Sex-Stratified Trends in Enrollment, Patient Characteristics, Treatment, and Outcomes Among Non–ST-Segment Elevation Acute Coronary Syndrome Patients

Insights From Clinical Trials Over 17 Years

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Background—Adequate representation by sex in trials allows generalizability of results. We examined representation of women in clinical trials during a 17-year period in which inclusion criteria were broadened and federal mandates for representativeness were launched.

Methods and Results—Using mixed models, we studied sex-stratified temporal trends in enrollment, clinical characteristics, treatment, and outcomes among 76,148 non–ST-segment elevation acute coronary syndrome patients using patient-level data merged from 11 phase III trials conducted from 1994 to 2010. Overall, 33.3% of patients were women, which changed minimally over time. Women were consistently 4 to 5 years older than men (median age 68 [interquartile range 61–75] versus 64 [interquartile range 56–72] years) and more frequently had diabetes mellitus, hypertension, and heart failure; men more frequently had prior myocardial infarction and revascularization. GRACE risk scores increased over time for both sexes with the inclusion of older patients with more comorbidities. Use of percutaneous coronary intervention, in-hospital and discharge angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, β-blockers, and lipid-lowering drugs also increased among both sexes. Kaplan–Meier estimates of 6-month mortality declined from 7.0% [95% confidence interval 6.5%–7.6%] to 4.5% [95% confidence interval 4.0%–5.0%] among women and 6.3% [95% confidence interval 6.0%–6.7%] to 3.1% [95% confidence interval 2.9%–3.4%] among men during the 17-year period.

Conclusions—The relative proportion of women in non–ST-segment elevation acute coronary syndrome trials changed minimally over time. Nevertheless, in parallel with men, use of evidence-based care and outcomes improved significantly over time among women. (Circ Cardiovasc Qual Outcomes. 2015;8:357-367. DOI: 10.1161/CIRCOUTCOMES.114.001615.)

Key Words: coronary disease • myocardial infarction • women

Acute coronary syndromes (ACS) are the leading cause of death among women in the United States (US) and worldwide, and each year, more women than men die from cardiovascular disease.1 With population aging and women’s longer life span, women will continue to compose a large proportion of patients with ACS, particularly among patients with non–ST-segment elevation myocardial infarction or unstable angina (NSTE ACS).1,2 We previously observed that despite trends for enrollment of higher-risk patients into phase III clinical trials of pharmacotherapy for NSTE ACS over time, in-hospital and 6-month mortality rates fell concurrently with increases in use of evidence-based pharmacotherapy and invasive treatments.3 Because representativeness of clinical trial populations supports generalizability of safety and efficacy...
WHAT IS KNOWN

- Overall, during a 15-year period, despite enrollment of higher-risk non–ST-segment elevation myocardial infarction/unstable angina (NSTE ACS) patients into phase III pharmacotherapy clinical trials, in-hospital and 6-month mortality rates declined in parallel with increases in use of evidence-based pharmacotherapy and invasive treatments.
- The National Institutes of Health Revitalization Act of 1993 legally requires inclusion of women and men in clinical trials to be consistent with the known sex-related prevalence of the disease under investigation.

WHAT THE STUDY ADDS

- Despite relaxation of age and other trial inclusion/exclusion criteria that might have biased against enrollment of women and despite federal mandates for representativeness, the proportion of women (33%) enrolled in NSTE ACS clinical trials changed minimally over time and remained disproportionate to representation of women among those with NSTE ACS in the general population (46%).
- Concurrent with risk enrichment in inclusion criteria, GRACE model-predicted mortality increased over time, but actual observed mortality significantly fell by half for both sexes.
- Mismatches between predicted and observed mortality rates likely reflect improved quality of care for both women and men because use of guidelines-recommended pharmacotherapies and an invasive strategy significantly increased among both women and men in parallel with the decrease in observed mortality.

Results to the general population of NSTE ACS patients, we evaluated trends in representation of women in NSTE ACS clinical trials over time.

Although there have been modest successes in increasing the balance of enrollment between women and men in cardiovascular clinical trials, it is less clear that these extend to trials of coronary artery disease secondary prevention and ACS. For example, the proportion of enrollment represented by women (33%) enrolled in NSTE ACS clinical trials changed minimally over time and remained disproportionate to representation of women among those with NSTE ACS in the general population (46%).

Concurrent with risk enrichment in inclusion criteria, GRACE model-predicted mortality increased over time, but actual observed mortality significantly fell by half for both sexes.

Mismatches between predicted and observed mortality rates likely reflect improved quality of care for both women and men because use of guidelines-recommended pharmacotherapies and an invasive strategy significantly increased among both women and men in parallel with the decrease in observed mortality.

Methods

Study Population

We included all phase III clinical trials of antithrombotic therapy in NSTE ACS in which the Duke Clinical Research Institute had a coordinating center role (n=8), plus 3 trials conducted elsewhere, for which we had access to patient-level data. A summary of key features of these trials is provided in Table 1.

Study Design

Baseline characteristics; in-hospital and discharge pharmacotherapy; coronary angiography and revascularization use; and in-hospital, 30-, and 6-month outcomes were available on a patient level across 17 years in the combined trial database. To maintain sample size homogeneity for display purposes, time trends were described across 4 prespecified periods (1994–1997, 1998–2001, 2002–2005, and 2006–2010). We did not describe or model trends in the use of glycoprotein IIb/IIIa inhibitors and heparins because these medications were part of the protocol-driven randomized treatment in most of the trials we examined. The Duke University Medical Center Institutional Review Board approved the current study with a waiver of written informed consent and Health Insurance Portability and Accountability Act authorization.

End Points

We studied the following postrandomization outcomes: in-hospital, 30-, and 6-month mortality; a composite of 30-day death or MI; in-hospital GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) bleeding (mild, moderate, and severe); and transfusion during index hospitalization. Observed 6-month mortality was compared with Global Registry of Acute Coronary Events (GRACE) score-predicted mortality, which used variables assessed at initial hospital presentation (age, history of heart failure, history of MI, presenting heart rate, presenting systolic blood pressure, and ST-segment depression) and during hospitalization (creatinine level, elevation of cardiac enzymes, and no in-hospital percutaneous coronary intervention [PCI]). Analyses and results of observed versus predicted mortality were limited to trials that collected GRACE score variables (Figure 1). We used MI as defined by the adjudication protocol of each trial.

Statistical Methods

Categorical variables were summarized using percentages and frequencies and continuous variables using medians and interquartile ranges. To test statistical significance of observed trends over time among women and men, we performed mixed model analyses. Observations with missing data were excluded from our analyses. The models included a temporal variable (actual month since the beginning of 1994) and sex and the interaction of these. Trial of origin was included as a random effect in the models to account for differences in patient enrollment. For binary outcomes, we used generalized linear mixed models, and for continuous outcomes, linear mixed models. To compare 6-month mortality, we used survival methods, including Kaplan–Meier estimated rates and a shared frailty model to assess time trends by sex. For 30-day mortality, we assessed homogeneity of trends by sex across trials by fitting additional interactions with trial; the result (P=0.37 for homogeneity) supports the merged trial analysis and reporting of aggregate results. Given that women who present with NSTE ACS often are older than men and that age is significantly
related to mortality, we compared our mixed model analyses for mortality with and without age as a covariate. Statistical significance was set at a $P$ value <0.05 without adjustments for multiple comparisons. All analyses were performed at the Duke Clinical Research Institute using SAS software, version 9.4 (SAS Institute, Cary, NC).

### Results

#### Patient Population

Of 76 148 patients, 46 196 presented with NSTE MI and 28 890 with unstable angina; 33.3% were women (N=25 174).

#### Sex-Stratified Temporal Trends in Enrollment

Overall, the relative proportion of women enrolled changed little over time (Table 1). There were no substantial differences in enrollment by sex by region (Table I in the Data Supplement).

#### Sex-Stratified Temporal Trends in Baseline Characteristics

Table 2 displays baseline characteristics stratified by sex for the prespecified time periods. Over time, there were modest increases in median age. Women were 4 to 5 years older than men across all time periods. History of diabetes mellitus and hypertension increased over time, and women with these preexisting conditions consistently outnumbered men. The same patterns applied for congestive heart failure, although the increase was more moderate. Women had higher median 6-month GRACE risk scores and had GRACE scores ≥140 more often than men. Compared with men, women less frequently had prior MI, PCI, and bypass surgery.

#### Sex-Stratified Temporal Trends in Pharmacological and Invasive Management

During the index hospitalization and at discharge, use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, thienopyridines, β-blockers, and lipid-lowering drugs significantly increased over time among both women and men (Table 3 and Figures 2 and 3). Use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers was lower among women than among men during the later time periods, despite starting out higher, and use of lipid-lowering drugs was lower among women than men throughout the entire period of observation (Figures 2 and 3). In-hospital use of aspirin was consistently high among both sexes throughout the entire study period, but aspirin use at discharge was higher from 1994 to 1997 compared with any subsequent time period for both sexes.

Coronary angiography and PCI increased among both sexes over time (Table 3). Relative to women, significantly more men had coronary angiography and PCI (Figure 4). Use

Table 1. Summary of Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Enrollment Period</th>
<th>Enrollment Criteria</th>
<th>Treatment Studied</th>
<th>Men</th>
<th>Women</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO Ib*</td>
<td>1994–1997</td>
<td>Chest discomfort &lt;12 h, ECG changes</td>
<td>Heparin, hirudin</td>
<td>5346 (66.7%)</td>
<td>2665 (33.3%)</td>
<td>8011</td>
</tr>
<tr>
<td>PRISM</td>
<td>1994–1997</td>
<td>Chest pain &lt;24 h, ECG changes, CK&gt;2× ULN or CK-MB&gt;ULN</td>
<td>Tirotiban, heparin</td>
<td>2194 (68.0%)</td>
<td>1031 (32.0%)</td>
<td>3225</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>1994–1997</td>
<td>Chest pain &lt;12 h, ECG changes, CK&gt;ULN or CK-MB&gt;ULN</td>
<td>Tirotiban, heparin, tirosiban plus heparin</td>
<td>1295 (67.6%)</td>
<td>620 (32.4%)</td>
<td>1915</td>
</tr>
<tr>
<td>PARAGON-A</td>
<td>1994–1997</td>
<td>Chest pain &lt;12 h, ECG changes</td>
<td>Low-dose lamifiban with and without heparin, high-dose lamifiban with and without heparin</td>
<td>1499 (65.7%)</td>
<td>783 (34.3%)</td>
<td>2282</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>1994–1997</td>
<td>Chest pain &lt;24 h, ECG changes, CK-MB&gt;ULN</td>
<td>Placebo, low-dose eptifibatide, high-dose eptifibatide</td>
<td>7090 (64.8%)</td>
<td>3858 (35.2%)</td>
<td>10948</td>
</tr>
<tr>
<td>PARAGON-B</td>
<td>1998–2001</td>
<td>Chest pain &lt;12 h, ECG changes, CK-MB or troponin I or T&gt;ULN</td>
<td>Lamifiban, heparin</td>
<td>3436 (65.8%)</td>
<td>1789 (34.2%)</td>
<td>5252</td>
</tr>
<tr>
<td>GUSTO IV-ACS‡</td>
<td>1998–2001</td>
<td>Chest pain &lt;24 h, ECG changes, troponin I, or T&gt;ULN</td>
<td>Heparin, 24 h abciximab, 48 h abciximab</td>
<td>4870 (62.4%)</td>
<td>2930 (37.6%)</td>
<td>7800</td>
</tr>
<tr>
<td>SYNERGY‡</td>
<td>1998–2001, 2002–2005</td>
<td>Chest pain &lt;24 h, ECG changes, CK-MB or troponin I or T&gt;ULN</td>
<td>Enoxaparin, unfractionated heparin</td>
<td>6598 (66.1%)</td>
<td>3390 (33.9%)</td>
<td>9978</td>
</tr>
<tr>
<td>EARLY ACS‡</td>
<td>2002–2005, 2006–2010</td>
<td>Chest pain &lt;24 h, ECG changes, CK-MB or troponin I or T&gt;ULN</td>
<td>Early, routine administration of eptifibatide, delayed, provisional administration</td>
<td>6431 (68.4%)</td>
<td>2975 (31.6%)</td>
<td>9406</td>
</tr>
<tr>
<td>TRACER§</td>
<td>2006–2010</td>
<td>Chest pain &lt;24 h, ECG changes, CK-MB or troponin I or T&gt;ULN</td>
<td>Placebo, voraxapar</td>
<td>9312 (71.9%)</td>
<td>3632 (28.1%)</td>
<td>12944</td>
</tr>
<tr>
<td>APPRAISE-2*</td>
<td>2006–2010</td>
<td>Recent ACS (MI, with or without STE or UA within 7 days), symptoms &gt;10 min at rest, ECG changes or elevated biomarkers</td>
<td>Placebo, apixaban</td>
<td>2903 (65.8%)</td>
<td>1511 (34.2%)</td>
<td>4414</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CK, creatine kinase; CK-MB, creatine kinase-MB; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; UA, unstable angina; STE, ST-segment elevation; UA, unstable angina; and ULN, upper limit of normal.

*Patients with STE ACS not included.
†NSTEMI/UA not undergoing planned early revascularization.
‡NSTEMI/UA undergoing early invasive management.
§Patients with transient STE ECG changes (<30 min) enrolled.
of coronary artery bypass graft surgery (CABG) increased slightly post-2000, but proportions of women and men (40% versus 60%) receiving CABG were consistent throughout the 17-year period (Table 3). In both sexes, median length of stay decreased by ≈3 to 4 days from 1994 to 2001 to 2002 to 2010.

**Temporal Trends in Clinical Outcomes by Sex**

Over time, observed in-hospital, 30-day, and 6-month mortality decreased significantly among both women and men (Figure 1 and Table 4). Any differences in the magnitude of decline in mortality between women and men were small and not affected by adjusting for age (Table II in the Data Supplement). Odds ratios for 30-day mortality comparing women with men were not significantly different over time (Figure I in the Data Supplement).

In a subset of trials in which GRACE risk scores were assessed, women had consistently higher GRACE model–predicted 6-month mortality compared with men; however, declines in observed 6-month mortality rates over time were similar among women and men (Figure 1). Trends for observed 6-month mortality were similar when considering all patients enrolled in trials with available 6-month follow-up information, even if not all variables were available to calculate GRACE-predicted 6-month mortality (Figure II in the Data Supplement). Substantial differences between GRACE model–predicted 6-month mortality and observed 6-month mortality were evident for both sexes, and although GRACE-predicted 6-month mortality increased over time, observed 6-month mortality fell by approximately half for both sexes (Figure 1).

Bleeding and transfusion rates were higher among women than men across all time periods, although changes in rates over time were similar by sex (Table 4). For both sexes, bleeding and transfusion rates increased from 1994 to 1997 and 1998 to 2001, peaked during 2002 to 2005, then fell to prior levels during 2006 to 2010. Blood transfusion rates were substantially higher than severe bleeding rates in both sexes, even after excluding CABG-treated patients (Table 4; Table III in the Data Supplement).

**Discussion**

This analysis of 76,148 patients with NSTE ACS from 11 multinational, phase III RCTs conducted between 1994 and 2010 revealed no overall change in the proportional enrollment of women relative to men over the 17-year period. Further, the proportion of enrollment represented by women (33%) was well below representation of women in US practice registries, in which women account for ≈40% to 46% of NSTE ACS patients.2,4,20 During the index hospitalization, use of evidence-based pharmacotherapy and revascularization increased significantly over time in both groups.

**Sex-Stratified Trends in Enrollment and Characteristics of NSTE ACS Trial Patients**

One might expect that relaxation of age and renal function restrictions to enrollment and selection for patients with diabetes mellitus might result in increased proportional representation of women in trials of NSTE ACS pharmacotherapy. However, despite these efforts and despite increasing awareness of underenrollment of women,3,5,7 the proportion of women enrolled in the NSTE ACS trials in our series was stable at around 33% over the 17-year period. These findings are particularly troubling because they occurred despite the ongoing American Heart Association Go Red For Women campaign and the National Institutes of Health Revitalization Act of 1993, which legally required inclusion of women
and men in clinical trials to be consistent with the known sex-related prevalence of the disease under investigation.\textsuperscript{4,5} The 33% representation of women that we observed was higher than previous assessments among coronary artery disease trial populations (25%) and similar to the ≈30% in other NSTE ACS phase III trials contemporary to those we examined but...
Concomitant Medications and Hospital Stay by Sex According to Period of Enrollment

<table>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>In-hospital treatments</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Catheterization</td>
<td>58.8% (17,419)</td>
<td>52.4% (8,949)</td>
<td>52.8% (8,672)</td>
<td>42.1% (4,927)</td>
</tr>
<tr>
<td>PCI</td>
<td>21.2% (17,423)</td>
<td>17.4% (8,955)</td>
<td>21.6% (8,672)</td>
<td>15.5% (4,927)</td>
</tr>
<tr>
<td>CAGB</td>
<td>13.8% (17,414)</td>
<td>9.9% (8,953)</td>
<td>11.0% (8,672)</td>
<td>6.9% (4,928)</td>
</tr>
<tr>
<td>Hospital LOS, median (IQR)</td>
<td>9 (6–14)</td>
<td>9 (6–15)</td>
<td>9 (6–13)</td>
<td>10 (7–14)</td>
</tr>
<tr>
<td>Patients alive at discharge</td>
<td>N=16,906</td>
<td>N=8,648</td>
<td>N=8,430</td>
<td>N=4,780</td>
</tr>
<tr>
<td>Discharge medications†</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Aspirin</td>
<td>71.0% (16,731)</td>
<td>70.0% (8,532)</td>
<td>99.1% (8,369)</td>
<td>98.2% (9,472)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>20.9% (16,893)</td>
<td>23.2% (8,638)</td>
<td>39.1% (7,037)</td>
<td>40.5% (9,507)</td>
</tr>
<tr>
<td>Thienopyridines</td>
<td>10.5% (11,724)</td>
<td>8.7% (6,081)</td>
<td>30.6% (3,703)</td>
<td>24.9% (9,507)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>47.7% (16,903)</td>
<td>46.6% (8,641)</td>
<td>66.8% (7,037)</td>
<td>65.8% (9,507)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>15.5% (16,892)</td>
<td>16.4% (8,639)</td>
<td>41.0% (7,037)</td>
<td>37.1% (9,507)</td>
</tr>
</tbody>
</table>

Data presented as % (N), unless otherwise indicated. ACE indicates angiotensin-converting enzyme; also including angiotensin II receptor blockers; CAGB, coronary artery bypass grafting; GP, glycoprotein; IQR, interquartile range/first and third quartile (25%, 75%); LOS, length of stay; and PCI, percutaneous coronary intervention.

*Information on ACE inhibitors not available from TRACER.
†Information on thienopyridines and GP IIb/IIIa inhibitors not available from GUSTO IIb.
‡Information on discharge medications not available from GUSTO IV-ACS.

Conducted by other centers. However, it is substantially below the 40% to 46% representation of women in NSTE ACS populations in US registries.2,4,10–26

Overall, between 1965 and 1998, cardiovascular RCTs funded by the National Heart, Lung, and Blood Institute met the representativeness by sex requirement, but National Heart, Lung, and Blood Institute–funded phase III and IV RCTs between 1997 and 2006 failed to achieve representativeness according to sex.5,11 These observations may reflect that drug intervention trials are more likely to exclude individuals because of concomitant medication use, medical comorbidities, or age (despite apparently more broad inclusion criteria and less restrictive exclusion criteria).5,7,21–27 or may reflect unmeasured factors that influence recruitment or participation of women in RCTs. We cannot address these potential factors from our trial series because parallel registries were not conducted to collect information on individuals screened but ultimately not approached or who did not consent to randomization if eligible.

We speculate there are likely many driving factors for the minimal change in enrollment of women over the 17 years studied. Age, renal function limits, and other comorbidities may select against women, even though these have been relaxed somewhat over time.28 Women often present later than men and may fall outside the temporal window for inclusion.28 However, APPRAISE-2,18 in which patients with NSTE ACS within 7 days were eligible, failed to enroll a higher proportion of women than other trials in our series. Likewise, the PROVE IT–TIMI 22 trial only enrolled 22% women, despite having a 10-day window for inclusion after ACS hospitalization.25 Overcoming this sex-based heterogeneity in trial enrollment is needed to ensure that results of NSTE ACS RCTs are as generalizable as possible.

Sex-Stratified Trends in Care and Mortality of NSTE ACS Trial Patients

In contrast to enrollment trends, there were substantial improvements over time in both evidence-based care and mortality in both sexes. Despite enrollment of patients with increasing numbers of comorbidities and GRACE model–predicted mortality, there were substantial declines in observed mortality rates among both women and men. We hypothesize that this divergence of observed from predicted mortality reflects better care because use of evidence-based therapies increased concurrently. Although we studied trends in a selected group of RCTs available to us, we saw similar trends in a literature review of similar NSTE ACS phase III RCTs conducted during the same periods but by other centers.21–26
Consistent with US registry trends, we found that women were treated with lipid-lowering drugs and PCI less often than men.20,29 Women were also treated less often with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers during the later time periods, despite having more hypertension, heart failure, and diabetes mellitus, for which use of these drugs is highly relevant. Because none of the trials in our merged trial database collected information on relative or absolute contraindications for these treatments or information on patient preferences, rates of use among eligible patients cannot be assessed. As we speculated for differences in enrollment, renal function limits (either age-related or as a result of diabetes mellitus) and other comorbidities may appropriately select more heavily against use of certain treatments in women.28 Although some registry-based studies have reported persistent differences in use after accounting for contraindications, others showed narrowing of gaps in rates of treatment among women and men consistent with adequately addressed contraindications to use.30–32 Given substantial increases in evidence-based treatment in both sexes and limited gaps in care between women and men, sex-related differences in use in our trial series may reflect appropriate use in the clinical context rather than actual disparities in care. Nevertheless, adequate representation of women in trials may facilitate eliminating remaining barriers to use that could be related to uncertainty about benefits and risks of treatment.

**Sex-Stratified Trends in NSTE ACS Bleeding and Transfusion Outcomes**

Relative to men, bleeding and transfusion rates were higher among women in our study. In a secondary analysis from the EARLY ACS trial (included in our pooled data set), women also had higher bleeding rates than men, but the association between bleeding and mortality was stronger among men than among women.33 Although female sex is an independent risk factor for bleeding, we found no sex-related differences in bleeding rates over time.
The intense antiplatelet and antithrombotic regimens used during 2002 to 2005, in conjunction with a mandate for early invasive care in the SYNERGY and EARLY ACS trials, likely contributed to higher rates of bleeding during this period. Furthermore, the nearly 2-fold higher use of CABG among both women and men may have also played a role in the higher bleeding rates seen during 2002 to 2005. However, excluding CABG-treated patients did not fully explain the disproportionate use of transfusions relative to severe bleeding.

**Strengths and Limitations**

No prior study has examined sex-related trends in enrollment, clinical characteristics, care, and outcomes among NSTE ACS clinical trial populations this large (>76,000 participants) over such a long period of time (17 years, 1994–2010), during which substantial relaxations in age and other risk factor inclusion/exclusion criteria occurred and federal mandates for increased representativeness of enrollment were enacted.

Although our sample size is large, our analyses are based on a convenience sample of clinical trials. Nevertheless, our observations were comparable to US registries and NSTE ACS phase III trials contemporary to those we studied. In addition, recent large, multinational, phase III NSTE ACS trials had comparable overall findings to the more recently conducted studies in our series, although even fewer women were included.
Despite efforts to increase representativeness in clinical trials, efforts to representatively enroll women in NSTE ACS trials are insufficient. Because safety and efficacy findings may differ according to sex, this disparity could undermine generalizability of clinical trial results to treatment of the overall NSTE ACS population.

**Conclusions**

Trial-to-trial heterogeneity in enrollment criteria, care, and end point reporting is inevitable. However, by treating trials as random effects in our mixed model analyses, we adjusted for this heterogeneity to the best of our ability. Increases in some pharmacotherapies (eg, statins and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers) reflect their emergence as evidence-based treatments during later time periods. Nevertheless, observed increases likely also reflect improvement in care related to overall process-improvement efforts.

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**Disclosures**

References


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Supplemental Table 1. Enrollment of women by region.

<table>
<thead>
<tr>
<th>Region</th>
<th>Total</th>
<th>Male</th>
<th>Male (%)</th>
<th>Female</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>27526</td>
<td>18107 (65.8%)</td>
<td>9419 (34.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>3341</td>
<td>2181 (65.3%)</td>
<td>1160 (34.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>39271</td>
<td>26432 (67.3%)</td>
<td>12839 (32.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>6010</td>
<td>4254 (70.8%)</td>
<td>1756 (29.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>76148</td>
<td>50974 (66.9%)</td>
<td>25174 (33.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Primarily Asia and Australia.
### Supplemental Table 2. Mortality rates by sex over time, unadjusted vs. adjusted for age.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men N=17424</td>
<td>Women N=8957</td>
<td>Men N=8675</td>
<td>Women N=4928</td>
<td>Men N=7453</td>
<td>Women N=3722</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>3.0% (17423)</td>
<td>3.4% (8956)</td>
<td>2.8% (8675)</td>
<td>3.0% (4928)</td>
<td>2.4% (7450)</td>
<td>2.6% (3720)</td>
</tr>
<tr>
<td>30-day death</td>
<td>3.4% (17423)</td>
<td>3.9% (8957)</td>
<td>3.5% (8675)</td>
<td>3.7% (4928)</td>
<td>2.9% (7453)</td>
<td>3.2% (3722)</td>
</tr>
<tr>
<td>6-month death*</td>
<td>6.1% (15229)</td>
<td>6.8% (7926)</td>
<td>5.4% (3805)</td>
<td>5.4% (1998)</td>
<td>5.4% (7453)</td>
<td>5.6% (3722)</td>
</tr>
</tbody>
</table>

*Kaplan-Meier rates (6-month mortality was not available from the GUSTO IV-ACS and PRISM trials).
Supplemental Table 3. Bleeding and transfusion use by sex among patients not treated with coronary artery bypass grafting.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>N</td>
<td>13382</td>
<td>7454</td>
<td>7163</td>
<td>4376</td>
</tr>
<tr>
<td>Mild bleeding</td>
<td>17.0%</td>
<td>21.7%</td>
<td>19.5%*</td>
<td>25.3%*</td>
</tr>
<tr>
<td>Moderate bleeding</td>
<td>2.1%</td>
<td>4.6%</td>
<td>4.0%*</td>
<td>6.3%*</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>0.6%</td>
<td>1.0%</td>
<td>0.4%*</td>
<td>0.8%*</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1.9%</td>
<td>4.5%</td>
<td>2.3%*</td>
<td>4.7%*</td>
</tr>
</tbody>
</table>

*Information on GUSTO bleeding and transfusion not available from GUSTO IV-ACS.
Supplemental Figure 1. Odds ratios with 95% confidence intervals of 30-day mortality for women versus men for each time period.
Supplemental Figure 2. Predicted 6-month mortality and observed Kaplan Meier rates for 6-month mortality

KM=Kaplan-Meier; Pred=GRACE model predicted 6-month mortality. Observed Kaplan-Meier rates are depicted for all patients with available GRACE score elements (KM GRACE) and for all patients with available 6-month follow-up (KM rate; not available for GUSTO IV-ACS and PRISM trial patients).