Outcomes and Optimal Antithrombotic Therapy in Women Undergoing Fibrinolysis for ST-Elevation Myocardial Infarction

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Background—The manifestations, complications, and outcomes of cardiovascular disease differ between women and men. The safety and efficacy of pharmacological reperfusion therapy in women with ST-elevation myocardial infarction are of particular interest.

Methods and Results—We investigated outcomes in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 study, which randomized ST-elevation myocardial infarction patients with planned fibrinolysis to enoxaparin or unfractionated heparin. Compared with men (n=15 696), women (n=4783) were older and more likely to have hypertension and diabetes ($P<0.001$). The unadjusted 30-day mortality rate for women was >2-fold higher than for men (13.2% versus 5.4%; odds ratio, 2.66; 95% CI, 2.40 to 2.96). After adjustment for age, fibrinolytic therapy, revascularization, region, and elements of the TIMI Risk Score, women had a 1.25-fold-higher 30-day risk of death (95% CI, 1.08 to 1.46) but similar risk of intracerebral hemorrhage (adjusted odds ratio, 0.81; 95% CI, 0.52 to 1.26). The 30-day rate of death or nonfatal MI in women was reduced by enoxaparin compared with unfractionated heparin in women (15.4% versus 18.3%; $P=0.007$). Major bleeding was more frequent in women receiving enoxaparin compared with those receiving unfractionated heparin (2.3% versus 1.4%; $P=0.022$) but similar among women and men receiving enoxaparin (2.3% versus 2.0%; $P=0.39$). The rates of death, nonfatal myocardial infarction, or nonfatal major bleeding (net clinical benefit) were lower with enoxaparin (absolute risk reduction, 2.6% in women [$P=0.02$] and 1.6% in men [$P=0.001$]).

Conclusions—In ExTRACT-TIMI 25, women presented with a profile of higher baseline risk and increased short-term mortality. In this large, contemporary clinical trial, women had similar relative and greater absolute risk reductions than men when treated with enoxaparin compared with unfractionated heparin as adjunctive therapy with fibrinolysis. **(*Circulation*. 2007;115:2822-2828.)**

Key Words: anticoagulants ■ fibrinolysis ■ myocardial infarction ■ sex

Cardiovascular disease is the leading cause of death in women in industrialized nations, including the United States. Since the mid-1980s, the total number of deaths attributed to cardiovascular disease has been greater for women than men, and women exhibit higher rates of mortality and reinfarction after acute coronary syndromes.[1–3] However, the evaluation of women with cardiovascular disease continues to be a challenge for healthcare providers, and traditional diagnostic tools established largely in men have variable utility in women.[4] At the same time, atypical ischemic symptoms (such as fatigue or nausea), more frequent in women, can be dismissed by both the female patient and medically trained professionals and can lead to delays in the presentation and treatment of coronary artery disease, especially acute coronary syndromes.[5] This delay contributes to the increased morbidity and mortality observed in women presenting with myocardial infarctions (MI).

Editorial p 2796
Clinical Perspective p 2828

The observed sex-related differences in cardiovascular disease presentation and outcome may, in part, also have pathobiological roots. Experimental and clinical data suggest that women differ from men in the structural plaque morphol-

Received November 27, 2006; accepted March 21, 2007.

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Guest Editor for this article was Robert Bonow, MD.

Clinical trial registration information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00077792.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.679548**

ogy leading to an MI. Additionally, women have more prominent contributions from endothelial and microvascular dysfunction and exhibit more frequent dysregulation of coronary vasomotor tone.[6–9]

Because of these sex-based differences in presentation, comorbid disease, and pathophysiology, the effects of medical and interventional therapies can differ in women and men. In 1993, the National Institutes of Health mandated that all National Institutes of Health–sponsored clinical trials include women and provide relevant analyses in female participants.[10] Yet, relative to disease prevalence, women continue to be underrepresented in randomized controlled trials of acute coronary syndromes, and questions have been raised regarding the outcomes achieved with specific interventions in women, including the safety of fibrinolytic and antithrombotic regimens.[11,12] The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 study allowed us to evaluate the treatment-specific outcomes and complications in the 4783 women with ST-elevation MI (STEMI) with planned fibrinolysis randomized to enoxaparin or unfractionated heparin (UFH).[13] Additionally, it provided the opportunity to examine the differences in baseline characteristics, rates of clinical events, and treatment strategies among the women and men in this large, contemporary clinical trial.

Methods

Patient Population

ExTRACT-TIMI 25 was an international, multicenter, randomized, double-blind, controlled trial that included 20 479 patients in the intention-to-treat population. The 4783 women (23%) and 15 696 men (77%) presented with STEMI and were scheduled to undergo fibrinolysis with streptokinase, tenecteplase, alteplase, or reteplase. Patients were treated with aspirin and assigned in a 1:1 fashion to receive an antithrombotic strategy of enoxaparin or UFH.[14] To participate in the trial, patients needed to be at least 18 years of age and present with ischemic symptoms and ST-segment elevation or new left bundle-branch block. Exclusion criteria included cardiogenic shock, pericarditis, or contraindications to fibrinolysis. At 30 days, 2 of 15 696 men (0.01%) and 1 of 4783 women (0.02%) did not have complete follow-up.

Treatments and End Points

Enoxaparin was administered as a 30-mg intravenous bolus, followed 15 minutes later by a subcutaneous injection of 1 mg/kg, with injections given every 12 hours. Enoxaparin was continued until hospital discharge or for a maximum of 8 days. In patients who were ≥75 years of age, the initial bolus was eliminated, and the maintenance dose was decreased to 0.75 mg/kg every 12 hours. The UFH was provided as a 60-U/kg intravenous bolus, and then within 15 minutes, an infusion of 12 $U \cdot kg^{-1} \cdot h^{-1}$ was initiated. The UFH infusion was to be given for at least 48 hours but could be continued for a longer period at the treating physician's discretion.

For both the overall study and the present substudy, the primary end point was defined as death or nonfatal recurrent MI. The main secondary end point was the composite of death, nonfatal recurrent MI, or urgent revascularization within 30 days. Bleeding events were classified according to TIMI criteria.[13] A blinded Clinical Events Committee adjudicated all ischemic and major bleeding events. Sex was included as a prespecified subgroup.

Statistical Analysis

The baseline characteristics of women and men were compared by the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. A χ^2 test was used to compare the unadjusted sex-related differences in outcomes. Given the large sample size and completeness of follow-up, the efficacy and safety of enoxaparin were first evaluated with the χ^2 test. Analyses adjusted for prior MI, smoking status, and clinical covariates in the TIMI STEMI Risk Score (age, hypertension, diabetes, angina, infarct location, systolic blood pressure, heart rate, weight, time to treatment, and Killip class) were further conducted with logistic regression. The interaction of sex and age was assessed with a logistic regression model. To facilitate comparison with the adjusted odds ratios (ORs) determined from logistic regression, the unadjusted risks associated with sex also are presented as ORs. Consistent with the primary analysis plan for the main trial, all evaluations of the efficacy of enoxaparin versus UFH are presented as relative risks. Values (2 tailed) of $P<0.05$ were considered to indicate statistical significance. All analyses were performed with STATA/SE 9.2 (STATA Corp, College Station, Tex). The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients

Compared with men, women were older (68 versus 57 years; $P<0.001$) and were more likely to have a history of hypertension, hyperlipidemia, diabetes mellitus, and prior angina pectoris (Table 1). Overall, women were at higher baseline mortality risk than men as assessed by a TIMI Risk Score >3 (59% versus 29%; $P<0.001$). They also experienced a longer delay from symptom onset to treatment with a lytic, with a median time of 3.5 hours compared with 3.0 hours for men ($P<0.001$). During the treatment phase and at hospital discharge, women were less likely than men to be prescribed antiplatelet agents, β-blockers, or statins (Table 1). Women underwent significantly fewer cardiac procedures, including angiography, percutaneous coronary intervention, and coronary artery bypass surgery ($P<0.001$ for each).

Clinical Outcomes

The unadjusted mortality rate for women was >2-fold greater than that for men (13.2% versus 5.4%; OR, 2.66; 95% CI, 2.40 to 2.96; $P<0.001$). Women were observed to have higher mortality rates without significant variation across age groups, as shown in Figure 1 ($P_{interaction}=0.19$). After adjustment for age, type of fibrinolytic, revascularization by 30 days, geographic region, and elements of the TIMI Risk Score (see above), women continued to have a higher 30-day risk of death (adjusted OR, 1.25; 95% CI, 1.08 to 1.46; $P=0.003$). Among TIMI risk categories, women had higher mortality at 30 days than men, with increasing absolute risk differences between women and men in higher TIMI Risk Score groups (Figure 2). The rates of nonfatal recurrent MI and TIMI major bleeding at 30 days were similar among women and men (3.7% versus 3.8%, $P=0.72$ [nonfatal MI]; and 1.9% versus 1.7%, $P=0.42$ [fatal and nonfatal bleeding]). Although women had higher rates of intracranial hemorrhage (ICH) than men (1.0% versus 0.7%; $P=0.007$), after adjustment for age and covariates of the TIMI Risk Score, the difference was no longer significant (adjusted OR, 0.81; 95% CI, 0.52 to 1.26; $P=0.35$).

TABLE 1. Characteristics of Women and Men

	Women (n=4783)	Men (n=15 696)	*P*
Baseline characteristics			
Age, y	68 (59, 75)	57 (49, 66)	<0.001
Weight, kg	70 (60, 79)	79 (70, 88)	<0.001
Creatinine clearance, mL/min	66 (51, 84)	87 (69, 109)	<0.001
Hypertension	2979/4746 (62.8)	5927/15 487 (38.3)	<0.001
Hyperlipidemia	729/3643 (20.0)	2188/12 326 (17.8)	0.002
Current smoker	1106/4778 (23.2)	8586/15 691 (54.7)	<0.001
Prior MI	560/4768 (11.7)	2099/15 636 (13.4)	0.003
Prior angina pectoris	1639/4749 (34.5)	4076/15 596 (26.1)	<0.001
Prior PCI	74/4782 (1.6)	586/15 679 (3.7)	<0.001
Diabetes mellitus	1057/4725 (22.4)	2003/15 524 (12.9)	<0.001
TIMI risk score >3	2779/4745 (58.6)	4444/15 531 (28.6)	<0.001
Index presentation and medications*			
Anterior MI	2051/4734 (43.3)	6882/15 599 (44.1)	0.335
Killip class ≥II	770/4782 (16.1)	1522/15 686 (9.7)	<0.001
Fibrinolytic			<0.001
Fibrin specific	3724 (77.9)	12 559 (80.0)	...
Streptokinase	1047 (21.9)	3092 (19.7)	...
None	12 (0.3)	45 (0.3)	...
Time from symptom onset to lytic, h	3.5 (2.4, 4.6)	3.0 (2.1, 4.2)	<0.001
Aspirin	4431/4783 (92.6)	15 045/15 696 (95.9)	<0.001
Clopidogrel	1059/4783 (22.1)	4668/15 696 (29.7)	<0.001
β-Blocker	4045/4783 (84.6)	13 511/15 696 (86.1)	0.009
ACE-I/ARB	3857/4783 (80.6)	12 460/15 696 (79.4)	0.059
Statin	3054/4783 (63.9)	11 173/15 696 (71.2)	<0.001
Procedures			
Angiography by 30 d	1072/4783 (22.4)	5013/15 696 (31.9)	<0.001
Any revascularization by 30 d	892/4783 (18.7)	4364/15 696 (27.8)	<0.001

Data are shown as n/N (%) for dichotomous variables and median (25th, 75th percentiles) for continuous variables. PCI indicates percutaneous intervention; ACE-I, angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

*Medications during index hospitalization.

Efficacy and Safety of Enoxaparin in Women and Men

The primary end point of death or nonfatal recurrent MI at 30 days was reduced by enoxaparin compared with UFH in both women ($P=0.007$) and men ($P<0.001$). The rate of the primary efficacy end point in women was 15.4% in the enoxaparin group and 18.3% in the UFH group, yielding a 2.9% absolute risk difference and 16% relative risk reduction

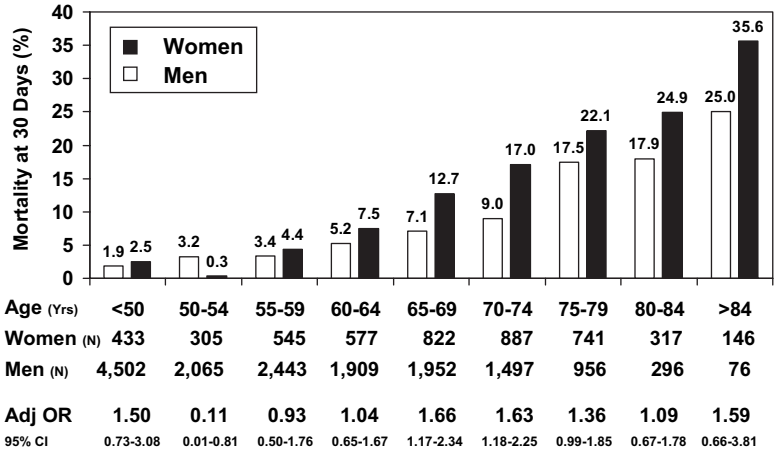

Figure 1. Rates of mortality at 30 days among women and men according to age group. In each age group, mortality rates were adjusted for smoking status, history of hypertension, history of diabetes, history of angina, prior MI, infarct location, systolic blood pressure, heart rate, weight, time from symptoms to treatment, and Killip class. The adjusted ORs (OR adj) and 95% CIs are provided.

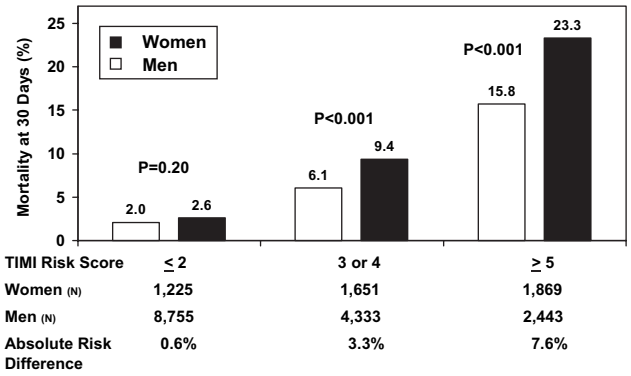

Figure 2. Rates of mortality at 30 days among women and men according to TIMI Risk Score group (≤2=low risk, 3 or 4=medium risk, ≥5=high risk).

compared with 1.9% and 19%, respectively, in men (Figure 3). The number needed to treat with enoxaparin to prevent 1 death or nonfatal recurrent MI was 34 among women and 53 among men. At 8 days, the benefit of enoxaparin in both women and men was already evident (Figure 4).

Major bleeding and minor bleeding were more frequent in women receiving enoxaparin versus UFH (Table 2). However, the rate of major bleeding was similar among women and men receiving enoxaparin (2.3% versus 2.0%; $P=0.39$). Rates of ICH also were higher among women treated with enoxaparin compared with UFH, but not significantly so.

In women and men, the rate of death, nonfatal recurrent MI, or major bleeding (a measure of net clinical benefit) was significantly lower with enoxaparin (Figure 3). The reductions in the absolute event rates of this composite end point were 2.6% in women and 1.6% in men, with 14% relative risk reductions in both groups. For every 1000 women treated with enoxaparin, 16 deaths, 13 nonfatal recurrent MIs, and 5 urgent revascularizations were prevented, whereas 5 additional nonfatal major bleeds were experienced (Figure 5).

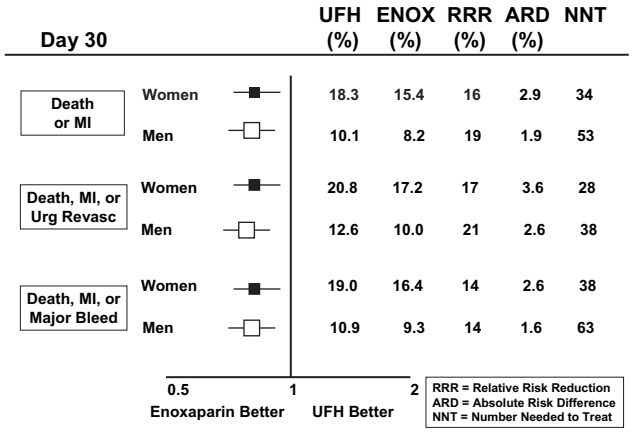

Figure 3. Absolute event rates and relative risks of 3 end points (death or nonfatal recurrent MI; death, nonfatal recurrent MI, or urgent revascularization; and death, nonfatal recurrent MI, or major bleed) for men and women measured at 30 days.

Discussion

The ExTRACT-TIMI 25 trial included 20 479 participants and demonstrated that, compared with the UFH strategy in patients receiving fibrinolysis for STEMI, the enoxaparin strategy reduced death and nonfatal recurrent MI and improved net clinical benefit at 30 days, despite an increase in major bleeding. In the analysis presented here, we focus on the 4783 women in the study, who were significantly older than the men and had higher baseline risk profiles with higher short-term mortality. Despite these findings, women and men in this trial derived a similar relative benefit when treated with a strategy of enoxaparin compared with UFH as adjunctive antithrombin therapy with fibrinolysis. Moreover, because of their higher risk, women derived a greater absolute benefit than men when treated with enoxaparin. Thus, our findings have implications for the care of women undergoing fibrinolysis for STEMI.

Evidence-Based Therapies

In this study, we observed that differences in care persisted even in the setting of a highly regulated, contemporary clinical trial with increased overall use of evidence-based treatments. At discharge, women were less likely than men to receive medications that have been shown to improve outcomes, consistent with prior observations.[15–17] Although there has been some improvement in the overall use of aspirin in recent years, gender disparities persist; in an analysis that included >25 000 patients with documented coronary artery disease, women were less likely than men to be taking aspirin (OR, 1.51; 95% CI, 1.35 to 1.71; $P<0.0001$).[18] Likewise, among post-MI patients with no contraindication to β-blockers, women have been shown to be significantly less likely than men to receive a prescription, and women with dyslipidemia are less likely than men to be treated with appropriate lipid-lowering agents.[19,20] In our analysis, we also noted treatment delays and differences in the percentage of women and men undergoing cardiac procedures (including angiography, percutaneous coronary intervention, and coronary bypass grafting), as has been described previously.[21–24]

Post-STEMI Mortality Rates

The 1.25-fold increase (adjusted for age, type of fibrinolytic, revascularization by 30 days, region, and elements of the TIMI Risk Score) in 30-day mortality among women in this contemporary population shows little amelioration of this risk compared with earlier findings.[25] Interestingly, in a previous analysis conducted in the National Registry of Myocardial Infarction 2 (NRMI-2), the mortality rate for younger women was more than twice that for men of the same age, an observation not seen among the older women.[3] In another registry-based study, younger women also were observed to have particularly high 30-day mortality rates after acute MIs, a finding that was ultimately linked to women's increased probability of surviving to reach a hospital compared with men.[26] In ExTRACT-TIMI 25, we did not detect a particular excess of mortality among younger women. This observation may be divergent from the prior reports because it is in the context of a randomized clinical trial population focusing exclusively on STEMI patients.

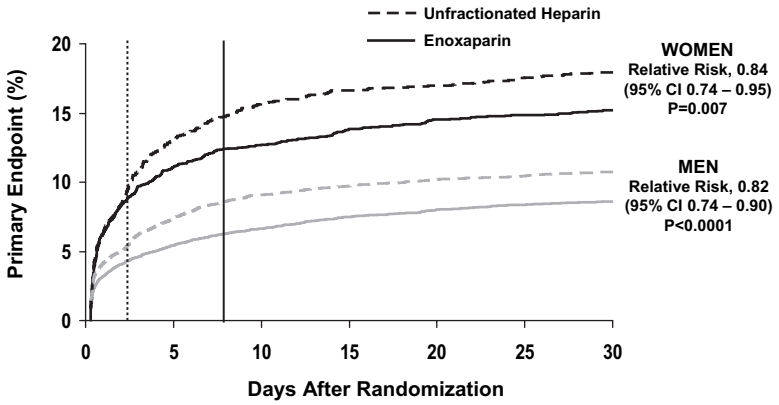

Figure 4. Cumulative incidence of the primary end point (death or nonfatal MI) at 30 days in women and men treated with enoxaparin and UFH. The interval shown is the time (in 24-hour intervals) from randomization to an event or the last follow-up visit. At 48 hours (dashed vertical line), the relative risk for enoxaparin vs UFH was 0.96 (95% CI, 0.79 to 1.15; $P=0.64$) in women and 0.85 (95% CI, 0.73 to 1.00; $P=0.049$) in men. At 8 days (solid vertical line), the relative risk for enoxaparin vs UFH was 0.83 (95% CI, 0.72 to 0.96; $P=0.01$) in women and 0.74 (95% CI, 0.65 to 0.83; $P<0.0001$) in men.

Optimal Antithrombotic Therapy in Women Undergoing Fibrinolysis

Possibly because of insufficient sample size, previous analyses have not been conclusive regarding the clinical outcomes of women treated with enoxaparin in conjunction with fibrinolysis. For example, in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 (ASSENT-3) study population, treatment with tenecteplase and enoxaparin resulted in lower rates of mortality at 30 days, refractory ischemia, or in-hospital reinfarction compared with treatment with tenecteplase and UFH.[27] The results for women in ASSENT-3 were directionally similar to those in men but did not reach statistical significance (relative risk, 0.87; 95% CI, 0.65 to 1.17). In evaluations of the efficacy plus safety composite end point (which included major bleeding and ICH) for women, the point estimates were on the line of unity. In ExTRACT-TIMI 25, the rate of death or nonfatal recurrent MI at 30 days was reduced with enoxaparin compared with UFH in women, with an absolute risk reduction of 2.9% and a relative risk reduction of 16%. The ability to evaluate clinical outcomes in >4700 women in ExTRACT-TIMI 25 may have allowed these treatment benefits to be observed. In future acute coronary syndrome trials, it will be important to include more women to be able to investigate thoroughly the effects of medical and interventional therapies in both sexes.

In addition, our observations provide encouraging new information with respect to safety in women undergoing fibrinolysis. Although previous studies have indicated that fibrinolytics are equally effective at restoring coronary artery patency in women and men,[28,29] women have experienced more fatal and nonfatal complications than men. In particular, women have been found to be 2 to 3 times more likely to sustain a hemorrhagic stroke after fibrinolytic therapy. In NRMI-2 and the Cooperative Cardiovascular Project, this difference in ICH persisted even after adjustment for age and clinical features.[29–31] The results from our analysis in ExTRACT-TIMI 25 show that with protocol-specified fibrinolytic and anticoagulant therapy, including dose adjustments of enoxaparin for age and renal dysfunction, major bleeding was similar among women and men at 30 days. Additionally, although women had higher unadjusted rates of ICH than men, adjustment for age eliminated this difference. Moreover, in examinations of the measures of net clinical benefit with enoxaparin

TABLE 2. Outcomes Among Women at 30 Days Treated With Enoxaparin and UFH

	Enoxaparin, % (n=2415)	UFH, % (n=2368)	Relative Risk (95% CI)	*P*
Efficacy outcomes				
Primary point	15.4	18.3	0.84 (0.74 to 0.95)	0.007
Death	12.3	14.0	0.88 (0.76 to 1.02)	0.094
Nonfatal recurrent MI	3.0	4.3	0.70 (0.52 to 0.94)	0.018
Death, nonfatal recurrent MI, urgent revascularization	17.2	20.8	0.83 (0.74 to 0.93)	0.002
Safety outcomes				
Major bleeding (with ICH)	2.3	1.4	1.64 (1.07 to 2.51)	0.022
ICH	1.2	0.8	1.43 (0.81 to 2.51)	0.22
Minor bleeding	4.4	2.9	1.51 (1.12 to 2.03)	0.006
Major or minor bleeding	6.6	4.2	1.56 (1.22 to 1.99)	<0.001
Net clinical benefit				
Death, nonfatal recurrent MI, or nonfatal major bleed	16.4	19.0	0.86 (0.76 to 0.98)	0.020

The primary end point included death and nonfatal MI. Bleeding was assessed according to TIMI criteria.

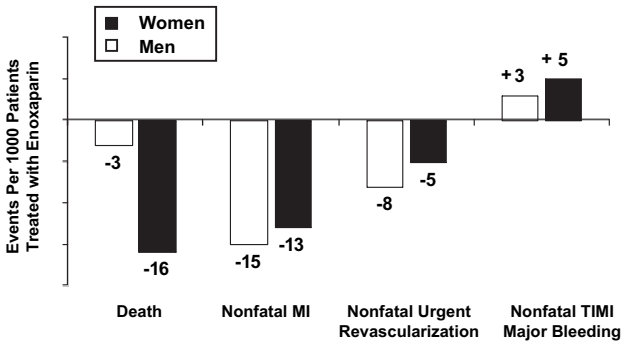

Figure 5. Events (death, nonfatal recurrent MI, nonfatal urgent revascularization, and nonfatal TIMI major bleed) per 1000 women and men treated with enoxaparin compared with UFH.

such as the composite of death, nonfatal recurrent MI, and major bleeding, our findings support the use of enoxaparin as adjunctive antithrombin therapy in women.

Study Limitations

First, ExTRACT-TIMI 25 was not specifically designed to have sufficient statistical power to discriminate a treatment difference or interaction with respect to sex. However, sex was a prespecified subgroup for analysis, and the number of women in the trial (4783) allowed a robust comparison. Second, although this study provides interesting data regarding sex and the use of enoxaparin in the setting of fibrinolysis for STEMI, it does not provide direct insight into the underlying pathobiology.

Conclusions

In ExTRACT-TIMI 25, women presented with a profile of higher baseline risk with higher short-term risk-adjusted mortality than men. Despite these differences, women had a similar relative and greater absolute benefit than men when treated with a strategy of enoxaparin compared with one of UFH as adjunctive antithrombin therapy with fibrinolysis. A higher rate of bleeding with enoxaparin was offset by the reduction in death or nonfatal MI, resulting in a superior net clinical benefit compared with UFH in women and men in this trial. In conclusion, these findings indicate that, as for men, in women receiving fibrinolytic therapy for STEMI, treatment with enoxaparin throughout the hospitalization should be considered a superior alternative to standard 48-hour intravenous therapy with UFH.

Source of Funding

A research grant was provided by Sanofi-Aventis to Brigham and Women's Hospital for the performance of the ExTRACT-TIMI 25 study.

Disclosures

Drs Morrow, Antman, and Braunwald report having received research grant support from, having received lecture fees from, and having served on paid advisory boards for Sanofi-Aventis. Drs Mega, Östör, and Dorobantu report having received research grant support from Sanofi-Aventis.

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CLINICAL PERSPECTIVE

The manifestations, complications, and outcomes of cardiovascular disease differ between women and men. Because of these differences, the safety and efficacy of pharmacological reperfusion and antithrombotic therapies in women with ST-elevation myocardial infarction have been of particular interest. The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 study provided the opportunity to evaluate the characteristics and treatment-specific outcomes of 4783 women with ST-elevation myocardial infarction with planned fibrinolysis randomized to enoxaparin or unfractionated heparin. In the present study, women presented with a profile of higher baseline mortality risk than men as assessed by a TIMI Risk Score >3 (59% versus 29%; $P<0.001$). After adjustment for age, fibrinolytic therapy, revascularization, region, and elements of the TIMI Risk Score, women compared with men had a 1.25-fold-higher 30-day risk of death (95% CI, 1.08 to 1.46) but similar risk of intracerebral hemorrhage (adjusted odds ratio, 0.81; 95% CI, 0.52 to 1.26). In the present study, the relative risk reduction in death and nonfatal MI for enoxaparin versus unfractionated heparin was similar in women (relative risk, 0.84; 95% CI, 0.74 to 0.95) and men (RR, 0.82; 95% CI, 0.74 to 0.90), with a larger absolute risk difference seen in women (15.4% versus 18.3% [women] and 8.2% versus 10.1% [men]). A higher rate of bleeding with enoxaparin compared with unfractionated heparin was seen among both women and men; however, the net clinical benefit strongly favored enoxaparin in both sexes. In conclusion, these findings indicate that in women receiving fibrinolytic therapy for ST-elevation myocardial infarction, a treatment strategy using enoxaparin is a superior alternative to standard 48-hour intravenous therapy with unfractionated heparin.