The Impact of Renal Dysfunction on Outcomes in the ExTRACT-TIMI 25 Trial

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Objectives
The ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) trial provided the opportunity to evaluate the impact of renal dysfunction on outcomes in patients with ST-segment elevation myocardial infarction (STEMI) and compare enoxaparin (ENOX) and unfractionated heparin (UFH).

Background
It is unclear how renal dysfunction influences the balance between benefit and risk of antithrombotic therapy.

Methods
In the ExTRACT-TIMI 25 trial, 20,479 patients were randomized to UFH or ENOX. A reduced ENOX dose was administered to patients age ≥75 years and those with an estimated creatinine clearance (CrCl) <30 ml/min.

Results
A powerful relationship was observed between the severity of renal dysfunction (per 10 ml/min decrement in CrCl) and death, stroke, intracranial hemorrhage, and major and minor bleeding (p <0.001 for each). There was a progressive increase in the treatment benefit with ENOX on death or nonfatal myocardial infarction (p <0.01) with better renal function. Net clinical benefit (death, nonfatal MI, or nonfatal major bleeding) was significantly superior with ENOX (p <0.001 for patients with a CrCl >90 ml/min) but in those with renal dysfunction there was a progressively greater increase in the risk of major and minor bleeding with ENOX.

Conclusions
Enoxaparin was superior to UFH for the majority of subjects. With more severe renal dysfunction, the net clinical benefit between ENOX and UFH did not differ, despite the rise in adverse events in both treatment groups. Future studies should take renal dysfunction into account when assessing antithrombotic regimens. (J Am Coll Cardiol 2007;49:2249–55) © 2007 by the American College of Cardiology Foundation

Patients with acute coronary syndromes and renal dysfunction have been observed to have increased risks of adverse events in epidemiological studies (1–5), observational studies, and clinical trials (6–13). These events include death, stroke, and bleeding. However, it is unclear whether renal dysfunction influences the balance between benefit and risk in the context of antithrombotic therapy in patients with ST-segment elevation myocardial infarction (STEMI) undergoing fibrinolysis. The issue is important, because worldwide the majority of patients with STEMI undergoing reperfusion continue to receive fibrinolytic therapy.

The ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) trial compared a strategy of enoxaparin (ENOX) with a strategy of unfractionated heparin (UFH) as an adjunct to fibrinolytic therapy for STEMI (14). The ENOX strategy was significantly superior to the UFH strategy in reducing death or nonfatal reinfarction through 30 days. Major bleeding was increased with ENOX, but net clinical benefit favored ENOX (14). The ExTRACT-TIMI 25 trial provides the opportunity to
evaluate the risk of varying degrees of renal dysfunction on outcomes in STEMI patients and to test whether the balance of risk versus benefit of ENOX compared with UFH was influenced by the extent of renal dysfunction.

**Methods**

The design, patient population, and study protocol have been reported in detail (15). In brief, 20,479 patients with STEMI formed the intention-to-treat cohort and were randomized within 6 h of onset of symptoms. They had ST-segment elevation or left bundle-branch block and were scheduled to undergo fibrinolysis. Patients were excluded if they had cardiogenic shock, contraindications to fibrinolysis, or known renal insufficiency with serum creatinine >200 \( \mu \text{mol}/\ell \) (2.5 mg/dl) for men and >175 \( \mu \text{mol}/\ell \) (2.0 mg/dl) for women (13). In addition to the fibrinolytic regimen all patients received 150 to 325 mg of aspirin and maintenance therapy of 75 to 325 mg of aspirin once daily. The evidence in favor of clopidogrel treatment for STEMI emerged while the ExTRACT-TIMI 25 trial was underway (16,17), and clinicians were allowed to administer clopidogrel at their discretion.

The study medication was administered in a double-blind fashion with a double-dummy design. In patients age <75 years, ENOX was administered as an initial 30-mg intravenous bolus followed by subcutaneous injections of 1.0 mg/kg every 12 h (15). For patients age ≥75 years, the intravenous bolus was omitted and the maintenance dose was reduced to 0.75 mg/kg every 12 h. For patients of any age with an estimated creatinine clearance (CrCl) <30 ml/min, the dose was reduced to 1 mg/kg every 24 h. The dosing strategy described in the preceding text was designed so as not to interfere with the goal of prompt administration of pharmacologic reperfusion (lytic and initial dosing of adjunctive therapy), because the adjustment of ENOX dosing for CrCl <30 ml/min does not need to occur until 12 h after the initial dose, by which time the serum creatinine has returned from the chemistry laboratory and CrCl can be estimated. The double-blind subcutaneous injections of ENOX or matching placebo were continued until hospital discharge or a maximum of 8 days. The UFH was administered as an intravenous bolus of 60 U/kg (maximum 4,000 U); this bolus was omitted in patients who had received open-label UFH within the 3 h prior to randomization. The UFH was administered according to the guideline recommended strategy for at least 48 h but could be continued longer at the treating physician’s discretion (18,19). The monitoring of UFH was performed in a blinded fashion.

The CrCl was estimated with the Cockroft-Gault formula (20,21), and the population was divided according to strata of CrCl (<30 ml/min, 30 to 60 ml/min, >60 to 90 ml/min, and >90 ml/min).

The primary end point of the trial was the composite of death from any cause or nonfatal recurrent myocardial infarction (MI) within the first 30 days of randomization (12,13). Bleeding was classified according to the TIMI criteria (15). All ischemic and clinically significant bleeding events were adjudicated in a blinded fashion by an independent clinical-events committee with prespecified definitions (15).

**Statistical analyses.** All efficacy analyses were based on the intention-to-treat principle. Safety analyses were performed according to the treatment actually received. Continuous variables are presented as median and interquartile range, and categorical variables are presented as frequencies. In the comparison of baseline characteristics stratified by CrCl strata (see preceding text), differences in continuous variables were analyzed with the Kruskal-Wallis rank test, and differences in categorical variables were analyzed with the chi-square test. Frequency of efficacy and safety outcomes at 30 days were compared with the categorical CrCl variable and analyzed with the chi-square test as well as the test for trend.

Logistic regression models for efficacy and safety outcomes were performed with a 10 ml/min decrease in CrCl, adjusting for components of the TIMI risk score (22) with the exception of age (which is included in the estimation of the CrCl by the Cockroft-Gault formula), and the results are presented as adjusted odds ratio (ORadj). The elements of the TIMI risk score for STEMI include: systolic blood pressure <100 mm Hg (3 points); heart rate >100 beats/min (2 points); Killip class II to IV (2 points); anterior ST-segment elevation or left bundle branch block (1 point); diabetes, history of hypertension, or history of angina (1 point); weight <67 kg (1 point); and time to treatment >4 h (1 point). The treatment effect of the randomization strategies (ENOX vs. UFH) was evaluated for efficacy and safety outcomes, stratified by CrCl group (see Table 1 for definitions of CrCl groups) with a chi-square test. All statistical analyses were performed with Stata/SE version 9.1 (Stata Corp., College Station, Texas).

**Results**

Assessment of baseline characteristics showed that for each of the major risk characteristics there was an inverse relationship between the stratum of CrCl and the severity of the risk characteristics (Table 1). For example, patients in each lower stratum of CrCl were older and more frequently had hypertension, diabetes, previous MI, and a higher TIMI risk score. Thus, the median age was 52 years in patients with CrCl >90 ml/min and 78 years in those with...
CrCl <30 ml/min. The percentage of low-risk patients (TIMI risk score ≤3) in these 2 groups was 85.3% and 8.5%, respectively. In addition, concomitant medications were used less frequently in patients with lower CrCl (Table 1).

**Effect of CrCl on outcomes (full trial population).** For all patients, a powerful and direct relationship was noted between the severity of renal dysfunction and death, stroke, major bleeding, intracranial hemorrhage, and minor bleeding (Table 2). A continuous inverse relationship was evident.
between CrCl and mortality (Fig. 1A), the primary end point (death or nonfatal recurrent MI) (Fig. 1B), major bleeding (Fig. 1C), and net clinical benefit (death or nonfatal recurrent MI or nonfatal major bleeding) (Fig. 1D).

In a univariate regression model, a 10-ml/min decrease in CrCl conferred an increased risk of death (OR 1.34, p < 0.001) and of stroke at 30 days (OR 1.22, p < 0.001). Similarly, a 10-ml/min decrease in CrCl increased the risk of both major (OR 1.15, p < 0.001) and minor bleeding (OR 1.19, p < 0.001).

In a multivariable regression model, adjusting for components of the TIMI risk score (excluding age), CrCl remained an independent predictor of death (ORadj 1.27, 95% confidence interval [CI] 1.24 to 1.31, p < 0.001). Multivariate analysis confirmed the effect of a 10-ml/min decrement in CrCl in predicting an increased risk of the following additional events at 30 days: death or nonfatal recurrent MI (ORadj 1.14, 95% CI 1.13 to 1.17), stroke (ORadj 1.26, 95% CI 1.19 to 1.35), intracranial hemorrhage (ORadj 1.24, 95% CI 1.15 to 1.35), major bleed (ORadj 1.16, 95% CI 1.10 to 1.22), minor bleed (ORadj 1.16, 95% CI 1.11 to 1.21) (p value for each <0.001). However, changes in CrCl were not predictive of nonfatal recurrent MI alone (ORadj 1.01, 95% CI 0.99 to 1.04).

Comparison between ENOX and UFH at varying levels of renal function. The rates of death were similar for ENOX and UFH, irrespective of CrCl (Table 3). However, for the composite of death or nonfatal recurrent MI at 30 days (the primary end point of the ExTRACT-TIMI 25 trial), there were significant differences in favor of ENOX (pinteraction = 0.005) (Table 3) that persisted after adjustment for baseline risk (Table 4, Fig. 2). Major bleeding was similar in the 2 treatment groups for patients with CrCl >90 ml/min, but with increasing renal dysfunction a progressive excess in bleeding was seen with ENOX (Tables 3 and 4). The rates of intracranial hemorrhage in the 2 treatment groups were low and did not differ across the range of renal dysfunction.

The primary end point, composite of death or nonfatal recurrent MI, and the net clinical benefit end point, a composite of the primary end point plus nonfatal major
bleeding, favored ENOX and achieved statistical significance in patients with preserved or only minor impairment of renal function (CrCl ≥60 ml/min) (Table 3). This constituted the majority (79.1%) of the study population.

**Discussion**

In this large, multinational, and well characterized clinical trial population, estimated CrCl varied substantially and impairment of renal function was a powerful determinant of adverse outcome. These observations are consistent with data from both epidemiological (1–5) and observational studies (6–10) as well as clinical trials in various population groups (11–13,23,24). Our findings illustrate the value of a large heterogeneous clinical trial population (as in the ExTRACT-TIMI 25 trial) to reflect clinical practice.

Renal dysfunction does not exist in isolation. The severity of renal dysfunction was strongly associated with a series of risk characteristics, evident at the time of presentation with STEMI. These include older age, male gender, hypertension, diabetes mellitus, previous MI, previous angina pectoris, heart failure, and a higher TIMI risk score (22). Nevertheless, previous studies have demonstrated the independence of renal dysfunction as a predictor of in-hospital and subsequent death (6,25). These findings are consistent with those seen from a broader range of patients with acute coronary syndromes. In the ExTRACT-TIMI 25 trial, CrCl remained an independent predictor of death, stroke, intracranial hemorrhage, and both major and minor bleeding, after adjustment for the components of the TIMI risk score (p < 0.001 for each comparison). Interestingly, no significant association was demonstrated with nonfatal recurrent MI.

Major bleeding and intracranial hemorrhage were systematically and prospectively captured, and the rates of these bleeding complications of fibrinolytic therapy were lower than those reported in recent similarly designed trials (26). Nevertheless, the longer-term adverse outcomes associated with bleeding have been increasingly recognized, and full assessment of adjunctive antithrombotic therapy requires evaluation of benefits against bleeding risks. With each successive 30-ml/min stratum of declining CrCl, the risk of major or minor bleeding increased by approximately 50% (ranging from 2.3% in patients with a CrCl >90 ml/min to 9.4% in those with a CrCl <30 ml/min). Even modest degrees of renal dysfunction (CrCl ≤60 ml/min) were associated with increased risks of major, minor, and

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Outcomes at 30 Days by Treatment Assignment</th>
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<tbody>
<tr>
<td>CrCl (ml/min)</td>
<td>ENOX (n = 1,813)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>19.4</td>
</tr>
<tr>
<td>30–60</td>
<td>25.7</td>
</tr>
<tr>
<td>&gt;60–90</td>
<td>33.0</td>
</tr>
<tr>
<td>&gt;90</td>
<td>36.9</td>
</tr>
</tbody>
</table>

Values shown in CrCl strata represent percentages. *p < 0.05 for interaction between randomization group and renal function group, †p < 0.01 for comparison of ENOX versus UFH. ‡p < 0.001 for comparison of ENOX versus UFH. §p < 0.05 for comparison of ENOX versus UFH. | Net clinical benefit.

**Table 4** Outcomes at 30 Days by Randomized Treatment (Odds Ratio [95% CI] ENOX vs. UFH), Adjusted for Baseline Risk

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>&lt;30</th>
<th>30–60</th>
<th>&gt;60–90</th>
<th>&gt;90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or nonfatal re-MI</td>
<td>0.74 (0.38–1.44)</td>
<td>0.94 (0.78–1.12)</td>
<td>0.78 (0.66–0.92)</td>
<td>0.69 (0.56–0.84)</td>
</tr>
<tr>
<td>Death</td>
<td>0.75 (0.37–1.50)</td>
<td>0.97 (0.79–1.19)</td>
<td>0.87 (0.71–1.06)</td>
<td>0.92 (0.67–1.28)</td>
</tr>
<tr>
<td>Nonfatal re-MI</td>
<td>0.93 (0.22–3.83)</td>
<td>0.88 (0.63–1.23)</td>
<td>0.68 (0.53–0.88)</td>
<td>0.58 (0.45–0.76)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.94 (0.12–7.35)</td>
<td>0.68 (0.43–1.08)</td>
<td>1.43 (0.93–2.21)</td>
<td>0.77 (0.38–1.54)</td>
</tr>
<tr>
<td>Major bleed (including ICH)</td>
<td>3.60 (0.67–19.21)</td>
<td>1.73 (1.11–2.70)</td>
<td>1.91 (1.30–2.82)</td>
<td>1.49 (0.89–2.48)</td>
</tr>
<tr>
<td>ICH</td>
<td>—</td>
<td>0.73 (0.37–1.42)</td>
<td>1.66 (0.99–2.81)</td>
<td>3.33 (0.92–12.13)</td>
</tr>
<tr>
<td>Minor bleed</td>
<td>1.68 (0.44–6.33)</td>
<td>1.46 (1.04–2.04)</td>
<td>1.51 (1.06–2.15)</td>
<td>1.37 (0.91–2.06)</td>
</tr>
<tr>
<td>Death/nonfatal re-MI, nonfatal major bleed*</td>
<td>0.83 (0.43–1.60)</td>
<td>0.98 (0.83–1.17)</td>
<td>0.83 (0.71–0.97)</td>
<td>0.71 (0.58–0.86)</td>
</tr>
</tbody>
</table>

Adjusted for components of TIMI risk score, with the exception of age (age included in the Cockcroft-Gault calculation of CrCl). *Net clinical benefit. CI = confidence interval; other abbreviations as in Tables 1 and 2.
intracranial bleeding, irrespective of assigned antithrombotic strategy. Although, by trial design, the dose of Enox was halved in those with CrCl <30 ml/min (1.0 mg/kg every 24 h), excess bleeding was still observed with Enox in this group. This observation, albeit limited by the small number of subjects, suggests that until alternative dosing regimens are developed, Enox should not be administered to patients with a known CrCl <30 ml/min.

For patients with well preserved renal function (CrCl >90 ml/min) major bleeding did not differ significantly between Enox and UFH, although a numerically higher bleeding rate was seen with Enox. However, with renal dysfunction, bleeding with Enox was significantly higher than with UFH. This raises the possibility that dose adjustment of Enox might be required in patients with even moderate renal dysfunction (e.g., CrCl 30 to 90 ml/min) (23,27) to achieve the benefits of administration of Enox throughout the index hospital stay while minimizing the risk of bleeding. This is beyond the steps taken in this trial to reduce the dose of Enox in those with estimated CrCl <30 ml/min as well as in patients ≥75 years of age.

Conclusions

Renal dysfunction is an important independent predictor of adverse outcome—death, stroke, and bleeding—in STEMI patients receiving fibrinolytic therapy. The net clinical benefit (the composite of death, nonfatal MI, or nonfatal major bleeding) was significantly superior for Enox for a large majority of the study population (the 79% of the trial population with CrCl >60 ml/min). With more severe degrees of renal dysfunction, net clinical benefit did not differ between patients treated with Enox and UFH.

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REFERENCES


