QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

Cost Effectiveness of Enoxaparin in Acute ST-Segment Elevation Myocardial Infarction

The ExTRACT–TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) Study

Leo Marcoff, MD,* Zugui Zhang, PhD,* Wei Zhang, MS,* Edward Ewen, MD,* Claudine Jurkovitz, MD, MPH,* Prisca Leguet, PHARMd,† Paul Kolm, PhD,* William S. Weintraub, MD*

Newark, Delaware; and Paris, France

Objectives

We used a U.S. model of health care costs to examine the cost effectiveness of enoxaparin compared with unfractionated heparin (UFH) as adjunctive therapy for fibrinolysis in patients with ST-segment elevation myocardial infarction (STEMI).

Background

The ExTRACT–TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) study, a large, randomized, multinational trial, demonstrated a reduction in death or nonfatal myocardial infarction when enoxaparin was used instead of UFH as adjunctive therapy for fibrinolysis in patients with STEMI.

Methods

We used patient-level clinical outcomes and resource use from the ExTRACT–TIMI 25 trial and estimates of life expectancy gains as a result of the prevention of the clinical events on the basis of the Framingham Heart Study.

Results

Index hospitalization costs trended lower by $126 in the enoxaparin group (95% confidence interval [CI]: $295 to $49). Thirty-day costs trended higher by $102 for enoxaparin (95% CI: $108 to $314). Patients receiving enoxaparin gained an average of 0.12 life-years relative to patients given UFH. Estimated total lifetime costs were $1,207 higher in the enoxaparin group (95% CI: $491 to $1,923). The incremental cost-effectiveness ratio of enoxaparin compared with UFH was $5,700 per life-year gained, with 99.9% of bootstrap-derived estimates <$50,000 per life-year gained. Using a probabilistic sensitivity analysis, there is a 90% probability that enoxaparin is cost effective for lifetime, provided that the willingness-to-pay value exceeds $50,000.

Conclusions

Based on a U.S. model of health care economics, the strategy of using enoxaparin instead of UFH as adjunctive therapy for fibrinolysis in patients with STEMI is cost effective according to commonly used benchmarks. (J Am Coll Cardiol 2009;54:1271–9) © 2009 by the American College of Cardiology Foundation
as adjunctive therapy for fibrinolysis in patients with STEMI.

Methods

Design of the ExTRACT–TIMI 25 trial. The ExTRACT–TIMI 25 study (Clinical Trial no. NCT000777792), a large, randomized, double-blind, multinational trial, has been described previously (1,2). Briefly, between October 24, 2002, and October 1, 2005, 20,506 patients with STEMI were randomized at 674 sites in 48 countries (Online Table A) to receive either enoxaparin or UFH as adjunctive therapy to fibrinolytic agents. Study medication was administered in a double-blind fashion with the use of a double-dummy design between 15 min before and 30 min after the initiation of fibrinolysis, and occurred within 30 min after randomization. Patients were eligible if they were at least 18 years of age, had at least 20 min of ischemic symptoms while at rest within 6 h before randomization, had ST-segment elevation of at least 0.1 mV in 2 limb leads or of 0.2 mV in at least 2 contiguous precordial leads or had left bundle branch block, and were scheduled to undergo fibrinolysis therapy with streptokinase, tenecteplase, alteplase, or reteplase. Exclusion criteria were cardiogenic shock, pericarditis, symptoms of aortic dissection, contraindications to fibrinolysis, receipt of a LMWH within the prior 8 h, known renal insufficiency (defined by a serum creatinine level of >220 μmol/l [2.5 mg/dl] for men and >175 μmol/l [2.0 mg/dl] for women), or a life expectancy of <12 months. The primary efficacy end point was the composite of death from any cause or nonfatal recurrent MI. In addition, net clinical benefit end points were pre-specified in the form of composites of death, nonfatal MI, and important safety outcomes, including nonfatal disabling stroke, nonfatal major bleeding, and nonfatal intracranial hemorrhage. Approval for the study was obtained through the local institutional review board at each participating center.

Economic analysis plan and cost assessment. We compared the costs of the 2 interventions and performed an incremental cost-effectiveness analysis (3,4). Costs and cost effectiveness were assessed at 30 days and lifetime. Direct medical care costs associated with index hospitalizations, subsequent hospitalizations, and subsequent outpatient procedures were considered in this analysis. Data were not available to calculate the costs of concomitant medication and indirect costs due to lost productivity, but the overall perspective was societal. Thirty-day costs were not discounted because the duration of the trial was <1 year. Costs beyond the trial period were discounted 3% annually after the first year. All costs used 2004 as the base year. The data collected at 30 days included the details of the index hospitalization, including length of stay, rehospitalizations, major procedures, interventions (for example, cardiac catheterization, percutaneous coronary intervention [PCI], coronary artery bypass graft surgery, intra-aortic balloon pump, computed tomography scan, and magnetic resonance imaging), and resource use associated with severe adverse events.

The index and subsequent hospitalizations for patients enrolled in the ExTRACT–TIMI 25 trial were assigned a diagnosis-related group (DRG) in accordance with U.S. Medicare diagnostic standards. Costs for each DRG were estimated using average Medicare reimbursement rates obtained from the Medicare Part A data file (5), and physician costs were estimated as a percent share by DRG according to the methods of Mitchell et al. (6). Outpatient procedures were coded by Current Procedural Terminology, and assigned a cost based on the Medicare fee schedule (Online Table B). Costs beyond the trial period were estimated as the average per capita participant national health expenditures of $5,219 in 2004 (7).

Given the high cost differences between enoxaparin and UFH, it is necessary to incorporate the cost of both enoxaparin and UFH in the economic analysis. Therefore, the costs of enoxaparin and UFH were included in the analysis based on the observed utilization in the ExTRACT–TIMI 25 study. As per protocol, treatment with enoxaparin lasted a median of 7.0 days (interquartile range [IQR] 4.5 to 7.5 days), and treatment with UFH lasted a median of 2.0 days (IQR 2.0 to 2.2 days). In the enoxaparin group, the initial bolus was 30 mg and the subsequent daily dose was 140 mg until hospital discharge. It was assumed that the treatment was given for an average of 7 days. In the UFH group, the initial bolus was assumed to be 4,000 IU, and the next infusion was 1,000 IU/h for 48 h. The unit prices for UFH and enoxaparin were derived from the prices in 2004. The cost of treatment with enoxaparin was estimated to be $214, and the cost of treatment with UFH was estimated to be $13.

Life expectancy estimation. Age- and sex-specific life expectancy was estimated from Framingham Heart Study data (8). In the event of death, life-years lost (LYL) were obtained by subtracting the in-trial survival times from estimated age- and sex-specific life expectancy estimates for patients with cardiovascular disease (9,10). For patients who experienced multiple events of different types during the trial, LYL was calculated assuming a hierarchy of death, stroke, and MI. Average LYL was calculated for both treatment groups, and their difference (UFH – enoxaparin) yielded an estimate of life-years gained (LYG) with enoxaparin. LYL were discounted 3% annually after the first year.

Estimation of cost effectiveness. The cost-effectiveness analysis was performed for periods of 30 days and lifetime.
The cost effectiveness was expressed as the incremental cost-effectiveness ratio (ICER), which is the cost divided by LYG. Bootstrap methods were used to estimate 95% confidence interval (CI) for both cost and LYG (11). To address the uncertainty of the effect of death, MI, or stroke on LYG, traditional 1-way sensitivity analyses were performed by varying LYG by 10%, 20%, 30%, and 40% (12). Probabilistic sensitivity analysis was conducted to assess the impact of all sources of uncertainty involved in the calculation of cost and LYG (13–15). The probability assumptions of effectiveness were derived from American Heart Association statistics (16) and the Cardiovascular Health Study (17). Monte Carlo simulation was performed to derive the differences in quality-adjusted life-years (QALY) and mean cost between the enoxaparin group and the UFH group. 

**Subgroup analysis and net benefit analysis.** Cost and effectiveness analysis were conducted for subgroups, defined according to age, sex, body mass index, prior MI, prior heart failure, diabetes mellitus, prior unstable angina, prior PCI or coronary artery bypass graft surgery, and platelet count. Net benefit analysis (net monetary benefit [NMB] and net health benefit [NHB]) were applied to the 30-day cost-effectiveness analysis (18,19).

Based on the method proposed by Manca et al. (20), NMB and NHB were calculated at the patient level (21) from patient level data on cost and effectiveness:

\[ \text{NMB}_i = E_i \lambda - C_i \]
\[ \text{NHB}_i = E_i - C_i / \lambda \]

where \( C_i \) and \( E_i \) are the cost and effectiveness (QALY) at the \( i \)-th patient, and \( \lambda \) is the willingness-to-pay value. Standard regression methods were applied to the analysis of treatment group differences with respect to NMB or NHB.

Because of the multisite, multicountry design of the trial, cost and effectiveness data were essentially clustered; that is, data specific to a given site or country may be correlated (21,22). Therefore, multilevel (hierarchical) regression models of net benefit were used to account for the intra-cluster correlation (ICC) (21,22). A 2-level hierarchical model method was applied: country-level and patient-level (23). An empirical Bayesian shrinkage factor was applied to estimate country-specific cost effectiveness.

To investigate the primary reason for discrepancy between NMB and NHB, the ICC was calculated based on the multilevel regression models. The ICC is defined from the variance components estimated from the multilevel regression models and takes values between 0 and 1 inclusively. It can be interpreted as the percentage of the total variance attributed to between-country variation. While a general ICC for country variation was reported based on the variance component specification, an ICC for each arm of the trial was defined based on the random coefficient specification. A high ICC indicates that the dataset is clustered, which means that variation between countries is an important component of the total variation and that countries differ substantially in measured health outcomes, namely, NMB and NHB, including cost and effectiveness.

### Table 1 Clinical Summary

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Enoxaparin (n = 10,256)</th>
<th>Heparin (n = 10,223)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>60 ± 12</td>
<td>60 ± 12</td>
<td>0.35</td>
</tr>
<tr>
<td>Male</td>
<td>7,841 (76)</td>
<td>7,855 (77)</td>
<td>0.52</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78 ± 15 (9.689)</td>
<td>77 ± 14 (9.697)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4,505/10,128 (45)</td>
<td>4,401/10,105 (44)</td>
<td>0.18</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4,855/10,254 (47)</td>
<td>4,837/10,215 (47)</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,545/10,145 (15)</td>
<td>1,515/10,104 (15)</td>
<td>0.64</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1,349/10,214 (13)</td>
<td>1,310/10,190 (13)</td>
<td>0.46</td>
</tr>
<tr>
<td>Unfractionated heparin within 3 h before randomization</td>
<td>1,634/10,255 (16)</td>
<td>1,608/10,223 (16)</td>
<td>0.69</td>
</tr>
<tr>
<td>LMWH within 7 days before randomization</td>
<td>43 (0.4)</td>
<td>50 (0.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>135 ± 35 (9,250)</td>
<td>127 ± 35 (9,318)</td>
<td>0.23</td>
</tr>
<tr>
<td>Time (h) from symptom onset to start of fibrinolytic therapy</td>
<td>3.3 ± 1.6 (10,206)</td>
<td>3.3 ± 1.4 (10,189)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

### Outcomes at 30 days

- **Primary efficacy end point (death or nonfatal MI)**: 1,017 (10) vs. 1,223 (12), \(<0.001\)
- **Death**: 708 (6.9) vs. 765 (7.5), 0.11
- **Nonfatal MI**: 309 (3.0) vs. 458 (4.5), \(<0.001\)
- **Urgent revascularization**: 213 (2.1) vs. 286 (2.8), \(<0.001\)
- **Death, nonfatal MI, or urgent revascularization**: 1,199 (12) vs. 1,479 (15), \(<0.001\)

### Net clinical benefit at 30 days

- **Death, nonfatal MI, or nonfatal disabling stroke**: 1,038 (10) vs. 1,260 (12), \(<0.001\)
- **Death, nonfatal MI, or nonfatal major bleeding**: 1,128 (11) vs. 1,305 (13), \(<0.001\)
- **Death, nonfatal MI, or nonfatal intracranial hemorrhage**: 1,040 (10) vs. 1,250 (12), \(<0.001\)

Values are mean ± SD, n (%), or mean ± SD (n).

LMWH = low molecular weight heparin; MI = myocardial infarction.
of death or nonfatal MI was 9.9% in the enoxaparin group but 3 patients in the intention-to-treat population. The rate formed in 2.8% of patients.

Therapy in 2.8% and as urgent or elective procedure in therapy only; PCI was used in 23.0% of patients (as rescue to 17 days). Most patients were treated with medical hospitalization for the study population was 10 days (IQR 7 days (IQR 2.0 to 2.2 days) (1). The median duration of treatments.

The majority of patients received all of the above blockers, and inhibitors of the renin-angiotensin system.

guideline-recommended treatments, such as aspirin, beta-inhibitors with respect to concomitant therapy with other (1)( Table 1). In addition, the treatment groups were well studied in contemporary trials of interventions for STEMI for baseline characteristics and were similar to populations intention-to-treat analysis. The patients were well matched with respect to concomitant therapy with other

*Life expectancy was estimated on the basis of the patient's age and estimated life-years lost due to events.

Table 3 Costs, Life-Years Lost, and QALY of 30 Days and Lifetime by Treatment Group

<table>
<thead>
<tr>
<th>Item</th>
<th>Enoxaparin (n = 10,256)</th>
<th>UFH (n = 10,223)</th>
<th>Δ (Enoxaparin − UFH)</th>
<th>95% CI of Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 30-day costs*</td>
<td>$11,129.00</td>
<td>$11,026.00</td>
<td>$102.50</td>
<td>$−108.50 to $313.60</td>
</tr>
<tr>
<td>Index hospitalization</td>
<td>$9,620.20</td>
<td>$9,745.80</td>
<td>−$125.60</td>
<td>$−294.60 to $49.20</td>
</tr>
<tr>
<td>Subsequent hospitalizations</td>
<td>$1,209.50</td>
<td>$1,171.00</td>
<td>$38.50</td>
<td>$−93.50 to $174.20</td>
</tr>
<tr>
<td>Subsequent outpatient procedures</td>
<td>$85.20</td>
<td>$96.50</td>
<td>−$11.4</td>
<td>$−28.50 to $4.20</td>
</tr>
<tr>
<td>Infusion drug cost</td>
<td>$214.00</td>
<td>$13.00</td>
<td>$201.00</td>
<td>$28.00 to $514.00</td>
</tr>
<tr>
<td>Life-years lost due to events (3% discount)</td>
<td>0.7644</td>
<td>0.8803</td>
<td>0.1158</td>
<td>0.0405 to 0.1880</td>
</tr>
<tr>
<td>Life expectancy* (3% discount)</td>
<td>13.0265</td>
<td>12.8149</td>
<td>0.2116</td>
<td>0.079 to 0.3442</td>
</tr>
<tr>
<td>Quality-adjusted life expectancy (3% discount)</td>
<td>12.9457</td>
<td>12.6908</td>
<td>0.2549</td>
<td>0.1206 to 0.3892</td>
</tr>
<tr>
<td>Cost beyond trial period</td>
<td>$67,986.00</td>
<td>$66,881.00</td>
<td>$1,105.00</td>
<td>$412.00 to $1,798.00</td>
</tr>
<tr>
<td>Lifetime cost</td>
<td>$79,115.00</td>
<td>$77,907.00</td>
<td>$1,207.00</td>
<td>$491.00 to $1,923.00</td>
</tr>
</tbody>
</table>

*Life expectancy was estimated on the basis of the patient’s age and estimated life-years lost due to events.
CI = confidence interval; Δ = change; QALY = quality-adjusted life-years; UFH = unfractionated heparin.

Results

Summary of clinical data. Of a total of 20,506 patients who were randomized, 20,479 were included in the intention-to-treat analysis. The patients were well matched for baseline characteristics and were similar to populations studied in contemporary trials of interventions for STEMI (1) (Table 1). In addition, the treatment groups were well matched with respect to concomitant therapy with other guideline-recommended treatments, such as aspirin, beta-blockers, and inhibitors of the renin-angiotensin system.

The majority of patients received all of the above treatments.

Treatment with enoxaparin lasted a median of 7.0 days (defined as 24-h intervals after randomization [IQR 4.5 to 7.5 days]), and treatment with UFH lasted a median of 2.0 days (IQR 2.0 to 2.2 days) (1). The median duration of hospitalization for the study population was 10 days (IQR 7 to 17 days). Most patients were treated with medical therapy only; PCI was used in 23.0% of patients (as rescue therapy in 2.8% and as urgent or elective procedure in 20.2%), and coronary artery bypass graft surgery was performed in 2.8% of patients.

The primary end point was ascertained at 30 days in all but 3 patients in the intention-to-treat population. The rate of death or nonfatal MI was 9.9% in the enoxaparin group and 12.0% in the UFH group (relative risk reduction 17%, 95% CI: 10% to 23%; absolute risk reduction 2.1%, p < 0.001) (Table 1). The beneficial effect of enoxaparin on the primary end point was consistent in the pre-specified subgroups. The treatment benefits of enoxaparin emerged at 48 h, at which time there was a 33% reduction in relative risk (95% CI: 13% to 48%) and a 0.5% in absolute risk reduction of nonfatal MI, as compared with treatment with UFH (p = 0.002). The incidence of major bleeding episodes was increased in the enoxaparin group (2.1% vs. 1.4%, p < 0.001); however, the net clinical benefit, demonstrated by decreased rates of the composites of death, nonfatal MI, or nonfatal intracranial hemorrhage, was observed in the enoxaparin group (relative risk reduction 17%, 95% CI: 0.10 to 0.23, p < 0.001; and absolute risk reduction 2.1%).

Costs and life-years lost, QALY lost for 30 days and lifetime. Table 2 lists Framingham data on life expectancy by age and sex (8,24). The index hospital lengths of stay were 11.3 ± 8.1 days for the enoxaparin group (n = 10,064) and 11.2 ± 8.0 days for the UFH group (n = 10,048; p = 0.64). The costs of the index hospitalization trended lower in the enoxaparin group ($9,620 vs. $9,746, difference: −$126, 95% CI: −$295 to $49) (Table 3). The point estimate of costs of subsequent hospitalization were $38 higher for the enoxaparin group ($1,210 vs. $1,171, 95% CI: −$93 to $174), and the costs of the subsequent outpatient procedure trended $11 lower for the enoxaparin group ($85 vs. $96, 95% CI: −$28.5 to $4.2). The cost of treatment with enoxaparin was estimated as $201 higher than with UFH, including index and follow-up infusion drug cost. Total 30-day costs trended $102 higher for enoxaparin ($11,129 vs. $11,016, 95% CI of the difference: −$109 to $314). Costs beyond the trial period were $1,105 higher in the enoxaparin group ($1,210 vs. $1,171, 95% CI: −$93 to $174), which was calculated on the basis of the remaining life expectancy of patients in treatment groups and the average per capita of $5,219 in 2004. Total lifetime costs (30-day costs plus the costs beyond trial period) were $1,207 higher in the enoxaparin group (95% CI: $491 to $1,923), consistent with the fact that patients in...
the enoxaparin group had a longer life expectancy (Table 3). The impact of end points on cost was reflected in the cost beyond the trial period and lifetime cost, which were significantly different between the 2 arms.

Cost-effectiveness analysis for 30 days and lifetime. Table 4 shows the cost-effectiveness analysis for 30 days and lifetime. Patients in the enoxaparin arm gained an average of 0.12 life-years relative to patients in the UFH arm. At 30 days, the use of enoxaparin in patients with STEMI resulted in a 17% relative risk reduction (95% CI: 0.10 to 0.23) and a 2.1% absolute risk reduction of death or nonfatal MI (p < 0.001).

Roughly 16.1% of all estimates were in the lower right quadrant of the cost-effectiveness plane, indicating a moderate probability of the enoxaparin strategy providing better clinical outcomes without additional cost (dominant), and only 0.06% in the upper left quadrant, indicating a low probability that the enoxaparin strategy provides worse clinical outcomes at greater cost (dominated). At 30 days, the ICER of enoxaparin compared with UFH was $880 per LYG, with 99.1% of observations <$10,000/LYG, and 99.9% <$50,000/LYG (Fig. 1). For lifetime, the ICER of enoxaparin compared with UFH was $5,700/LYG, with 99.9% of estimates falling below the $50,000/LYG threshold.

Similar results were observed when cost per QALY was used to calculate ICER ($4,700/LYG) (Table 4) (Fig. 2). The QALYs were estimated on the basis of the different utilities for the quality of life impact of stroke and MI. The utilities were taken from the Cost-Effectiveness Analysis Registry (25). The utility of a patient suffering a stroke was estimated at 0.6 with a range of 0.4 to 0.8, and the utility of MI was 0.8 with a range of 0.3 to 0.9.

The results for subgroup analysis for 30 days and lifetime, net benefit, and multinational clinical trial data and country-specific cost-effectiveness analysis are shown in the Online Appendix.

Sensitivity analysis for 30 days and lifetime. The life expectancy gain with enoxaparin relative to UFH may be smaller or larger than projected, which would then affect the ICER. To account for this, we varied LYG with enoxaparin systematically by 10%, 20%, 30%, and 40%, and calculated the ICERs associated with these estimates. Over a lifetime, if the estimated LYG with enoxaparin relative to UFH decreased by 10%, 20%, 30%, and 40%, the ICERs would increase from $5,700 to $6,300, $7,100, $8,200, and $9,500 per LYG, respectively (Fig. 3). In contrast, if the estimated LYG with enoxaparin relative to UFH increased by 10%,
20%, 30%, and 40%, the ICERs would decrease from $5,700 to $5,200, $4,800, $4,400, and $4,100 per LYG, respectively. For QALYs estimated based on the different utilities for the quality of life impact of stroke and MI, the ICER would be $4,700 per QALY gained. The ICERs range from $3,400 to $7,900 per QALY gained by assuming additional 10%, 20%, 30%, and 40% increase or decrease of LYG with enoxaparin relative to UFH (Fig. 3).

The characteristics of variables used in the probabilistic sensitivity analysis are shown in Table 5. The distributional assumptions of the cost data were based on the actual data in this study, and their ranges come from relevant literature (14,15). Probabilities of effectiveness were derived from American Heart Association statistics and other cardiovascular studies (26,27). The contour plot of simulated distribution of mean differences in cost and effectiveness in QALYs based on the probabilistic sensitivity analysis over a lifetime is shown in Figure 4A. The plot of the joint posterior illustrates the positive dependent correlation between mean differences in cost and effectiveness in QALYs. The ellipses indicate 50%, 95%, and 99% CIs of the simulated lifetime ICERs. It reveals that the lifetime QALY gained could range from 0 to about 1 year for the enoxaparin compared with the UFH group, and the cost for the enoxaparin group would vary from about the same to $5,000 higher, compared with the UFH group, indicating a more effective strategy at a higher cost.

The cost-effectiveness acceptability curve (Fig. 4B) shows that the variation in this sensitivity analysis was greater than noted purely by the play of chance in the base case (Fig. 2), and that there was about 90% probability of the enoxaparin being cost effective at the $50,000 threshold. Taking into account a number of different probabilities for variables in the cost-effectiveness analysis, the posterior probability is 0.96 that enoxaparin is more effective, 0.06 that it costs less, and approximately 0.03 that it dominates UFH.

**Discussion**

We performed the first cost-effectiveness analysis of the ExTRACT–TIMI 25 trial. When thrombolytic therapy is used in the setting of STEMI, enoxaparin is both effective and cost effective compared with UFH, with an ICER of $5,700/LYG and 99.8% of estimates falling below the $50,000/LYG benchmark (28,29). A strength of our analysis is the fact that patient-level data were used directly from the ExTRACT–TIMI 25 trial. In addition, the sensitivity analyses for 30 days and lifetime confirmed the robustness of the results. To account for uncertainty in the input variables in the cost-effectiveness calculations, probabilistic sensitivity analysis was performed, providing a more comprehensive approach to sensitivity analysis than traditional 1-way and multiway analyses, and confirming the high probability that enoxaparin is cost effective.

The use of enoxaparin, as compared with UFH, as adjunctive therapy for fibrinolysis in patients with STEMI results in reduction of death or nonfatal recurrent MI and reduction in the composite of death, nonfatal reinfarction, or urgent revascularization (1). Net clinical benefit of enoxaparin over UFH was demonstrated by reduction in the rates of composites of death, nonfatal MI, nonfatal disabling stroke, nonfatal major bleeding, and nonfatal intracranial hemorrhage in the enoxaparin group, despite a higher incidence of major bleeding episodes among patients randomly allocated to enoxaparin. Subsequent analyses have shown that this strategy reduces death and recurrent MI in patients who achieve early ST-segment resolution after thrombolytic therapy (30). The clinical benefits of using enoxaparin instead of UFH as adjunctive therapy for fibrinolysis in patients with STEMI appears to be independent of the lytic choice and has been observed with fibrin-specific lyrics as well as with streptokinase (31). Concomitant treatment with clopidogrel does not reduce these benefits (32). The net clinical benefit of this strategy has also been shown in patients with renal dysfunction (33). In addition,
the use of enoxaparin was associated with decreased incidence of death or recurrent MI in those patients who underwent subsequent PCI (34) without an increased risk of bleeding complications. Women appear to have similar relative and greater absolute risk reductions than men when enoxaparin is used with lytic therapy (35). Elderly patients gain benefits from this strategy that are similar to those for younger patients (36).

**Study limitations.** ExTRACT–TIMI 25 was a multinational trial with few patients enrolled in the U.S. We applied U.S. costs to trial-wide hospitalizations on the basis of DRGs. This method may not fully account for potential differences in treatment practices and resource use between countries or health care systems. A large proportion of patients came from countries like the Russian Federation (2), where the threshold for hospitalization may be significantly different from that in a U.S. hospital, and physician costs may be underestimated or overestimated. In addition, in the U.S., most patients with STEMI would undergo primary PCI, rather than fibrinolysis. Cost-effectiveness analyses have also been conducted

**Table 5** Characteristics of Variables in the Analysis of Probabilistic Sensitivity Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Value</th>
<th>Range</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease (mortality)</td>
<td>0.0787</td>
<td>0.003–0.20</td>
<td>Beta</td>
</tr>
<tr>
<td>AMI (prevalence)</td>
<td>0.1185</td>
<td>0.037–0.30</td>
<td>Beta</td>
</tr>
<tr>
<td>Stroke (prevalence)</td>
<td>0.0257</td>
<td>0.016–0.40</td>
<td>Beta</td>
</tr>
<tr>
<td>Quality-adjusted life-years lost</td>
<td>0.8063</td>
<td>0.50–2.60</td>
<td>Gamma</td>
</tr>
<tr>
<td>Utility for stroke</td>
<td>0.60</td>
<td>0.40–0.80</td>
<td>Beta</td>
</tr>
<tr>
<td>Utility for MI (including AMI)</td>
<td>0.80</td>
<td>0.30–0.90</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial cost</td>
<td>$2,400</td>
<td>$1,200–$6,710</td>
<td>Gamma</td>
</tr>
<tr>
<td>Revascularization hospitalization</td>
<td>$4,600</td>
<td>$1,840–$10,760</td>
<td>Gamma</td>
</tr>
<tr>
<td>Other cardiovascular hospitalization</td>
<td>$3,600</td>
<td>$1,200–$9,620</td>
<td>Gamma</td>
</tr>
<tr>
<td>Medication: enoxaparin</td>
<td>$210</td>
<td>$100–$400</td>
<td>Log-normal</td>
</tr>
<tr>
<td>Medication: UFH</td>
<td>$15</td>
<td>$10–$80</td>
<td>Log-normal</td>
</tr>
<tr>
<td>Outpatient service</td>
<td>$200</td>
<td>$50–$670</td>
<td>Gamma</td>
</tr>
<tr>
<td>Bleeding</td>
<td>$200</td>
<td>$100–$1000</td>
<td>Normal</td>
</tr>
<tr>
<td>Beyond trial period</td>
<td>$65,000</td>
<td>$45,000–$109,000</td>
<td>Normal</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; other abbreviations as in Tables 1 and 3.
based on a different costing system for Canada, Italy, and Spain, and the results indicate similar conclusions.

We used the Framingham study data, an external database, to estimate life expectancy. The Framingham database may not reflect multiple advances in medical care, specifically in cardiovascular medicine, that have occurred since that database was created. The life expectancy estimated in our analysis may not include the potential mortality benefits of contemporary therapy. This strengthens our results by making them more conservative. In addition, use of enoxaparin as an adjunct to fibrinolysis for STEMI remains favorable after application of various assumptions in estimating lost life expectancy due to death, MI, and stroke, which makes the results of this economic analysis robust.

**Conclusions**

The cost-effectiveness analysis of the ExTRACT–TIMI 25 trial data shows that, using a U.S. model of health care economics, the strategy of using enoxaparin instead of UFH as adjunctive therapy for fibrinolysis in patients with STEMI is cost effective according to commonly used benchmarks.

**REFERENCES**


Key Words: enoxaparin • thrombolysis • STEMI.

For supplementary information and Tables, please see the online version of this article.