion is more common in women.<sup>50</sup> These basic mechanistic differences may in part explain some of the sex-based differences in outcomes following ACS. Unfortunately, ante mortem data such as ours cannot address the differences in anatomic substrate determined postmortem as described above; however, there was no interaction between angiographic disease burden and sex with regard to risk found in our cohort.

### Strengths and Limitations

The use of a pooled clinical trials database has several advantages.<sup>53,54</sup> First, pooling from several studies allowed the analysis of a very large sample size and secondarily the exploration of coronary angiography findings in a large number of patients. The uniform inclusion and exclusion criteria used for enrollment of both sexes helped to ensure that no systematic biases occurred in diagnosis or sampling between men and women. Similarly, although care in clinical trials may differ from that in the community and may not be generalizable to all men and women presenting with ACS, it is possible that care within a clinical trial setting may be more uniform and therefore more reflective of underlying differences in pathophysiology. Finally, by using patients enrolled in a clinical trial, all data points were collected independently and carefully monitored.

Our study has some limitations. As an observational study, residual confounding or selection bias cannot be completely excluded as an alternative explanation of our findings, even after adjusting for a wide range of patient characteristics. The database merged several clinical trials and intertrial variability in care may exist that could have influenced results in the pooled patient population. However, only those trials that included both men and women in their study populations were pooled and adjustment for trial did not change the observed differences in mortality between women and men. Similarly, although the data in our trials were accrued over decades, during which diagnostic standards (eg, use of troponins), use of procedures and adjunctive therapies, and guidelines adherence all evolved, any relevant changes are likely to have had similar effect on both men and women in each trial. Furthermore, there was no interaction between sex and trial that would have been expected if such temporal changes influenced the results. Additionally, because all patients in our analysis were part of a clinical trial for ACS, we were unable to address the

possibility of a differential attrition rate in the prehospital phase by sex. Because catheterization was not mandated as part of the trials' protocols, patient selection may have introduced potential referral bias and survival bias, and therefore should be interpreted with caution. Some variables of interest (eg, creatinine clearance) were not available in all trials and, therefore, the relationship between sex and mortality was not explored. Nevertheless, the final adjusted model had a C index of 0.81, indicating excellent discriminatory ability for 30-day mortality. Finally, this was an observational study with complex interactions; therefore, even a large database may not be definitive without replication.

### Conclusions

Our study suggests a better understanding of the observed sex-based differences. Sex-based differences exist in 30-day mortality among patients with ACS and vary depending on clinical presentation. However, these differences are markedly attenuated following adjustment for clinical differences and angiographic data. The attenuation in the difference in mortality suggests that much of the crude differences are explained by these factors. This study further highlights the clinical and angiographic differences among men and women at presentation with ACS. Understanding and considering these differences may lead to better risk stratification and treatment of all patients with ACS.

**Author Contributions:** Dr Berger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Berger, Califf, Becker, Douglas.

**Acquisition of data:** Granger, Armstrong, White, Topol, Califf, Douglas.

**Analysis and interpretation of data:** Berger, Elliott, Gallup, Roe, Granger, Armstrong, Simes, White, Van de Werf, Topol, Hochman, Newby, Harrington, Califf, Becker, Douglas.

**Drafting of the manuscript:** Berger, Elliott, Becker. **Critical revision of the manuscript for important intellectual content:** Berger, Elliott, Gallup, Roe, Granger, Armstrong, Simes, White, Van de Werf, Topol, Hochman, Newby, Harrington, Califf, Becker, Douglas. **Statistical analysis:** Berger, Elliott, Gallup.

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**Study supervision:** Berger, Roe, Armstrong, Van de Werf, Hochman, Califf, Becker, Douglas.

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**A full list of study investigators and coordinators** for each trial has been published previously.<sup>25-35</sup>

**Additional Information:** An online eTable is available at <http://www.jama.com>.

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