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Sex Differences in Mortality Following Acute Coronary Syndromes

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Abstract

Context—There is conflicting information about whether sex-differences modulate short-term mortality following acute coronary syndromes (ACS).

Objective—To investigate the relationship between sex and 30-day mortality in ACS, and determine whether this relationship is 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—Data from 11 ACS trials from 1993 to 2006 were pooled. Of 136,247 patients, 38,048 (28%) were women; 102,004 (26% women) STEMI, 14,466 (29% women) NSTEMI and 19,777 (40% women) unstable angina (UA).

Main Outcome Measure—Thirty-day mortality following ACS.

Results—Mortality at 30 days 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). Importantly, a significant sex by type of ACS interaction was demonstrated (P<0.001). In STEMI, 30-day mortality was higher among women (adjusted OR 1.15, 95% CI 1.06–1.24), whereas NSTEMI (adjusted OR 0.77, 95% CI 0.63–0.95), and UA 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 non-obstructive (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-value for interaction =0.70),

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There are no conflicts of interest to report.

Conclusions—Sex-based differences exist in 30-day mortality among ACS patients and vary depending on clinical presentation. However, these differences are markedly attenuated following adjustment for clinical differences and angiographic data.

Cardiovascular disease is the leading cause of death in both men and women, accounting for one third of all deaths[1]. Although several studies have shown an improvement of prognosis in women over time[2], overall outcomes remain worse for women compared with men[3], 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 noted conflicting results, even after adjustment for demographics and clinical characteristics[4-17]. In a large systematic review comparing short-term mortality between women and men,[3] Vaccarino and colleagues concluded that after adjustment for differences in age and baseline prognostic factors, some, but not all, of the excess mortality was explained.

Several reports have offered novel approaches to understanding sex-based differences following ACS[14, 18-21]. A large cohort analysis from the National Registry of Myocardial Infarction demonstrated a higher risk of early death for younger women, but not older women[14]. A prior analysis from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO IIb) found that women and men have outcomes that differ according to the type of ACS[22]. Compared with men, women had lower rates of adverse events in unstable angina [UA]; while no significant difference was seen 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 [22]. In addition to clinical differences between women and men, many studies have noted sex-based differences in angiographic severity in ACS[8, 21-24]. 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

Patients were pooled from a convenience sample of 11 independent, international randomized ACS clinical trials whose databases are maintained at the Duke Clinical Research Institute (DCRI) and were available in existing merged datasets prior to our analysis (Table 1). The methods of each individual trial have been previously reported along with definitions for each clinical syndrome[25-35]. For this analysis, demographic information, clinical characteristics, angiographic data and mortality at 30 days 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 summarized in Table 1.

Obstructive coronary disease was defined as greater 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. The race and ethnicity of each patient was noted by a check mark on the case report form selected by the investigator.

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

Statistical Analysis

All analyses were performed in 4 populations: all patients with ACS, and three subgroups, including STEMI, NSTEMI and UA. Baseline characteristics are described for each group and subgroup reporting percentiles for discrete variables and medians (25th, 75th percentiles) for continuous factors.

Multivariable logistic regression models were used to evaluate the relationship between sex and 30 day mortality, while controlling for important clinical characteristics. Extensive work has been done to identify clinical risk factors in 30 day mortality models developed from the GUSTO-I[36] (STEMI patients) and PURSUIT (NSTEMI/UA patients)[37] databases. Variables that were predictive in either patient group were included in the current analysis whenever possible, based on the available data. These included age, heart rate, systolic blood pressure, weight, height, race, Killip class, interaction between age and Killip class, current smoking, former smoking, history of diabetes, history of CHF, history of MI, history of CABG, history of PCI, history of hypertension. Due to extensive missing data we were unable to consider a history of PVD or CVA. To ensure that these were not a source of confounding we conducted sensitivity analysis on the patients for whom these data was 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 n=115,389 and in the cohort with angiographic data there were n=32,599. The variables with the most missing data (greater than 1% missing) were height, heart rate, blood pressure and Killip class. Analysis was conducted on complete cases.

Our data consists of multiple trials which were conducted at different times. We conducted sensitivity analysis to account 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 was no interaction between sex and trial, nor sex and randomization date. Thus we felt confident in our aggregate analysis over trials.

Our primary purpose was to assess the sex effect within the subgroups of acute coronary syndrome (STEMI, NSTEMI, or UA), although we also present 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 done by including the interaction between sex and acute coronary syndrome (STEMI, NSTEMI, or UA) 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 of female vs. male, conditional on the ACS category, 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 odds ratios of female vs. male, conditional on disease severity. This final analysis was conducted for all ACS and repeated in the subgroups of STEMI, NSTEMI and UA patients.

In the present paper our goal is to assess the adjusted effect of sex. Unadjusted analyses have been reported previously, and we include these results for the purpose of comparison. The unadjusted frequency of 30 day mortality is presented as well as the unadjusted (OR) with 95

percent confidence intervals. Our primary analyses consist of tests for a sex effect in ACS categories, tests for interaction between sex and ACS, and interaction between sex and angiographic disease severity in adjusted models. We use the Bonferonni correction to adjust for multiple comparisons in our primary analyses. The Bonferonni adjusted threshold for statistical significant is 0.005. SAS version 8.2 was used for all statistical analyses.

Each participating center obtained approval from its local ethics board prior to patient enrollment. The current analysis was performed as part of institutional review board-approved subanalyses of the DCRI 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 UA (40% women). Baseline characteristics for women and men are shown in Table 2. Approximately, 40% of women and men were enrolled from North America. 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 myocardial infarction and prior bypass surgery. These differences were consistent across the entire spectrum of ACS. Patients with NSTEMI or UA had a higher prevalence of risk factors and previous cardiac disease than those with STEMI.

Angiographic Disease Severity

Among the 35,128 patients who had catheterizations (26% of the overall population), 9,399 (27%) were women. Among patients who had catheterization 20,352 presented with STEMI (24% women), 6,743 with NSTEMI (26% women), and 8,033 with UA (35% women). Angiographic severity among those selected for angiography differed by sex across the spectrum of ACS (Figure 1). Overall, women who underwent catheterization were more likely to have non-obstructive disease and less likely to have multi-vessel disease compared with men. The difference in non-obstructive coronary disease prevalence was most notable in the NSTEMI and UA groups in which women had a 2-fold higher prevalence of non-obstructive disease than men. Of note, more than a quarter of all women with UA 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 noted in NSTEMI or UA. Left main disease was more frequent among men compared with women in the overall cohort (5.9 (5.6–6.2)% vs. 4.7 (4.3–5.1)%), STEMI (4.0 (3.7–4.3)% vs. 3.0 (2.6–3.5)%), NSTEMI (9.0 (8.2–9.8)% vs. 7.3(6.0–8.5)%) and UA (8.7 (7.9–9.5)% vs 6.0 (5.1–6.8)%) populations.

Mortality

Women had a significantly higher unadjusted mortality at 30 days compared with men (OR 1.91, 95% CI 1.83–2.00) (Table 3). 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) (Figure 2). Of note, a significant interaction existed between sex and ACS type ($P<0.001$). Among STEMI patients, 30-day mortality was significantly higher among women compared with men, yet 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% 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 0.64, 95% CI 0.51–0.80).

The relationship between angiographic disease and sex-specific mortality across the spectrum of ACS is displayed in Table 4. Among those who underwent cardiac catheterization (n=35,128), we observed no significant interaction between sex and severity of disease on 30-day mortality (p-value for interaction=0.70) the more severe the angiographic disease the worse the prognosis regardless of sex (**Supplementary Index**). When angiographic severity was included in the 30-day mortality models containing co-morbidities and sex, there were no longer any statistically significant 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=0.681) or between sex and diabetes (P=0.118).

Discussion

The association between sex and mortality among patients with cardiovascular disease has been a major topic of study over the past several decades. Despite the increased attention, this relationship is poorly understood. Some studies demonstrate increased rates of mortality among women, some report no difference, and others show lower rates of mortality for women compared with men[3-12, 15, 16]. By pooling 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 were higher for women than men, however, much of this difference was attenuated following adjustment for baseline differences. In addition to those clinical parameters included in the adjusted model, differences in a number of variables were identified which could affect the relationship between mortality and sex. These include additional comorbidities, disease presentation, and coronary anatomy.

Consistent with previous findings[3, 22, 38, 39], 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 myocardial infarction or bypass surgery. Further, 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 UA than in STEMI.

The reduction in the magnitude of differences in outcomes after multivariable adjustment is consistent with the 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 was identified as primary confounders (age, smoking, hypertension, heart rate and height) which had the largest impact on the sex-specific differences. 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).

Previous analyses demonstrated that certain risk factors, such as age and diabetes confer a different mortality risk in women compared with men[13, 14, 18-20, 40]. Data from NRMI found an increased short-term mortality risk for young women compared with young men, with no mortality difference in the older population[14]. However, in the current analysis no significant

interaction was detected between sex and age (P=0.681) in the overall population. Other studies have found that diabetes is associated with a greater mortality risk among women than men[18, 19]. However, in our study the differences in mortality between diabetics and non-diabetics were similar for women and men across the spectrum of ACS, and no significant interaction was detected between sex and diabetes (P=0.118). Differences in inclusion criteria, study design, or endpoint 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<0.001) such that 30-day mortality risk among women was higher than men only for those presenting with STEMI. In NSTEMI and UA, women had a lower adjusted 30-day mortality risk than men. These results are in part consistent with prior studies that noted decreased risk of adverse events following UA among women compared with men.[4, 22] In the present study we extended these findings to evaluate the relationship between type of myocardial infarction and mortality by sex, demonstrating that women with STEMI have higher mortality than men with STEMI. Thus, there is a gradient of differential risk between the sexes in relation 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 UA should not be combined, but evaluated separately.

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[4, 5, 12, 41]. In contrast, studies of women at higher risk note similar or increased risk compared with men[6, 9, 16]. In our study, 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. While 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.

Alternative explanations for differences in mortality may relate to differences in pathophysiology of ACS according to type of ACS, and by sex. Whereas STEMI is more likely to be caused by acute plaque rupture, NSTEMI/UA often originates from a moderate coronary stenosis[42, 43]. It is possible that intrinsic differences in angiogenesis and collateralization between women and men[22, 44] play a role, such that a sudden coronary occlusion puts women at greater risk in the setting of STEMI creating more transmural infarcts associated with higher complications. Conversely, in syndromes like NSTEMI/UA without epicardial occlusion, women's lesser angiographic disease burden is associated with a better prognosis. Sex-based differences in the culprit lesion of acute myocardial infarction also exist[45-47]. Plaque rupture is more common in men, yet, plaque erosion is more common in women[45]. 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 post mortem as described above; however, there was no interaction between angiographic disease burden and sex with regard to risk found in our cohort.

It is also possible that the differential risk of death in women following ACS is due to 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[44,

[48-51]. However, the relationship between overall burden of coronary disease and mortality is well established[52]. Similar to previous studies[8, 21-24], 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 UA 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. (Table 4). 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 with UA, as the adjusted odds ratio 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.

Strengths and Limitations

The use of a pooled clinical trials database has several advantages[53, 54]. First, pooling from several studies allowed us to interrogate a very large sample size, and secondarily to explore 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, while 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 we ensured that all data points were collected independently and carefully monitored.

Our study does have some limitations. As an observational study, we cannot completely exclude residual confounding or selection bias as an alternative explanation of our findings, although we were able to adjust for a wide range of patient characteristics. The database we used merged several clinical trials and inter-trial 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 (e.g.: use of troponins), use of procedures and adjunctive therapies and guidelines adherence all evolved, any relevant changes are likely to have had similar impact on both men and women in each trial. Furthermore, there was no interaction between sex and trial which would have been expected if such temporal changes influenced the results. Additionally, since all patients in this analysis were part of a clinical trial for ACS, we were unable to address the possibility of a differential attrition rate in the pre-hospital phase by sex. Since 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 (e.g. creatinine clearance) were not available in all trials and therefore were unable to explore their relationship with sex and mortality. 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, thus even a large database may not be definitive without replication.

Conclusions

Sex-based differences exist in 30-day mortality among ACS patients and vary depending on clinical presentation. However, these differences are markedly attenuated following adjustment for clinical differences and angiographic data. The complex interplay of known characteristics and the remaining unexplained sex-based differences suggest that sex is an important factor in the study of ACS, and should be considered in planning and analyzing future research and in delivering care to men and women with ACS. Understanding these may lead to better risk stratification and treatment of all patients with acute coronary syndromes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The complete list of study investigators and coordinators for each trial has been previously published.

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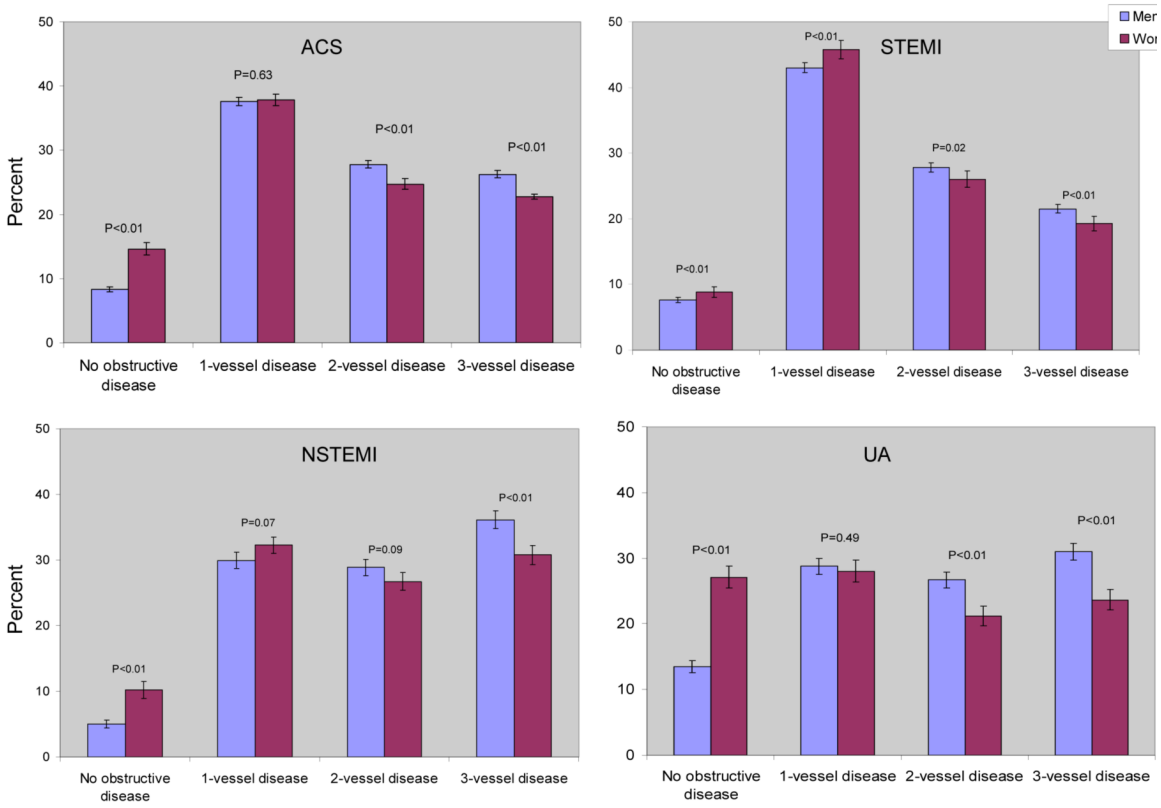

Figure 1. Angiographic data in women and men presenting with ACS, STEMI, NSTEMI or unstable angina

In the complete ACS cohort (n=35,128), there were 25,729 men and 9,399 women. In the STEMI cohort (n=20,352), there were 15,564 men and 4,788 women. In the NSTEMI cohort (n=6,743), there were 4,971 men and 1,772 women. In In the UA cohort (n=8,033), there were 5,194 men and 2,839 women.

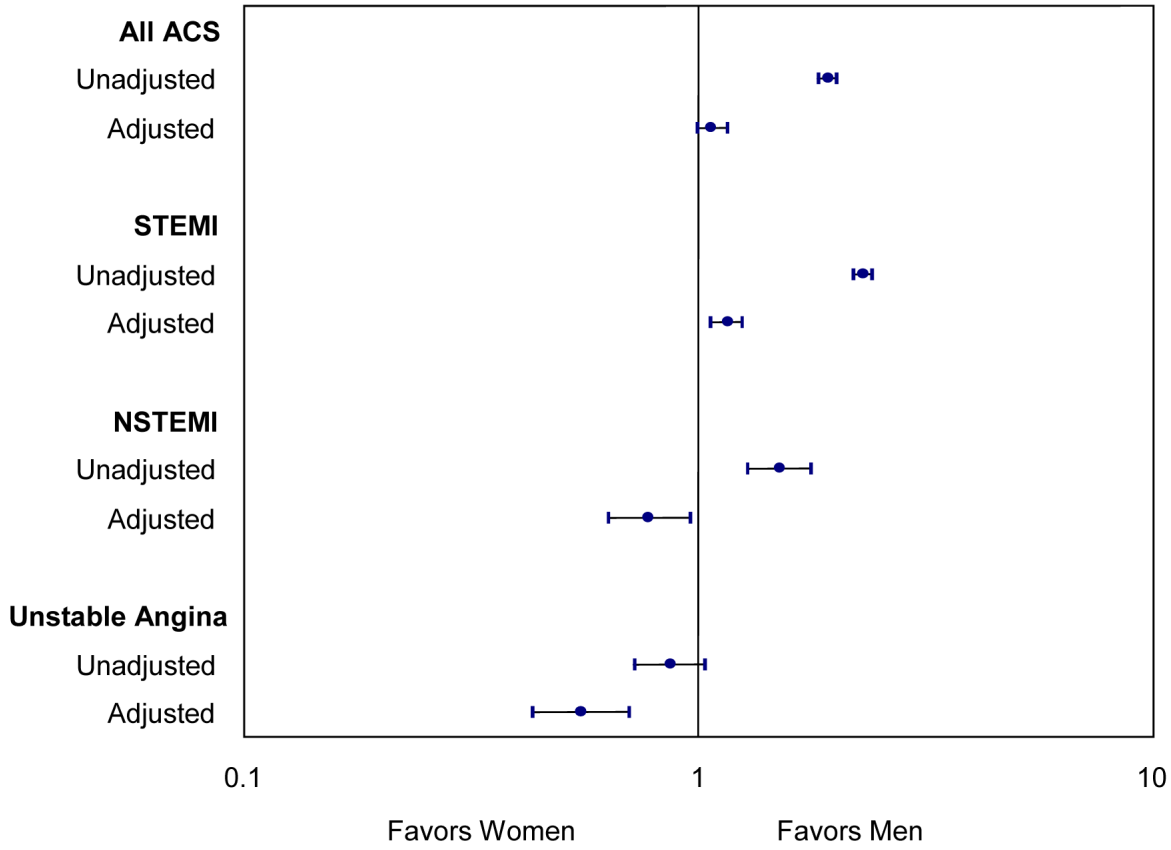

Figure 2. Unadjusted and multivariable adjusted 30-day mortality models (odds ratio ± 95% confidence interval) in women versus men across the spectrum of acute coronary syndromes in the overall cohort (n=136,247)

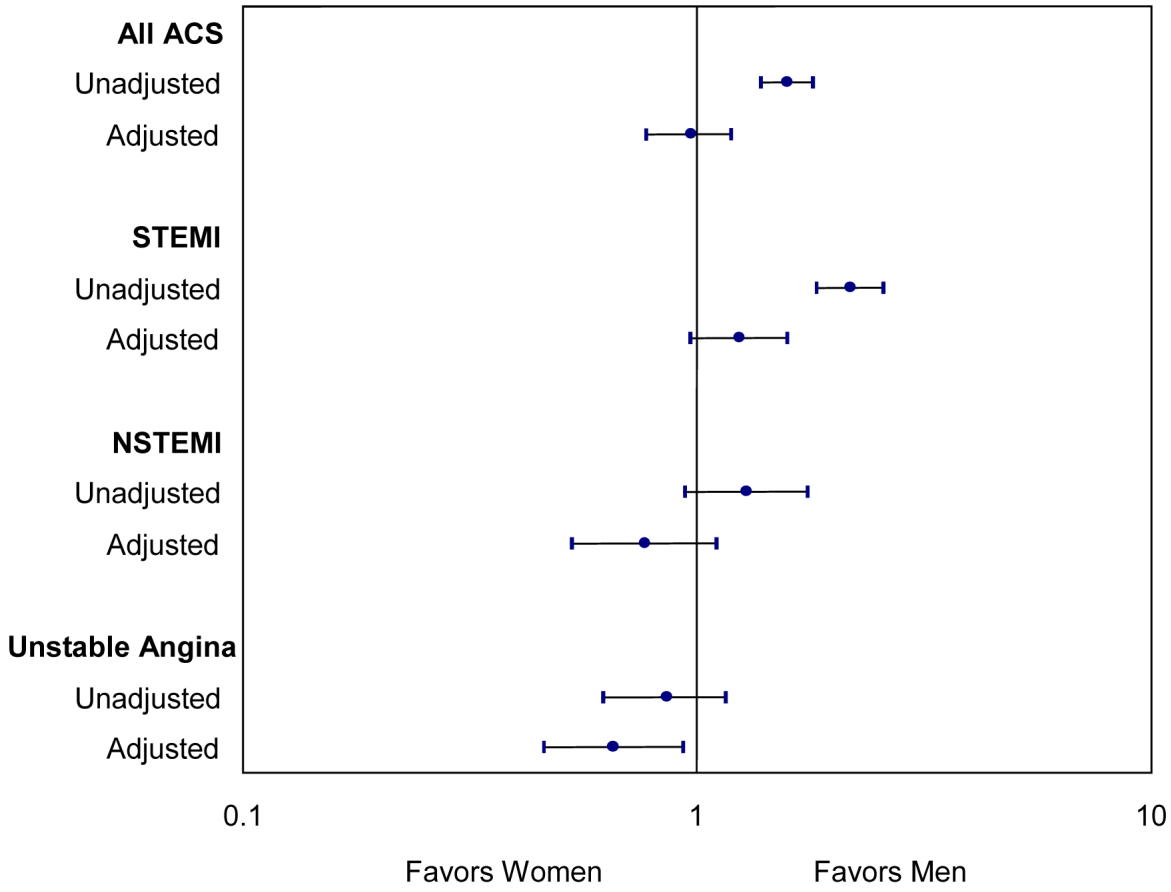

Figure 3. Unadjusted and multivariable adjusted + angiographic disease severity 30-day mortality models (odds ratio ± 95% confidence interval) in women versus men across the spectrum of acute coronary syndromes in subjects with angiographic data (n=35,128)

Table 1

Summary of Trials Used

Trial	Number of Pts Enrolled	Women N (%)	Men N (%)	Type of ACS evaluated	Intervention
GUSTO I [25] (1993)	41,021	10,315 (25.2)	30,653 (74.8)	STEMI	t-PA; Sk + IV heparin; Sk + t-PA; Sk + SQ; Heparin; Hirudin
GUSTO IIb[26] (1996)	12,142	3,661 (30.2)	8,479 (69.8)	STEMI, NSTEMI, UA	Heparin; Hirudin
GUSTO III[27] (1997)	15,059	4,124 (27.4)	10,935 (72.6)	STEMI	t-PA; r-PA
ASSENT II[29] (1999)	17,005	3,930 (23.1)	13,074 (76.9)	STEMI	t-PA; TNK
ASSENT III[30] (2001)	6,116	1,438 (23.5)	4,678 (76.5)	STEMI	Full-dose TNK + Heparin; Full-dose TNK + Enoxaparin; Half-dose TNK + Abciximab
ASSENT III+[34] (2003)	1,639	378 (23.1)	1,261 (76.9)	STEMI	Full-dose TNK + Heparin; Full-dose TNK + Enoxaparin
HERO 2[35] (2001)	17,089	4,850 (28.4)	12,237 (71.6)	STEMI	Bivalirudin; Heparin; Sk
PURSUIT[31] (2000)	10,948	3,857 (35.2)	7,090 (64.8)	NSTEM, UA	Placebo; Low-dose Eptifibatide; High-dose Eptifibatide
PARAGON A[28] (1998)	2,282	776 (34.3)	1,486 (65.7)	NSTEMI, UA	Low-dose Lamifiban with and without Heparin; High doseLamifiban with and without Heparin
PARAGON B[32] (2000)	5,225	1,789 (34.2)	3436 (65.8)	NSTEMI, UA	Lamifiban; Heparin
GUSTO IV[33] (2001)	7,800	2,930 (37.6)	4,870 (62.4)	NSTEMI, UA	Heparin; 24 hour Abciximab; 48 hour Abciximab
Total	**136,247**	**38,048 (27.9)**	**98,199 (72.1)**		

Abbreviations: ACS, acute coronary syndromes; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-STEMI; UA, unstable angina; t-PA, tissue plasminogen activator; Sk, streptokinase; TNK, tenecteplase.

Table 2

Baseline Characteristics of Women and Men Presenting with any ACS, STEMI, NSTEMI or UA

	All Patients with ACS		Patients with STEMI		Patients with NSTEMI		Patients with UA	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
Number (%)	38,048 (28%)	98,199 (72%)	26,032 (26%)	75,972 (75%)	4,159 (29%)	10,307 (71%)	7,857 (40%)	11,920 (60%)
Demographics								
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 No. (%)	30,083 (92)	77,215 (92)	19,162 (93)	56,644 (92)	3,819 (92)	9,557 (93)	7,102 (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 (%)	9,845 (26)	38,482 (40)	7,728 (30)	31,523 (42)	870 (21)	3,647 (36)	1,247 (16)	3,312 (28)
Geographic region No. (%)								
North America	14,874 (40)	36,760 (38)	11,128 (44)	29,811 (41)	1,510 (36)	3,568 (35)	2,236 (29)	3,381 (28)
Western Europe	11,702 (31)	33,774 (35)	6,938 (27)	23,438 (32)	1,635 (39)	4,631 (45)	3,129 (40)	5,705 (48)
Eastern Europe	6,576 (18)	12,140 (13)	4,192 (17)	9,516 (13)	643 (16)	1,040 (10)	1,741 (22)	1,584 (13)
Other*	4,184 (11)	13,028 (14)	3,062 (12)	10,710 (14)	371 (9)	1,068 (10)	751 (10)	1,250 (11)
Clinical History No. (%)								
Hypertension	21,738 (57)	37,719 (39)	14,167 (55)	27,323 (36)	2,632 (63)	4,618 (45)	4,939 (63)	5,778 (49)
Diabetes	8,496 (22)	14,229 (15)	5,442 (21)	10,052 (13)	1,107 (27)	1,923 (19)	1,947 (25)	2,254 (19)
Hyperlipidemia	12,181 (39)	25,926 (33)	7,095 (36)	17,356 (31)	1,780 (43)	3,944 (39)	3,306 (43)	4,626 (40)
Prior MI	6,783 (18)	20,641 (21)	3,625 (14)	12,936 (17)	1,042 (25)	3,302 (32)	2,116 (27)	4,403 (37)
Prior CABG	1,471 (4)	6,009 (6)	564 (2)	3,025 (4)	260 (6)	1,220 (12)	647 (8)	1,764 (15)
Heart Failure	2,391 (6)	3,180 (3)	997 (4)	1,455 (2)	533 (13)	759 (7)	861 (11)	966 (8)
Clinical Presentation								
Heart rate median (IQR), beats per minute	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), mmHg	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)
Killip class No. (%)								
I	28,567 (82)	80,564 (87)	20,771 (81)	65,199 (87)	2,864 (82)	7,569 (88)	4,932 (90)	7,796 (92)
II	5,120 (15)	10,201 (11)	4,126 (16)	8,677 (12)	521 (15)	892 (10)	473 (9)	632 (7)
III/IV	1,050 (3)	1,619 (2)	880 (2)	1,399 (1)	99 (3)	144 (2)	71 (1)	79 (1)

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

* Others include Latin America, Australia, New Zealand, Israel, South Africa, Asia and Arab region

Table 3

Risk of 30 day Mortality for Women Compared with Men, Following ACS in the Overall Cohort (n=136,247)

	Event Rates		Odds Ratio (95% Confidence Interval)	
	Women	Men	Unadjusted	Adjusted
All ACS	3654/37904 9.6%	5166/97768 5.3%	1.91 (1.83, 2.00)	1.06 (0.99, 1.15)
STEMI	3198/25903 12.3%	4385/75577 5.8%	2.29 (2.18, 2.40)*	1.15 (1.06, 1.24)*†
NSTEMI	265/4156 6.4%	9850/10297 4.3%	1.50 (1.28, 1.75)*	0.77 (0.63, 0.95)*
Unstable Angina	191/7845 2.4%	334/11894 2.8%	0.86 (0.72, 1.03)*	0.55 (0.43, 0.70)*†

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

Odds ratios of female vs. male and 95% CI obtained through logistic regression including the following covariates: Age, Killip class, interaction between age and Killip class, heart rate, systolic blood pressure, weight, height, history of CHF, history of MI, history of CABG, history of diabetes, history of PCI, history of hypertension, current smoking status, and former smoking status along with type of ACS

* Includes ACS*sex interaction to obtain the sex effect conditional on ACS categories

† Statistically significant difference in overall mortality at 30 days between women and men under the Bonferroni-adjusted significance level 0.005 (= . 05/10)

Table 4

Risk of 30 day Mortality for Women Compared with Men, Following ACS in the Cohort with Angiographic Data (n=35,128)

	Event Rates		Odds Ratio (Confidence Interval)	
	Women	**Men**	**Unadjusted**	**Adjusted†**
All ACS	354/9375 3.8%	625/25653 2.4%	1.57 (1.38, 1.79)	0.96 (0.77, 1.18)
STEMI	230/4771 4.8%	355/15506 2.3%	2.16 (1.83, 2.56)*	1.23 (0.96, 1.57)*
NSTEMI	61/1770 3.5%	135/4966 2.7%	1.28 (0.94, 1.74)*	0.76 (0.53, 1.10)*
Unstable Angina	63/2834 2.2%	135/5181 2.6%	0.85 (0.62, 1.15)*	0.65 (0.46, 0.93)*

Abbreviations, as above

Odds ratios of female vs. male and 95% CI obtained through logistic regression including the following covariates (age, Killip class, interaction between age and Killip class, heart rate, systolic blood pressure, weight, height, history of CHF, history of MI, history of CABG, history of diabetes, history of PCI, history of hypertension, current smoking status, and former smoking status) along with type of ACS and angiographic disease severity

* Includes ACS*sex interaction to obtain the sex effect conditional on ACS categories

† There was no significant difference in overall mortality at 30 days between women and men under the Bonferroni-adjusted significance level 0.005 (= .05/10)