Impact of Female Sex on Death and Bleeding After Fibrinolytic Treatment of Myocardial Infarction in GUSTO V

Harmony R. Reynolds, MD; Michael E. Farkouh, MSc, MD; A. Michael Lincoff, MD; Amy Hsu, MS; Eva Swahn, MD; Zygmunt P. Sadowski, MD; Jennifer A. White, MS; Eric J. Topol, MD; Judith S. Hochman, MD; for the GUSTO V Investigators

Background: Women with acute myocardial infarction are more likely than men to experience reinfarction, bleeding, or death. This difference has been hypothesized to be due to older age, treatment delay, and comorbidities in women. Use of diagnostic and therapeutic modalities may also differ. There is controversy regarding whether female sex is an independent risk factor for death and/or bleeding.

Methods: The GUSTO (Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes) V Investigators studied standard-dose reteplase vs standard-dose abciximab plus half-dose reteplase in patients with myocardial infarction.

Results: Women were older and more often had diabetes mellitus and hypertension. Angiography and percutaneous coronary intervention were less frequent in women. Death (9.8% vs 4.4% at 30 days; odds ratio [OR], 2.00; 95% confidence interval, 1.59-2.53; P < .01) were more common in women. There was no association between treatment assignment and death in either sex; bleeding was more common in both sexes receiving combination therapy. Female sex was independently associated with mortality. After Killip class greater than 1 (OR, 4.7), female sex (OR, 2.0) was the strongest correlate of death. Female sex was independently associated with bleeding for both treatments.

Conclusions: Female sex is independently associated with death and bleeding complications among fibrinolytic-treated patients with myocardial infarction. There remains a sex differential in the use of angiography and, therefore, percutaneous coronary intervention after fibrinolysis. Further research will determine what mediates excess risk in women.

Trial Registration: clinicaltrials.gov Identifier: NCT00245648

Arch Intern Med. 2007;167(19):2054-2060

Author Affiliations:
Cardiovascular Clinical Research Center, New York University School of Medicine, New York (Drs Reynolds, Farkouh, and Hochman); Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio (Drs Lincoff and Topol and Mss Hsu and White); Department of Cardiology, Heart Centre, University Hospital, Linkoping, Sweden (Dr Swahn); and National Institute of Cardiology, Warsaw, Poland (Dr Sadowski). Ms White is now with the Duke Clinical Research Institute, Durham, North Carolina.

Group Information: A list of the members of the GUSTO (Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes) V Investigators appears in Lancet (2001;357[9272]:1905-1914).
The design, methods, and primary results of the GUSTO V trial have been published elsewhere.\textsuperscript{13} In brief, 16,588 patients were enrolled at 820 hospitals in 20 countries between July 7, 1999, and February 16, 2001. Inclusion criteria were continuous symptoms of chest discomfort for between 30 minutes and 6 hours associated with ST-segment elevation or new left bundle-branch block on electrocardiogram. Patients for whom immediate percutaneous intervention was planned were excluded from enrollment. Also excluded were patients with active bleeding, known hemorrhagic diathesis, a systolic blood pressure level higher than 180 mm Hg, diastolic blood pressure level higher than 110 mm Hg, stroke within 2 years, hemorrhagic stroke at any time, a structural central nervous system abnormality, major surgery or trauma within 6 weeks, ongoing oral anticoagulation, noncompressible vessel puncture within 24 hours, use of a glycoprotein IIb/IIIa inhibitor within 7 days, or documented thrombocytopenia (platelet count, \(<100 \times 10^9/\mu L\)). The protocol was approved by the institutional review board at each clinical site, and all patients provided written informed consent.

**STUDY PROTOCOL**

Patients were randomized to receive either a standard dose of reteplase (two 10-U boluses, 30 minutes apart) or the combination of a standard dose of abciximab (a 0.25-mg/kg bolus and a 0.125-μg/kg/min infusion [maximum, 10 μg/min] for 12 hours) and a half dose of reteplase (two 5-U boluses, 30 minutes apart) intravenously.

All patients were treated with daily aspirin beginning at randomization and for the remainder of the study period. Unfractionated heparin was given intravenously according to a nomogram to achieve an activated partial thromboplastin time of 50 to 70 seconds for 24 hours; initial doses were a 5000-U bolus followed by a 1000-U/h (or 800 U/h for weight <80 kg) infusion in the reteplase monotherapy group and a 60-U/kg (maximum, 5000 U) bolus followed by 7-U/kg/h infusion in the abciximab and reteplase (combination therapy) group. Coronary angiography and revascularization could be performed if indicated by the patient’s clinical course according to the treating physician. All other medical therapies were left to the discretion of the treating physician.

The primary end point was all-cause mortality at 30 days after randomization. Other end points included the incidence of myocardial reinfarction as evidenced by new electrocardiographic changes or elevation in cardiac enzyme levels with recurrent chest pain within 7 days, bleeding, stroke, intracranial hemorrhage (ICH), and complications of MI. Bleeding was classified according to the GUSTO scale as severe when associated with hemodynamic compromise, moderate when requiring transfusion without hemodynamic compromise, and mild without transfusion or hemodynamic compromise. These latter end points were assessed at hospital discharge or at 7 days (whichever came first). Mortality at 1 year was a prospectively defined secondary outcome measure.

**STATISTICAL ANALYSIS**

Group comparisons were completed by using Wilcoxon 2-sample tests for continuous variables. The \(\chi^2\) or Fisher exact test (if small expected cell frequencies) was used for categorical variables. Results were considered statistically significant if \(P \leq .05\). Multivariate logistic regression was performed for death (at 7 and 30 days) and bleeding. Multivariate Cox proportional hazards regression was performed for 1-year death. The stepwise selection technique was used for multivariate logistic regression, and all variables selected were validated by bootstrapping. Stepwise selection and backward elimination were considered in model selection. \(P = .10\) was used for enrollment, and \(P = .05\) was considered statistically significant. The variables in the multivariate models included age, sex, race, weight, body mass index, pulse, blood pressure level, infarct location, prior MI, prior coronary artery bypass grafting, heparin dose, hypertension, diabetes mellitus, treatment group, time from symptom onset to study agent administration, Killip class, and US vs non-US site location. All statistical tests were performed using SAS statistical software, version 8.0 (SAS Institute Inc, Cary, North Carolina).

**RESULTS**

**BASELINE CHARACTERISTICS**

Women in GUSTO V were older and shorter than men and had higher rates of diabetes mellitus, hypertension, and hypercholesterolemia. More men were current smokers at enrollment. The index MI was more likely to be a first cardiovascular event for women (Table 1). There were no significant differences in baseline characteristics between treatment arms among either women or men (data not shown). Women were less likely to be prescribed aspirin or β-blockade at discharge (Table 1).

**PRIMARY OUTCOME**

At 30 days, women had a higher mortality than men (9.8% vs 4.4%; \(P < .001\)). There was no difference in mortality between treatment groups in either sex. After adjustment for other univariate predictors (Figure 1), female sex was associated with twice the odds of death at 30 days (odds ratio [OR], 2.00; 95% confidence interval [CI], 1.59-2.53; \(P < .001\)). Among tested variables, only Killip class had a higher OR for death at 30 days. Mortality was higher for women among younger patients (those <75 years: 5.6% vs 3.1%; \(P < .001\)) and older patients (those \(\geq 75\) years: 19.6% vs 14.7%; \(P < .001\)). There was no interaction between sex, age, and death, but this analysis was limited by the small sample size for younger women.

Women also had a higher risk of death between 30 days and 1 year (3.8% vs 2.5%; \(P < .01\)). Female sex was an independent predictor of death at 7 days (multivariate OR, 1.61; 95% CI, 1.34-1.89; \(P = .002\)) and at 1 year (multivariate hazard ratio, 1.14; 95% CI, 1.01-1.29; \(P = .03\)). Figure 2 displays the Kaplan-Meier curves for death over 1 year.

**CORONARY ANGIOGRAPHY AND REVASCULARIZATION**

Women were referred for coronary angiography (37.8% vs 42.3%; \(P < .001\)) and percutaneous coronary intervention (PCI) (23.9% vs 27.6%; \(P < .001\)) significantly less often than were men. Use of coronary angiography and revascularization did not differ between treatment groups among women. Among patients in whom angiography was performed, rates of PCI were similar:
Table 1. Baseline Characteristics by Sex*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 12498)</th>
<th>Women (n = 4090)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.5 ± 11.7</td>
<td>67.0 ± 11.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients aged ≥ 75 y</td>
<td>1358 (10.9)</td>
<td>1213 (29.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.7 ± 13.2</td>
<td>69.8 ± 13.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.6 ± 7.2</td>
<td>161.1 ± 6.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1 ± 3.9</td>
<td>27.0 ± 5.1</td>
<td>12</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>3680 (29.7)</td>
<td>1919 (47.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>2023 (16.6)</td>
<td>722 (18.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1765 (14.4)</td>
<td>848 (21.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2025 (16.4)</td>
<td>503 (12.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>462 (3.7)</td>
<td>91 (2.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>933 (7.5)</td>
<td>180 (4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous CHF</td>
<td>320 (2.6)</td>
<td>162 (4.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6157 (49.7)</td>
<td>1389 (34.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Infract location</td>
<td>4295 (34.4)</td>
<td>1372 (33.6)</td>
<td></td>
</tr>
<tr>
<td>Other location</td>
<td>7004 (56.2)</td>
<td>2234 (54.8)</td>
<td></td>
</tr>
<tr>
<td>Not localized</td>
<td>358 (2.9)</td>
<td>165 (4.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Multiple locations</td>
<td>761 (6.1)</td>
<td>281 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Medications at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>11 250 (90.0)</td>
<td>3517 (86.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>7010 (56.1)</td>
<td>2344 (57.3)</td>
<td>.17</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>9704 (77.6)</td>
<td>3011 (73.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symptom to study agent</td>
<td>2.9 ± 2.5</td>
<td>3.2 ± 1.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class at baseline</td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>1</td>
<td>11 177 (89.5)</td>
<td>3479 (85.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1129 (9.0)</td>
<td>510 (12.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>123 (1.0)</td>
<td>60 (1.5)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>53 (0.4)</td>
<td>31 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Data are given as mean ± SD.

63.2% of women underwent PCI compared with 65.2% of men (P = .17). Overall, 23.6% of women compared with 27.4% of men underwent PCI (P < .01). Referral to coronary artery bypass grafting also did not differ significantly between the sexes (3.1% for women vs 3.4% for men; P = .45).

Overall, 30-day mortality was higher in those patients who did not undergo coronary angiography during the index hospitalization (7.5% without angiography vs 3.3% with angiography, with or without revascularization; P < .001). This relationship held true in women (12.9% without angiography vs 4.7% with angiography, with or without revascularization; P < .001) and in men (5.6% without angiography vs 2.9% with angiography, with or without revascularization; P < .001).
patients had more than 1 complication. Patients could have more than 1 complication.

**Intracranial Hemorrhage**

Women were more likely than men to have an ICH (25.6% for women [37.4% vs 33.2% for men] [P = .004]). In men, the excess of complications was driven by statistically significant differences in reinfarction (31.3% for the reteplase alone group vs 25.6% [P = .001]). In women, this difference was driven by an excess of reinfarction in those treated with reteplase alone (4.5% vs 2.6% in women receiving combination therapy; P = .002). In men, the excess of complications in the reteplase arm was driven by statistically significant differences in reinfarction (31.3% for the reteplase alone group vs 25.3% for the combination therapy group; P = .003). Recurrent ischemia (12.0% vs 10.5%; P = .01), and ventricular tachycardia (2.8% vs 2.1%; P = .01).

**Comment**

Even in the current era, there is a striking excess risk of death from STEMI for women after thrombolytic therapy. The risk of death by 30 days among women in GUSTO
V was twice that of men after adjustment for baseline differences, including lower rates of prescription of aspirin and β-blockers at discharge in women. The increased risk could be related, at least in part, to the increased risk of complications of MI among women. Death risk continued to be elevated for women from 30 days to 1 year, although excess risk was lower in this later period. Given the 8.4% rate of death by 1 year in GUSTO V, the hazard ratio of 1.14 for women compared with men transited into a substantial excess of events. Poorer prognosis for women with STEMI has been demonstrated previously. However, in contrast to the present study, several previous analyses found that adjustment for differences in baseline variables abolished this finding. Some have suggested that underuse of reperfusion therapy may be the cause of the difference in risk; this cannot be the explanation in GUSTO V, in which all patients received thrombolytic therapy.

In GUSTO V, angiography and revascularization were used less often in women. Whether this was because of differences in overall risk profile or bias is uncertain. The lower rates of angiography and revascularization in women, a group at higher risk of events, are consistent with prior reports of inappropriate preferential use of interventions for low-risk patients. Although it is possible that this differential in care affects the prognosis of women with MI, routine angiography after treatment with thrombolytic agents has yet to be reported to improve survival. In the primary analysis of GUSTO V, there was a higher rate of use of urgent angiography in the group that received fibrinolysis alone; this seems to have been limited to men. The lower rate of angiography is particularly noteworthy in light of the significantly higher rate of recurrent ischemia in women.

Previous analyses of large MI cohorts have shown that the adverse impact of female sex on prognosis is strongest in younger women. A similar multivariate analysis by age cohort was undertaken for GUSTO V, but was limited by a small number of women in younger age groups.

In GUSTO V, women had an excess risk of bleeding independent of other baseline variables, including body weight and heparin dose. This finding is not specific to trials involving MI: increased bleeding risk has been demonstrated for women who are treated for deep venous thrombosis, thromboembolism, and atrial fibrillation. One might suspect that lower average body weight among women would be an important factor in this association. However, excess bleeding risk for women receiving heparin has been shown to be independent of body size and achieved partial thromboplastin time. Moreover, excess bleeding risk in women receiving abciximab has been shown to be independent of heparin dose, platelet count, and activated clotting time. Bleeding risk is known to be higher for women, even with weight-based thrombolytic dosing.

The heparin dose used in GUSTO V (maximum, 5000-U bolus and 1000-U/h infusion) was consistent with contemporary guidelines. However, the current guidelines recommend a maximum 4000-U bolus. Use of this lower-dose regimen has resulted in lower bleeding rates during heparin therapy for MI. Further investigation is needed to determine the optimal dose of heparin in the context of thrombolysis for women and men.

Interestingly, a recent survey of patients with STEMI did not find a significant difference in risk of stroke or other complications of MI between the sexes. This may be because of the smaller sample size in the survey, the use of primary PCI rather than thrombolysis in a substantial minority of the patients, and/or the observational nature of the survey.

One possible unifying explanation for this increase in risk of bleeding and thrombotic complications (including reinfarction) may be related to renal dysfunction; creatinine clearance is lower in women than in men, independent of age and body weight. Women and patients with renal insufficiency are more likely to receive an overdose of antithrombotic therapy for acute coronary syndromes, resulting in excess bleeding risk. Even after adjustment for overdosing, women have higher bleeding risk with glycoprotein IIb/IIIa inhibition. The risk of bleeding events increases as creatinine clearance declines, even when dosing is weight adjusted. Bleeding events commonly lead to cessation of antithrombotic therapy, which would be expected to increase risk of reinfarction. This may partly explain the independent association of abnormal renal function with adverse outcomes, including death and reinfarction in MI and acute coronary syndrome studies and acute coronary syndrome registries in which a variety of antithrombotic agents were used. More women in each study had abnormal creatinine clearance, and after adjustment for creatinine clearance, female sex was not a significant predictor of mortality in the meta-analysis. Creatinine levels were not collected in GUSTO V.

Another area that deserves further study is the link between female sex and complications of MI. Age and sex are independently associated with myocardial rupture. The finding of a greater incidence of rupture in women is of particular interest and may relate to underlying differences in extracellular matrix or the inflammatory response. For example, women have higher C-reactive protein levels than do men, and higher C-reactive protein levels have been associated with an increased risk of myocardial rupture. Perhaps the elevation in C-reactive protein indicates a more vigorous inflammatory response, including activation of matrix metalloproteinases, which could be the cause of rupture of infarcted myocardium. A potential link between bleeding risk and myocardial rupture relates to properties of the interstitial connective tissue in the myocardium and surrounding the vasculature. Additional investigation is needed to delineate these and other possible causative links.

Another potential explanation for these risk differences may be a systematic sex difference in the coagulation and fibrinolytic cascades. Levels of certain anticoagulant proteins are higher in women than in men, and different thrombogenic factors are associated with recurrence of MI in the sexes. In addition, women are reported to have less collateral flow than men, a factor that could predispose to rupture.

This study is a subgroup analysis of a randomized clinical trial that was not designed to investigate sex differences in demographics, treatment, and outcome. The pa-
tients in this population would be expected to be representative of men and women who receive thrombolytic therapy for STEMI; however, patients who present atypically or late might not be considered for thrombolytic therapy, and these men and women enrolled in clinical trials may be at lower risk than the general population. Multivariate analysis was used to examine the independent effect of sex on outcome, but residual confounding remains possible as an explanation for our findings. Furthermore, treatment within the trial was highly standardized and true sex differences may be different outside of the clinical trial setting.

In conclusion, female sex is independently associated with death and bleeding complications among patients with acute MI treated with a fibrinolytic regimen. Women also have a higher risk of complications, including reinfarction, stroke, and mechanical complications. There remains a differential between the sexes in the use of angiography and, therefore, PCI after fibrinolysis.

Now that the nature of sex differences in the presentation, outcome, and management of acute MI has been well established, further investigation is needed to improve our basic understanding of these differences. The key to improving outcomes in women with coronary artery disease may lie not only in ensuring that their treatment is equal to that of men but also in developing diagnostic and therapeutic approaches specific to sex.

Accepted for Publication: May 22, 2007.
Correspondence: Harmony R. Reynolds, MD, 530 First Ave, Skirball Ste 9R, New York, NY 10016 (Harmony.Reynolds@nyumc.org).

Author Contributions: Study concept and design: Farkouh, Lincoff, Swahn, and Hochman. Acquisition of data: Lincoff, Hsu, Swahn, Sadowski, and Hochman. Analysis and interpretation of data: Reynolds, Farkouh, Lincoff, Hsu, White, Topol, and Hochman. Drafting of the manuscript: Reynolds, Farkouh, and Topol. Critical revision of the manuscript for important intellectual content: Lincoff, Hsu, Swahn, Sadowski, Topol, and Hochman. Statistical analysis: Hsu and White. Obtained funding: Topol. Administrative, technical, and material support: Lincoff and Hochman. Study supervision: Farkouh, Lincoff, Sadowski, Sadowski, and Hochman.

Financial Disclosure: Drs Lincoff and Hochman received research funding from Centocor/Lilly for the conduct of the trial.

Funding/Support: The GUSTO V trial and data management and statistical support for this study were funded by Centocor, Malvern, Pennsylvania, and Eli Lilly, Indianapolis, Indiana.

Role of the Sponsor: The funding bodies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation of the manuscript. The funding bodies did review and approve the manuscript.

REFERENCES


