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APPLICATION NUMBER:

22-138

20-164 S-075

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type: NDA (New Efficacy Supplement)
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Reviewer Name: Khin Maung U
Through: Avi Karkowsky
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Established Name: Enoxaparin sodium solution for injection
(Proposed) Trade Name: Lovenox[®]

Therapeutic Class: Anticoagulants (ATC Code: B01AB05)

Applicant: Sanofi Aventis

Priority Designation: P

Formulation: Solution for injection

Dosing Regimen: 30-mg single iv bolus plus a 1 mg/kg sc dose followed by 1 mg/kg sc every 12 hours;
Patients with severe renal impairment: 30-mg single iv bolus plus a 1 mg/kg sc dose followed by 1 mg/kg SC once daily;
Geriatric patients ≥ 75 years of age, 0.75 mg/kg sc every 12 hours without an initial IV bolus

Indication: Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)

Intended Population: Patients with STEMI, including patients to be managed medically or with Percutaneous Coronary Intervention (PCI)

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1.1 Recommendation on Regulatory Action

From an efficacy perspective, the ExTRACT-TIMI 25 study showed that enoxaparin significantly ($p = 0.000003$) *reduced* the incidence of the composite primary efficacy endpoint (all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization) compared to UFH (9.9% in the enoxaparin group vs 12% in the UFH group, 17% relative risk reduction).

From the safety perspective, enoxaparin was associated with an *increase* in adjudicated TIMI major bleeding at 30 days compared with UFH in patients with acute STEMI (2.1% in enoxaparin group vs 1.4% in UFH group, $p < 0.0001$), without a statistically significant ($p = 0.1443$) increase in intracranial hemorrhage (ICH) between the enoxaparin group (0.8%, 84 of 10,176 patients) and UFH group (0.7%, 66 of 10,151 patients).

The net clinical benefit significantly ($p < 0.001$) favored enoxaparin-treated patients: for every 1000 STEMI patients treated with enoxaparin, there would be:

- 6 fewer deaths,
- 15 fewer non-fatal myocardial re-infarctions, and
- 7 fewer episodes of urgent revascularization,

at a cost of an increase of 4 non-fatal major hemorrhages, with no increase in the number of non-fatal intracranial hemorrhage.

Based on the finding of a clinically important net beneficial effect of enoxaparin in the balance of efficacy and safety endpoint events in STEMI patients treated with enoxaparin in the ExTRACT-TIMI 25 study, I recommend “**approval**” for this application after the sponsor has complied with the changes I suggested in the “Indications” and “Clinical Studies” sub-sections of “Section 9.4 Labeling Review” of this clinical review.

1.2 Recommendation on Postmarketing Actions

Not applicable.

1.2.1 Risk Management Activity

Not applicable.

1.2.2 Required Phase 4 Commitments

Not applicable.

1.2.3 Other Phase 4 Requests

Not applicable.

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1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

At an End of Phase II Meeting on 20-Nov-2001, the sponsor discussed the ExTRACT-TIMI 25 study with the Agency (Division of Medical Imaging and Hematology Products - DMIHP). The Agency approved the protocol, following review of a Request for Special Protocol Assessment submitted on 18-Mar-2002, with substantial FDA input (from both DMIHP and the Division of Cardiovascular and Renal Products - DCaRP).

The FDA emphasized that

- (i) the study must show a clear superiority of enoxaparin over UFH with regard to BOTH efficacy and safety, as otherwise a comparison of UFH for 48 hours vs enoxaparin for 2-8 days may not be interpretable,
- (ii) a double-blind, double-dummy design must be used to minimize bias,
- (iii) the primary efficacy endpoint should be assessed at 30-days,
- (iv) the definition for major hemorrhage must include intraocular, retroperitoneal, and intracranial hemorrhages,
- (v) the formulation and dose regimens of the thrombolytic agents should be approved in the US,
- (vi) all patients should receive aspirin which is now part of the standard of care for STEMI, and
- (vii) for this single study to be approvable, the strength of the results (i.e., a high level of significance) will determine whether the results support the efficacy claim.

The ExTRACT-TIMI 25 study enrolled 20,506 patients with STEMI who were eligible for fibrinolytic therapy (at the treating physician's discretion, streptokinase [capped at 5000 patients], alteplase, tenecteplase or reteplase). The study was conducted during 24-Oct-2002 through 01-Oct-2005 at 674 sites in 48 countries including the United States (9 sites).

The primary efficacy endpoint was a composite of all-cause death and non-fatal myocardial re-infarction within 30 days after randomization. Patients were followed up for 30 days (visit in person or by telephone contact) for the efficacy and safety endpoints of the study. Six and 12-month follow-up visits were made by telephone contact.

All efficacy analyses of endpoint events were based on adjudicated data from an independent Clinical Events Committee (CEC). The primary efficacy endpoints between the two groups were compared using a Chi-square test based on the intent-to-treat (ITT) patient population. A patient with multiple events was counted only once in the incidence-based analysis.

Of 20,506 patients randomized (10,273 enoxaparin and 10,233 UFH), 27 (17 enoxaparin and 10 UFH) did not receive study drug and had no follow-up information. Thus, the ITT population was 20,479 (10,256 enoxaparin and 10,223 UFH) patients.

An independent Data Safety Monitoring Board (DSMB) reviewed unblinded results at 25%, 50% and 75% of the total targeted primary events.

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The qualifying infarction was treated with medical therapy alone in 74.3% of patients, with PCI in 23.0% (as rescue therapy in 2.8%, and as an urgent or elective procedure in 20.2%), and coronary artery bypass surgery in 2.8% of patients.

In brief, patients were comparable at baseline regarding demographic and cardiovascular characteristics. A fibrinolytic agent was administered to 99.7% patients, with 79.5% receiving a fibrin-specific agent and 20.2% (4139 patients) receiving streptokinase.

The mean duration for enoxaparin/enoxaparin placebo sc injection was 6.6 days (median duration = 7 days) with 74.5% of patients treated for ≥ 6 days. The mean duration of UFH/UFH placebo iv infusion was 53.7 hours (median duration = 48 hours) with 89.6% of patients treated for ≥ 36 hours.

Concomitant medications prior to and during hospitalization were comparable between the enoxaparin and UFH groups, with aspirin in 94.8% and 95.4%, β -blockers (excluding eye drops) in 85.9% and 85.5%, ACE inhibitors in 78.5% and 77.8%, statins in 69.5% and 69.5%, clopidogrel in 27.2% and 28.7%, oral anticoagulants in 2.1% and 2.5%, and thrombolytics (other than those of index MI) in 4% and 0.5%, respectively, of patients.

There were also 6 previous enoxaparin clinical trials conducted between 1995 and 2005, which enrolled an additional 10,171 patients with STEMI. Of these:

- ASSENT 3, ASSENT 3+, ENTIRE-TIMI 23, and HART II were *open-label* studies, and
- AMI-SK and TETAMI studies were *double-blind, placebo-controlled* studies, of which
 - AMI-SK study evaluated reperfusion (TIMI flow grade 3) by angiography, and
 - TETAMI study enrolled *non-thrombolyzed* patients with STEMI (i.e., *STEMI patients ineligible for reperfusion*) only, and showed that enoxaparin did *not* reduce the 30-day incidence of death, reinfarction and recurrent angina significantly compared with UFH in non-reperused STEMI patients.

The main difference between the ExTRACT-TIMI 25 study and the 6 previous studies was that enoxaparin was administered without dose modifications for age or renal impairment in the 6 previous studies. Due to differences in study designs and endpoints, no integrated analyses were performed on efficacy and safety data from the ExTRACT-TIMI 25 and efficacy and safety data in the 6 previous studies.

1.3.2 Efficacy

The ExTRACT-TIMI 25 trial showed that enoxaparin significantly ($p = 0.000003$) reduced the incidence of the composite primary efficacy endpoint (all-cause death and non-fatal myocardial re-infarction within 30 days after randomization) compared to UFH (9.9% in the enoxaparin group vs 12% in the UFH group, 17% relative risk reduction).

This benefit was contributed mainly by a significant reduction in the incidence of non-fatal myocardial re-infarction (3.0% in enoxaparin group vs 4.5% in UFH group, 33% relative risk reduction, $p < 0.001$), whereas the reduction in all-cause deaths (6.9% in enoxaparin group vs 7.5% in UFH group, 8% relative risk reduction) was not statistically significant ($p = 0.11$).

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The time-to-composite-endpoint (of death or non-fatal myocardial re-infarction) also showed a statistically significant reduction in the enoxaparin group compared to the UFH treatment group (HR = 0.83, 95% CI 0.77 – 0.90, 17% relative risk reduction, P<0.001).

The treatment benefit of enoxaparin became evident at 48 hours, and was significantly positive at Day 8 and at Day 30.

This clinical benefit of treatment with enoxaparin was consistently demonstrated:

- across pre-specified subgroups of
 - age (<75 years vs ≥75 years),
 - infarct location,
 - presence of prior MI,
 - presence of diabetes mellitus,
 - presence of severe renal function impairment,
 - treatment with PCI or medical treatment,
 - types of fibrinolytic agent used,
 - concomitant medications (with the exception of non-use of β-blockers), and
 - Killip Class I/II heart failure (with the exception of severe heart failure or cardiogenic shock (Killip Class III/IV),
- as positive findings when myocardial ischemia leading to urgent revascularization or disabling stroke were added to the primary efficacy endpoint (composite secondary efficacy endpoints), and
- as positive findings in the tertiary composite endpoints.

In the ExTRACT-TIMI 25 study, the Kaplan-Meier curves for death for 12 months for enoxaparin and UFH run closely together. The ASSENT 3 study also showed similar findings in the Kaplan-Meier curves for death up to 12 months.

Despite the separation of the survival curves over 12 months for the composite endpoints of (a) death and myocardial re-infarction, and (b) death, myocardial re-infarction and disabling stroke, an analysis of clinical events at 6- and 12- months showed an excess of deaths and myocardial re-infarction when (1) deaths at day 30 post-randomization were excluded, and (2) patients who experienced the composite primary efficacy endpoint (death or non-fatal myocardial re-infarction) were excluded.

Thus, I think that the clinical benefit produced by enoxaparin does not appear to extend beyond the 30 days post-randomization.

1.3.3 Safety

The ExTRACT-TIMI 25 study provided safety data for 20,327 patients with STEMI (enoxaparin: 10,176 patients; UFH: 10,151 patients) who received at least one dose of study treatment. The primary safety endpoint was TIMI major hemorrhage within 30 days after randomization. The Fisher's Exact test was used to evaluate differences between the treatment groups for this primary safety endpoint.

The majority (82%) of patients in each group completed the assigned treatment regimen.

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17.6% (1790 of 10,256) patients in enoxaparin group and 18% (1830 of 10,223) patients in UFH group discontinued, most frequently due to a hemorrhagic adverse event (AE) (34.1% in enoxaparin group vs 24% in UFH group) or PCI-related reasons (48.5% (128 of 525) patients in enoxaparin group and 51.5% (136 of 625) patients in UFH group).

The safety data from 6 previously conducted studies for 10,040 randomized patients with STEMI (4128 enoxaparin patients, 5673 UFH patients, and 239 placebo patients) were also reviewed. A majority (58%) of patients in each of the 6 studies completed the assigned treatment. Hemorrhagic events were the most frequent AEs that resulted in treatment discontinuation in all of these studies.

The safety findings in the ExTRACT-TIMI 25 study are:

- (i) Enoxaparin was associated with an *increase* in adjudicated TIMI major bleeding compared with UFH in patients with STEMI (2.1% vs 1.4%, $p < 0.0001$).
- (ii) No statistical difference ($p = 0.1443$) was detected in ICH between the enoxaparin group (0.8%, 84 of 10,176 patients) and UFH group (0.7%, 66 of 10,151 patients).
- (iii) The incidences of non-hemorrhagic AEs were similar between treatment groups.
- (iv) The results of subgroup analyses for the primary safety endpoint in the ExTRACT study did not identify treatment by subgroup interactions.

The balance of efficacy and safety was assessed as “net clinical benefit” using the following composite endpoints:

- death/re-infarction/nonfatal disabling stroke,
- death/re-infarction/ nonfatal major bleeding, and
- death/re-infarction/non-fatal ICH.

The incidence of events for each of the composite “net clinical benefit” endpoints was significantly ($P < 0.001$ for all comparisons) lower at 30 days in the enoxaparin group compared with the UFH group. Reductions in the absolute event rates of 1.8 to 2.2 percentage points corresponded to relative risk reductions of 14% to 18%, supporting the overall positive effect of enoxaparin on clinically important efficacy and safety endpoints.

Thus, despite an increase in episodes of TIMI major bleeding, early and sustained reduction in ischemic events and the net positive balance of efficacy and safety endpoint events demonstrated the beneficial effect of the regimen of enoxaparin as the adjunctive antithrombin regimen in patients with STEMI who were treated medically and with fibrinolytic therapy, whether or not they underwent subsequent PCI.

1.3.4 Dosing Regimen and Administration

For treatment of patients with STEMI, the recommended dose is:

- Patients with STEMI < 75 years old: 30-mg single iv bolus plus a 1 mg/kg sc dose followed by 1 mg/kg sc *every 12 hours*;
- Patients with severe renal impairment: 30-mg single iv bolus plus a 1 mg/kg sc dose followed by 1 mg/kg SC *once daily*;
- Geriatric patients ≥ 75 years of age: *0.75 mg/kg sc every 12 hours without an initial IV bolus*

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When administered in conjunction with a thrombolytic (fibrin-specific or non-fibrin specific) agent, enoxaparin should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy.

For patients managed with Percutaneous Coronary Intervention (PCI): If the last sc dose of enoxaparin was given < 8 hours before balloon inflation, no additional dosing is needed. If the last enoxaparin sc dose was given \geq 8 hours before balloon inflation, an iv bolus of 0.3 mg/kg of enoxaparin injection should be administered.

All patients should receive acetylsalicylic acid (ASA) as soon as they are diagnosed as having STEMI, and maintained with 75 to 325 mg once daily unless contraindicated.

The recommended duration of enoxaparin treatment is 8 days or until hospital discharge, whichever comes first.

1.3.5 Drug-Drug Interactions

The sponsor submitted that no drug interaction studies were conducted for this submission.

1.3.6 Special Populations

Elderly patients: In elderly (\geq 75 years old) patients *the initial bolus is not administered*, and a reduced dose of 0.75 mg/kg sc every 12 hours (maximum 75 mg for the first two doses, followed by 0.75 mg/kg for the remaining doses) is proposed to reduce the risk of bleeding.

Renal impairment: Impaired renal function results in a proportional decrease in enoxaparin and anti-Xa clearance, thereby increasing the risk of bleeding in patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$). Using the population PK model, a simulation of a dose-regimen of 1 mg/kg once daily in patients with severe renal impairment demonstrates an exposure at steady state that is similar to that at a dose of 1 mg/kg twice daily in healthy subjects, and similar peak levels at steady state. This dose adjustment has now been implemented in enoxaparin labeling in several countries, including the US.

Percutaneous coronary intervention (PCI). To maintain anti-Xa levels between 0.6 and 1.8 IU/mL based on PK simulation data, the ExTRACT-TIMI 25 protocol required that (i) patients undergoing PCI receive an iv bolus of enoxaparin 0.3 mg/kg if the last sc dose was given \geq 8 hours before balloon inflation, and (ii) if the last sc dose of enoxaparin was given <8 hours before inflation, no additional dosing was required.

Pregnancy and Lactation: A total of 1800 cases of drug exposure during pregnancy and lactation were recorded from the first marketing authorization up to May 2006 in the sponsor's post-marketing global pharmacovigilance database. There are no adequate and well-controlled studies in pregnant women. Only data from animal studies were available which are not always predictive of human response. Thus, enoxaparin should be used during pregnancy only if the physician has established a clear need.

It is not known whether enoxaparin is excreted in human milk.

2. INTRODUCTION AND BACKGROUND

This submission is an efficacy supplement. Please refer to the original NDA 20-164 review.

2.1 Product Information

Lovenox® (Enoxaparin sodium) is a low molecular weight heparin (LMWH) obtained by depolymerization of standard heparin.

It belongs to the pharmacotherapeutical group of anticoagulants (ATC Code: B01AB05).

The proposed indication for this NDA efficacy supplement is:

- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI)

For treatment of acute STEMI, the recommended dose is:

- 30-mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg sc *every 12 hours*
- for patients with severe renal impairment: 30-mg single IV bolus plus a 1 mg/kg sc dose followed by 1 mg/kg SC *once daily*
- for geriatric patients ≥ 75 years of age, 0.75 mg/kg sc *every 12 hours without an initial IV bolus.*

2.2 Currently Available Treatment for Indications

Fibrinolytic agents, aspirin, and more recently, PCI or stent placement, are used to prevent thrombus propagation or re-thrombosis, and to restore blood flow in the infarct related artery (IRA). In 2004, the American College of Cardiology (ACC) and the American Heart Association (AHA) published updated recommendations on STEMI (Table 1)¹.

Prompt reperfusion therapy is a key part of the treatment of STEMI. Reperfusion therapy, as the standard of care for patients with STEMI, has improved the prognosis of patients with STEMI over the last decade^{2,3}. However, the current practice of using fibrinolytics, aspirin, and antithrombin {iv unfractionated heparin (UFH)} still results in at least a 10% rate of death or re-infarction within 1 month following treatment^{4,5,6,7,8,9}.

While the ACC/AHA guideline recommends UFH as ancillary therapy to reperfusion in the treatment of STEMI, there is still some controversy regarding its role. In a systematic review of 26 randomized clinical trials that assessed the effects of anti-coagulant therapy in patients with acute myocardial infarction (MI), risk reduction for death and myocardial re-infarction was observed in patients who were not routinely receiving aspirin; for patients treated with aspirin, UFH failed to demonstrate a similar reduction in mortality¹⁰. The review concluded that the routine addition of intravenous (iv) or subcutaneous (sc) heparin

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for the treatment of acute MI could not yet be justified by the evidence from randomized clinical trials. In many countries UFH has not been specifically approved for the treatment of acute STEMI. Based on this information, the sponsor contends that there is a need for an effective and safe antithrombin agent for the treatment of STEMI.

Table 1 ST-Segment Elevation Myocardial Infarction (STEMI): Acute Medical Therapy

General treatment measures

- Aspirin
- Analgesics
- Nitrates
- Oxygen

Infarct size limitation

- Bed rest and postural maneuvers
- β -Blockers (decrease heart rate)
- ACE inhibitors (unless patient is hypotensive)

Reperfusion

- Primary PCI or coronary thrombolysis (primary PCI preferred after 3 hours)

Antithrombotic and antiplatelet therapy

- Aspirin (75–162 mg, chronic dose)
- UFH or consider LMWH (egg, enoxaparin)
- If PCI:
 - Clopidogrel
 - GP IIb/IIIa inhibitors

ACE = angiotensin-converting enzyme; GP =glycoprotein; LMWH =low-molecular-weight heparins; PCI =percutaneous coronary intervention; UFH =unfractionated heparin.

2.3 Availability of Proposed Active Ingredient in the United States

Lovenox® (enoxaparin sodium) is currently available in the US, being approved by FDA for marketing for the indications of:

- Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism:
 - abdominal surgery at risk for thromboembolic complications;
 - hip replacement surgery, during and following hospitalization;
 - knee replacement surgery;
 - in medical patients with severely restricted mobility during acute illness.
- inpatient treatment of acute DVT with or without pulmonary embolism.
- outpatient treatment of acute DVT without pulmonary embolism.
- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (NSTEMI).

The proposed labeling change for this NDA efficacy supplement concerns the inclusion of a new indication for the prevention of thrombotic events in patients suffering from STEMI including patients to be managed medically or with subsequent PCI.

2.4 Important Issues with Pharmacologically Related Products

Existing antiplatelet therapies show only limited efficacy. In the "Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events" (CURE) study, clopidogrel plus aspirin showed only a 20% relative risk reduction (9.3% vs. 11.4%) in the primary outcome (CV death, MI, or stroke) than aspirin alone and safety concerns (a 3.7% incidence of major bleeding events for the combination).

In ESTEEM, a randomized, placebo-controlled phase II dose-ranging study in patients with recent MI, ximelagatran (Exanta™) was found to be more effective than placebo in reducing the composite endpoint of death, non-fatal re-infarction, and severe recurrent ischemia among patients who also received 160 mg aspirin daily¹¹. The magnitude of benefit (3-6% absolute risk and 24% relative risk reduction) was similar to that observed by adding either warfarin or clopidogrel to aspirin. However, as with these other combination regimens, there were complications. Addition of ximelagatran was associated with a doubling of bleeding complications, although major hemorrhage was rare (23 patients, 1.8%, vs. six patients, 0.9%) in a treatment period averaging 3.5 months. Ximelagatran was also associated with a four-fold excess in liver enzyme elevations which occurred in 199 (16%) of patients, but these were not associated with clinical complications.

The Cardiovascular and Renal Drugs Advisory Committee met on September 10, 2004, to discuss ximelagatran _____ mg tablets for the proposed indication of the prevention of venous thromboembolism (VTE) in patients undergoing knee replacement surgery, the prevention of stroke, and other thromboembolic complications associated with atrial fibrillation (AFib) and the long term secondary prevention of VTE after standard treatment of an episode of acute VTE. The Advisory Committee recommended non-approval of ximelagatran. b(4)

An indirect Factor Xa inhibitor, fondaparinux (Arixtra®) has been approved for prevention of VTE following knee and hip surgery, and for treatment of DVT¹². It showed better efficacy than LMWHs, which are the current standard of treatment. _____ b(4)

2.5 Presubmission Regulatory Activity

The original NDA 20-164 for Lovenox® and its related IND 31,532 both reside in the Division of Medical Imaging and Hematology Products (DMIHP). The following is a list of important regulatory activities between DMIHP and the sponsor:

- The ExTRACT study was discussed with DMIHP at an End of Phase II Meeting on 20-Nov-2001.
- A Request for Special Protocol Assessment of the EXTRACT (Serial No. 614) protocol was submitted on 18-Mar-2002, and FDA's clinical recommendations were issued on 02-May-2002.
- EXTRACT Protocol and CMC information amendment (Serial No. 626) were

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submitted on 19-Jun-2002, and FDA's clinical recommendations were issued on 24-Sep-2004.

- EXTRACT Protocol Amendment 1 (Serial No. 671), containing dose modifications for the elderly (75 years) and patients with impaired renal function, was submitted on 13-Feb-2003. Sponsor's response to FDA's clinical comments on the protocol amendment and recommendations (Serial No. 679) was submitted on 03-Apr-2003.
- Statistical Analysis Plan (Serial No. 734) was submitted on 24-Oct-2003.
- Protocol Amendment 2 (Serial No. 789) containing proposed revisions to the EXTRACT protocol for CK/CK-MB analysis was submitted on 31-Aug-2004.
- Request for a waiver of pediatric studies for the treatment of patients with STEMI (Serial No. 860) was submitted on 23-May-2006. FDA letter granting the sponsor's request for the waiver of pediatric studies for the treatment of patients with STEMI was issued on 14-Jul-2006.

A Pre-sNDA Meeting consultation was submitted on 28-Mar-2006. With input from both DMIHP, and the Division of Cardiovascular and Renal Products (DCRP), FDA made a written response on 08-May-2006.

The following is a list of important regulatory activities between DCRP and the sponsor:

- Phone discussion on 21-Jun-2006 related to the requirement of new IND to be filed with DCRP for the coming EXTRACT sNDA, and the requirements for filing this IND
- Initial IND was filed under DCRP on 10-Aug-2006.
- FDA letter dated 30-Aug-2006 accepted the IND filing.
- The NDA was filed on 17-Nov-2006.

Important meeting outcome:

At a meeting between the sponsor and FDA on 15-Dec-2001, FDA provided the following suggestions regarding the proposed ExTRACT Study design, including objectives, inclusion / exclusion criteria, primary and secondary efficacy outcomes, statistical assumptions and methods, and sample size calculations so that the study would be acceptable as the single adequate and well-controlled pivotal trial for the intended indication:

- A clear superiority of enoxaparin sodium over UFH with regard to both efficacy and safety must be established in the study as otherwise a comparison of treatment with heparin for *48 hours vs treatment with enoxaparin sodium for 2-8 days, or until discharge, but not greater than 8 days may not be clinically interpretable.*
- The primary efficacy endpoint should be assessed at 30 days. Assessments at 14 days and other time points may be secondary analyses. Time-to-event analyses may be of interest as secondary analyses.
- Consider requiring co-administration of aspirin (at a dose of 81-325 mg daily), since this is generally a part of the standard of care for acute MI and since there is some evidence that aspirin may give an additional benefit in acute MI when used in combination with thrombolytics. Alternatively, the study could be stratified and sized to clearly demonstrate safety and efficacy with and without aspirin (with the consideration that the actual mg dose of aspirin may influence bleeding rate in this study).

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- Conduct this protocol as a double-blind, double-dummy study to minimize bias. Some of the potential biases in an open-label study include:
 - (1) Influence on the nature and timing of intervention(s).
 - (2) Influence on the objectivity of the investigator.
- The definition for major hemorrhage must include a statement that intraocular, retroperitoneal, and intracranial hemorrhages are always considered major hemorrhage.
- In the protocol, clearly describe the 48 hour intervention restriction. Provide historical data regarding the percent of AMI patients who undergo diagnostic or therapeutic procedures in the first 48 hours of medical care. The historical data should include country specific information.
- Provide information regarding how the proposed dosing regimen for enoxaparin sodium was established.
- Clarify whether the formulations and dose regimens of the thrombolytic agents will be those approved in the United States. The labeling would only address use of enoxaparin sodium an adjunct to U.S. approved thrombolytics and regimens.
- In the protocol, describe how treatment-by-center interaction would be evaluated. (Any center effect on results could be confounded with specific thrombolytic effect if a particular thrombolytic agent was preferred by a particular center; how this would be addressed needed to be explained in the protocol.
- Prior heparin use for the acute MI which led to study entry must be addressed as a possible confounder in the analysis of the study results.
- Regarding the statistical analysis, clearly describe/define in the statistical analysis plan, the following: (1) The proposed “adjusted Chi-square” analysis; (2) The procedure(s) associated with the interim analysis; and (3) The procedure(s) for dealing with multiple comparisons.
- Provide drug-drug interaction studies between enoxaparin sodium and the thrombolytic agents to be used in the study.
- The acceptance of the single study as a sufficient scientific and regulatory basis for approval of enoxaparin sodium for the desired indication will be determined by its adequacy to support the efficacy claim based on strength of the results (Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998). In general, results from any trial should be independently substantiated. The size of the proposed study, the multi-center design, and the mortality endpoint are consistent with the single study criteria. However, statistically persuasive data would need to be provided. Results barely significant at usual levels would likely not be considered very persuasive ($p < 0.05$). Accordingly, a larger study might be considered, with sample size calculated on the basis of a smaller level of significance.
- Verify that there are two different boards (with different members) – one for safety evaluation the other for efficacy adjudication:
 - Identify the activities and responsibilities of the Data Safety Monitoring Board including membership, how frequently the board meets, how the board communicates to the investigators, ways the safety will be monitored, how

frequently the safety will be monitored, and how interactions with the Steering Committee and Critical Event Committee will be regulated.

- Identify the activities of the blinded efficacy adjudication board.
- Provide narratives for the following: patients experiencing any serious and unexpected adverse events; patients experiencing study agent discontinuations due to adverse events; patients discontinuing study participation due to adverse events.
- Provide CRFs for all deaths, all patients who had study agent discontinuation due to adverse events, and all patients who discontinued study participation due to adverse events. CRFs must contain all the data available on serious adverse events (e.g., Medwatch forms). Additional CRFs may be requested during review and must be supplied within 7 days.

2.6 Other Relevant Background Information

Lovenox/Clexane (enoxaparin sodium) was first approved in France in April 1987. At the time of submission of this NDA supplement, it has been approved for marketing in Australia, Canada, the US, and > 96 countries worldwide for the indications mentioned in Section 2.3, which may vary by country. In some countries, enoxaparin sodium is also indicated for prevention of thrombosis formation in extracorporeal circulation during hemodialysis.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Not applicable.

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable.

3.2 Animal Pharmacology/Toxicology

Not applicable.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of the data used in the review was the data from the clinical trials in the enoxaparin development program. The focus was on the ExTRACT-TIMI 25 study involving 20,506 randomized patients with STEMI. The ExTRACT-TIMI 25 study was the only randomized, double-blind, double-dummy, parallel-group, multinational study evaluating a clinical efficacy endpoint.

Electronic CRFs were reviewed as needed. Where appropriate, literature searches were conducted.

The application was submitted as an electronic NDA. All materials submitted electronically are located at \\ CDSesub1\N20164 (or N22138) \S 073\2006-11-17

4.2 Tables of Clinical Studies

Enoxaparin efficacy was evaluated in the ExTRACT-TIMI 25 study involving 20,506 randomized patients with STEMI who were randomized at 674 sites in 48 countries including the United States (9 sites).

The ExTRACT-TIMI 25 study was the only randomized, double-blind, double-dummy, parallel-group, multinational study in the enoxaparin development program evaluating a clinical efficacy endpoint in STEMI patients eligible for fibrinolytic therapy.

There were also 6 previous studies conducted under IND 31,532 involving an additional 10,171 patients with STEMI. These studies were conducted between 1995 and 2005 (Table 2 and Table 3; please see Appendix, Section 10.1.2, of this review for a brief review of each of these 6 clinical trials in patients with STEMI). Four of these were open label studies, and two were double-blind placebo-controlled studies. Briefly, these 6 studies are:

1. **ASSENT 3:** A phase IIIb, randomized, *open label* trial with three parallel groups: full dose tenecteplase together with heparin sodium, full dose tenecteplase together with enoxaparin, and half dose tenecteplase together with abciximab and unfractionated heparin in patients with acute myocardial infarction." This study was conducted under _____
2. **ASSENT 3 Plus:** A phase IIIb-IV, randomized, *open label* trial on efficacy and safety with two parallel groups: full dose tenecteplase combined with unfractionated heparin or enoxaparin in acute myocardial infarction in the prehospital setting (Satellite study to ASSENT 3)." This study was conducted under _____
3. **ENTIRE-TIMI 23:** "A phase II stratified, randomized, *open-label*, angiographic trial to assess the safety and efficacy of enoxaparin as an adjunct to thrombolytic with or without GPIIb/IIIa therapy in patients with ST elevation MI." This study was

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conducted under IND 31,532.

4. **HART II:** “An *open label*, randomized, parallel, multicenter trial comparing the safety and efficacy of subcutaneous enoxaparin to intravenous unfractionated heparin as an adjunct to thrombolytic therapy in patients presenting with acute myocardial infarction.” This study was conducted under IND 31,532.
5. **AMI-SK:** “The safety and efficacy of subcutaneous enoxaparin and streptokinase in patients presenting with acute myocardial infarction: an international, *double-blind, placebo controlled*, randomized, parallel group multicenter study.” This study was conducted under IND 31,532. This study evaluated reperfusion (TIMI flow grade 3) by angiography as the primary efficacy endpoint.
6. **TETAMI:** “The safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and tirofiban versus placebo in the treatment of acute ST-segment elevation myocardial infarction patients *ineligible for reperfusion*.” This study was conducted under IND 31,532. This was a *double-blind placebo-controlled* study. The study enrolled *non-thrombolized* patients with STEMI (i.e., *STEMI patients ineligible for reperfusion*) only. This trial showed that enoxaparin did not significantly reduce the 30-day incidence of death, reinfarction and recurrent angina compared with UFH in non-reperfused STEMI patients.

Thus, this NDA efficacy supplement consists of only one well-controlled study – the ExTRACT-TIMI 25 study – as the pivotal study to support the indication claimed for this drug.

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Table 2 List of clinical trials

Study / Centers / Countries	Design and Objectives Aspirin	Number of patients	Dosage / Timing / Frequency / Route / Device	Duration / Follow up	Primary Efficacy Endpoint / Statistical test
ExTRACT TIMI 25 674 centers 48 countries	R, DB, DD, PG, MN To evaluate efficacy and safety of enoxaparin vs UFH in patients with acute STEMI receiving fibrinolytic therapy	Tot=20,479 10,256 10,223	Enoxaparin (as described in review) UFH (as described in review)	8 days 48 hours FU = 30 days	The composite endpoint of all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization Chi-square test
ASSENT 3 575 centers 26 countries	R, OL, PG, MN To compare (a) full-dose TNK-tPA + heparin sodium vs (b) full-dose TNK-tPA + enoxaparin vs (c) half-dose TNK-tPA + UFH Age ≥18 years STEMI or LBBB ≤6 h Aspirin 150-325 mg/d	Tot= 6,095 2,038 2,040 2,017	(a) TNK-tPA iv bolus + UFH iv bolus 60 IU/kg, then iv infusion 12 IU/kg h 1-3, then per aPTT monitoring; (b) TNK-tPA iv bolus + enoxaparin iv bolus 30 mg, then 1 mg/kg sc q 12 h; (c) TNK-tPA iv bolus + Abciximab iv bolus and infusion + UFH iv bolus 40 IU/kg, then iv infusion 7 IU/kg h 1-3, then per aPTT monitoring	48 hours Till hospital discharge or revascularization or 7 days, whichever came first 48 hours FU = 30 days	The efficacy composite endpoint of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia The efficacy and safety composite endpoint of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia or in-hospital intracranial hemorrhage or in-hospital major bleeding (other than intracranial hemorrhage) Chi-square test
ASSENT 3+ 88 centers 12 countries	R, OL, PG, MN To compare the safety and efficacy of full dose TNK-tPA + UFH vs full dose TNK-tPA + enoxaparin Age ≥18 years STEMI or LBBB ≤6 h Aspirin 150-325 mg/d	Tot= 1,639 821 818	(a) TNK-tPA iv bolus + UFH iv bolus 60 IU/kg (max 4000 IU), then iv infusion 12 IU/kg h 1-3 (max 1000 IU/h), then per aPTT monitoring; (b) TNK-tPA iv bolus + enoxaparin iv bolus 30 mg, then 1 mg/kg sc q 12 h (max 100 mg each of first 2 inj.) (first sc dose to be given within 5 min of iv bolus);	48 hours Till hospital discharge or revascularization or 7 days, whichever came first FU = 30 days	The efficacy composite endpoint of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia The efficacy and safety composite endpoint of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia or in-hospital intracranial hemorrhage or in-hospital major bleeding (other than intracranial hemorrhage) Chi-square test
HART II 23 centers 3 countries	R, OL, PG, MN To compare safety & efficacy of enoxaparin vs UFH as an adjunct to thrombolytic therapy in patients with STEMI Age ≥18 years STEMI or LBBB ≤6 h Aspirin: not specified	Total =400 200 200	Enoxaparin : iv bolus 30 mg, then 1 mg/kg sc 12 h (max 72 h) (first sc dose to be given within 15 min of iv bolus) + rt-PA; UFH : Initial 4000 to 5000 IU iv bolus, then iv infusion 15 IU/kg/h for 77 h (dose based on aPTT)	72 hours 77 hours FU = 30 days	The reperfusion rate of the IRA at the 90-min post-rt-PA angiogram (TIMI flow grades 2 and 3), as provided by a core laboratory Non-inferiority test
AMI-SK 37 centers 5 countries	R, DB, placebo-controlled, PG, MN To evaluate the efficacy and safety of enoxaparin vs placebo as an adjunct to streptokinase therapy in patients with STEMI	Total =496 253 243	Enoxaparin : iv bolus 30 mg within 1 h of streptokinase, then sc 1 mg/kg q 12 h (first sc dose to be given within 15 min of iv bolus) Placebo : iv bolus 30 mg within 1 h of streptokinase, then sc 1 mg/kg q 12 h	3 to 8 days 3 to 8 days	The percentage of patent infarct related arteries (TIMI flow grade 3) on Day 8 angiogram provided by the core laboratory Chi-square test

R= randomized, DB= double-blind, DD= double dummy, PG= parallel group, MN= multinational study, OL= open-label; FU= follow up

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Table 3 List of clinical trials (continued)

Study / Centers / Countries	Design and Objectives Aspirin	Number of patients	Dosage / Timing / Frequency / Route / Device	Duration / Follow up	Primary Efficacy Endpoint / Statistical test
ENTIRE TIMI 23 43 centers 6 countries	R, OL, PG, MN Stratified, R, OL, PG, MN, angiographic study To compare safety and efficacy of sc enoxaparin vs UFH as an adjunct to thrombolytic therapy	Total = 488	(A) UFH: iv bolus 60 IU/kg (max 4000 IU), then iv infusion 12 IU/kg per h for 36 h (max 1000 IU/h during first 6 h) (infusion starts ≤ 5 min after iv bolus); (B1) Enoxaparin: iv bolus 30 mg, then 1 mg/kg sc for dose 1 and 2 (max 100 mg), then 1 mg/kg q 12 h (first sc dose to be given ≤ 5 min of iv bolus); (B2) Enoxaparin: no iv bolus, 1 mg/kg sc for dose 1 & 2 (max 100 mg), then 1 mg/kg q 12 h; (C1) Enoxaparin: no iv bolus, 0.3 mg/kg sc for dose 1 & 2, then 1 mg/kg q 12 h; (C3) Enoxaparin: iv bolus 30 mg, then 0.3 mg/kg sc for dose 1 and 2 (max 100 mg), then 1 mg/kg q 12 h (first sc dose to be given ≤ 5 min of iv bolus); (C4) Enoxaparin: no iv bolus, 0.75 mg/kg sc for dose 1 & 2, then 1 mg/kg q 12 h D: UFH: iv bolus 40 IU/kg (max 3000 IU), then iv infusion 7 IU/kg / h (max 800 IU/h in ≤ 6h) (infusion starts ≤ 5 min after iv bolus);	36 hours	The percentage of patients who reached TIMI flow grade 3 in the IRA at 60 minutes post TNK-tPA bolus measured by the core laboratory
		82		8 days	
		81		8 days	
		79		8 days	
		48		8 days	
		77		8 days	
39	Age 21 - 75 years STEMI ≤ 6 h	FU = 30 days	Chi-square test		
77	Aspirin 150-325 mg/d (initial dose ≥ 160 mg po or 250-500 mg iv)				
TETAMI 91 centers 14 countries	R, DB, placebo-controlled, 2 x 2 factorial design, MN To compare safety and efficacy of enoxaparin vs UFH and of tirofiban vs placebo in non-thrombolized patients with STEMI	Tot= 1,225 299	Enoxaparin + placebo: Enoxaparin iv bolus 30 mg + heparin placebo iv bolus, then enoxaparin sc 1 mg/kg q 12 h (dose 1 ≤ 15 min of iv bolus) + heparin placebo iv infusion; then tirofiban placebo iv bolus 200µL/kg + maint infusion 2µL/kg/m; Enoxaparin + tirofiban: Enoxaparin iv bolus 30 mg + heparin placebo iv bolus, then enoxaparin sc 1 mg/kg q 12 h (dose 1 ≤ 15 min of iv bolus) + heparin placebo iv infusion; then tirofiban iv bolus 200µg/kg + maint infusion 0.1µg/kg/m; UFH + placebo: Enoxaparin placebo 20 mg + UFH iv bolus 70 U/kg (max 5000 U), then enoxaparin placebo, sc 1 mg/kg q 12 h + UFH 15 U/kg/h to maintain aPTT of 1.5 - 2.5 x control; then tirofiban placebo iv bolus 200µL/kg + maint infusion 2µL/kg/m;	2 to 8 days	The incidence of death, re-infarction or recurrent angina at Day 30 post-randomization
		305		2 to 8 days	
		306		2 to 8 days	
				FU = ??30 days	Chi-square test

R= randomized, DB= double-blind, DD= double dummy, PG= parallel group, MN= multinational study, OL= open-label; FU= follow up

4.3 Review Strategy

First, I reviewed the medical literature related to clinical trials of antithrombin therapies in patients with STEMI as well as in patients with acute coronary syndromes (ACS) other than STEMI, namely, unstable angina and non-STEMI (NSTEMI).

Secondly, I reviewed the published literature related to the 6 previous clinical studies of enoxaparin involving an additional 10,171 patients with STEMI. As mentioned above, four studies (ASSENT 3, ASSENT 3+, ENTIRE-TIMI 23, and HART II) were open-label, and two studies (AMI-SK and TETAMI) were double-blind and placebo-controlled. The AMI-SK study evaluated reperfusion (TIMI flow grade 3) by angiography. The TETAMI study enrolled only non-thrombolized patients with STEMI (i.e., STEMI patients ineligible for reperfusion). Thus, I focused my data review on the only well-controlled study – the ExTRACT-TIMI 25 study – which is submitted as the pivotal study to support the indication claimed for this drug.

The primary efficacy endpoint data from clinical trial sites that enrolled relatively large numbers (≥ 100 patients each) in the pivotal ExTRACT-TIMI 25 study do not appear to be driving the statistical analysis of the ExTRACT-TIMI 25 trial. Thus, I recommended not to request FDA good clinical practice (GCP) inspections. (Please see Section 4.4 below).

I performed a clinical review of the primary efficacy endpoint data and evaluated the statistical findings, including some reanalysis using JMP 5.0 statistical software.

I reviewed the safety data including, particularly, the data related to TIMI major bleeding, intracranial hemorrhage and strokes, and the safety data in special populations of patients such as the elderly, and patients with impaired renal function.

On 26-Jan-2007, I requested the sponsor to provide data to determine:

- (i) the relationship of TIMI major hemorrhages and intracranial hemorrhage (ICH) to the primary efficacy endpoint events (I constructed Venn-diagrams of these efficacy and safety outcome findings);
- (ii) the relationship of the composite primary efficacy endpoint events, TIMI major hemorrhages and intracranial hemorrhage (ICH) to the duration of treatment with enoxaparin and UFH;
- (iii) the incidence of deaths at 30 days post-randomization in patients who a non-fatal myocardial infarction during 30 days post-randomization;
- (iv) mortality outcome at 6 months and 1 year in all patients, in all surviving patients after 1 month (i.e., removing all deaths within the first 30 days), and in all patients who did not experience a primary efficacy endpoint event.

For patients who reached the composite primary efficacy endpoint event (including all-cause deaths) at the large trial sites, I reviewed a random selection of case report forms (CRFs) and narratives to determine that these patients indeed qualified for enrollment and to verify that the primary efficacy endpoint data recorded in the CRFs were appropriately adjudicated and accurately reported to FDA in data line-listings. I reviewed also the CRFs and narratives of a random selection of patients who experienced the safety endpoints (particularly, major TIMI bleeding and intracranial hemorrhage).

4.4 Data Quality and Integrity

On 04-Dec-2006, I requested the sponsor to provide information related to the primary efficacy endpoint, protocol violations and early withdrawals, AEs and SAEs at all sites in the ExTRACT TIMI-25 trial.

On 08-Jan-2007, I received the requested data from the sponsor.

Of 674 sites (with only 9 sites in the US and 15 sites in Canada) that participated in the ExTRACT TIMI-25 trial, there were 42 sites that enrolled ≥ 100 patients: none was domestic; all 42 sites were in foreign countries.

All of the sites that enrolled the largest numbers of patients were in the Russian Federation:

1. The largest site (308 patients enrolled) was in Krasnoyarsk (PI = Vladimir Shulman, MD); 15 patients in *each* of the enoxaparin and UFH treatment arms experienced the composite primary efficacy endpoint events.
2. The second largest site (299 patients enrolled) was in Moscow (PI = Viktor Lusov, MD), where 22 patients *each* in the Enoxaparin and UFH treatment arms experienced the composite primary efficacy endpoint events.
3. The third largest site (298 patients enrolled) was in St. Petersburg (PI = Alexander Vishnevsky, MD), 17 patients and 21 patients in the enoxaparin and UFH treatment arms, respectively, experienced the composite primary efficacy endpoint events.
4. The fourth largest site (235 patients enrolled) in Barnaul (PI = Alexey Duda, MD) had 11 and 15 patients in the enoxaparin and UFH treatment arms, respectively, who experienced the composite primary efficacy endpoint events.

These four sites together contributed to the primary efficacy endpoint results as follows:

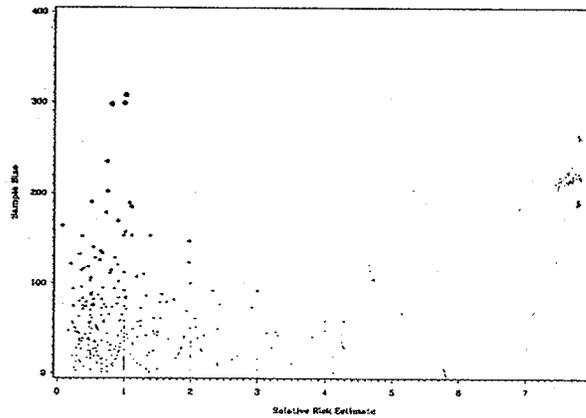
- 65 (6.4% of the total of 1,017) composite primary efficacy endpoint events in enoxaparin treatment group, and
- 73 (6.0% of a total of 1,223) composite primary efficacy endpoint events in UFH treatment group.

There is no site where the composite primary efficacy endpoint data are driving the statistical analysis of the ExTRACT TIMI 25 trial biased in favor of enoxaparin treatment. Thus, I recommended *not* requesting the Division of Scientific Investigations for GCP inspections for this NDA supplement.

On 26-Jan-2007, I requested the sponsor to provide funnel plots of the primary efficacy endpoint events by site, by country and by region. On 09-March-2007, the sponsor submitted the funnel plots in which the plots are sized according to the number of patients.

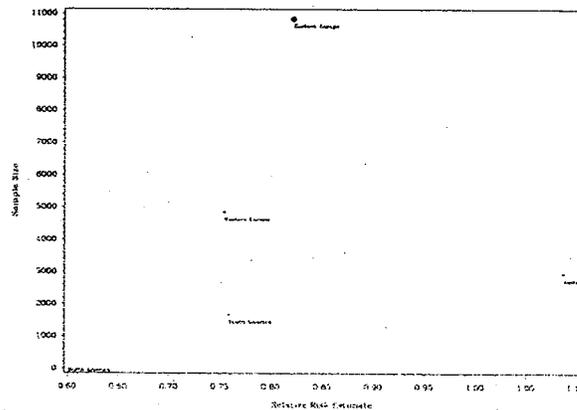
In Figure 1, which shows the primary endpoint event relative risk (RR) on the X-axis vs sample size on the Y-axis, sites with relatively small sample sizes showed a $RR > 1$. Sites with larger sample sizes showed a relative risk reduction for the primary efficacy endpoint events with enoxaparin vs unfractionated heparin (UFH).

In Figure 2, which shows the primary efficacy endpoint events by region, the RR in North America was 0.6, with Australia the only region with an $RR > 1$.



Note: Plots have been sized according to the number of patients considered by site.

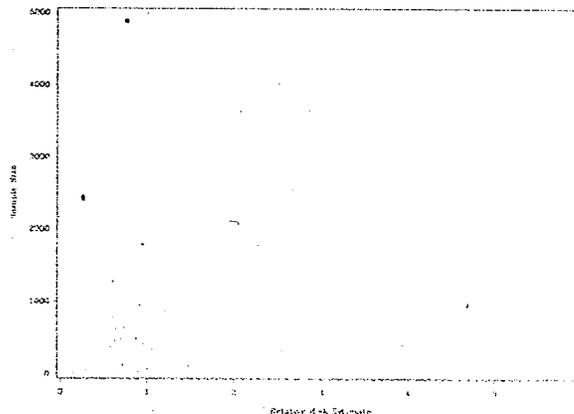
Figure 1 Funnel plot of primary efficacy endpoint events at 30 days by site (ITT population)



Note: Plots have been sized according to the number of patients considered by region.

Figure 2 Funnel plot of primary efficacy endpoint events at 30 days by region (ITT population)

In Figure 3, which shows primary efficacy endpoint events by country, most countries that enrolled larger numbers of patients had an $RR < 1$, suggesting a reduction in relative risk.



Note: Plots have been sized according to the number of patients considered by country.

Figure 3 Funnel plot of primary efficacy endpoint events at 30 days by country (ITT population)

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4.5 Compliance with Good Clinical Practices

Sanofi-Aventis U.S. LLC certifies that it has not used in any capacity the services of any person debarred pursuant to section 306(a) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 335(a) and (b)] in connection with this application.

The sponsor certified that this study was conducted in accordance with ICH E6 Guideline for Good Clinical Practice, May 9, 1977, in agreement with the latest revision of the Declaration of Helsinki (52nd WMA General Assembly, Edinburg, Scotland, October 2000) and local regulations, and that the study was conducted under the Investigational New Drug (IND) application and in compliance with the US Code of Federal Regulations (Title 21, Parts 50, 56, and 312).

The submission also contains sample copies of informed consent used at the sites (with English translations for consent forms used at foreign sites). A review of sample consent forms shows that they contain all of the elements of informed consent as described in 21 CFR 50.25 and 50.27, the ICH Harmonised Tripartite Guideline for GCP and the Declaration of Helsinki.

4.6 Financial Disclosures

This submission consists of one pivotal, phase III study, XRP4563B/3001 (ExTRACT TIMI-25), in support of the use of enoxaparin in the treatment of patients with STEMI.

In compliance with 21 CFR Part 54 and the March 20, 2001 FDA Guidance, "Financial Disclosure by Clinical Investigators", the sponsor provided a list of principle investigators participating in the ExTRACT study, and submitted certification that all of the principle investigators who participated in the ExTRACT study declared that they had no financial interests in the outcome of the study.

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5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

After sc injection of enoxaparin, anti-Xa activity reached the maximum plasma levels at 3 to 5 hours after administration. Enoxaparin has a half-life of 4 to 7 hours; steady-state concentrations are attained after 7 administrations with twice daily sc dosing. With the 1 mg/kg twice daily dosing regimen, the mean plasma anti-Xa concentrations at steady-state range between 0.5 and 1.1 IU/ml.

Enoxaparin clearance is mainly affected by body weight and renal function (assessed by creatinine clearance (Cr_{Cl}): Cr_{Cl} was calculated either using the ratio of urine creatinine / serum creatinine concentrations or the Cockcroft-Gault formula). To minimize between-subject variability, enoxaparin doses were adjusted to patient body weight. Severe renal impairment is associated with increased incidence of major hemorrhage, due to a reduction in anti-Xa clearance. A recommended dosage regimen in patients with impaired renal function is 1 mg/kg *once* daily.

A summary of the clinical pharmacology studies included in the current submission is presented in Table 4.

Table 4 Summary of available pharmacokinetic studies

	Healthy subjects	Patients with STEMI							
	XRP54563Q-142	EXTRACT ^a		AMI-SK ^b	ENTIRE				
		Age group			Standard Lytic group ^c		Combination Reperfusion Therapy group ^d		
		<75 yrs	≥75 yrs		Panel B1	Panel B2	Panel C1	Panel C3	Panel C4
Enoxaparin iv bolus (mg)	30	30	None	30	30	None	None	30	None
First 2 sc injections (mg/kg) Q12h	1.0	1.0 (first sc)	0.75 (first sc)	1.0	1.0	1.0	0.3	0.3	Range: 0.75
Subsequent sc injections (mg/kg) Q12h		1.0 (Q24h in case of severe renal impairment)		1.0	1.0	1.0	1.0	1.0	1.0
Number of patients for PK analysis	16	76		244	209				
Day of PK sampling (No. of samples)	D1 (n=14) D2, D3 (peak and trough) D4 (n=12)	D1 (n=2: 0.5-2.5 h, 4-12 h)		D1 (n=2) D3 (n=2)	D1 (n=2) D2 or D3 (n=2)				
Type of analysis	NCA	Bayesian estimation ^e		Bayesian estimation ^e	Population PK				

^a Streptokinase, TNK-tPA, alteplase, reteplase

^b Streptokinase (1.5 million units over 60 minutes)

^c Full dose TNK-tPA (0.53 mg/kg - dose max 50 mg)

^d Half dose TNK-tPA (0.27 mg/kg - dose max 25 mg) + abciximab (0.25 mg/kg bolus and 0.125 µg/kg infusion)

^e Using the population PK model developed from TIMI 11A data (26)

STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; iv = intravenous; sc = subcutaneous; Q12h = every 12 hours; Q24h = every 24 hours; h = hour(s); PK = pharmacokinetic(s); D = day; NCA = noncompartmental analysis; TNK-tPA = tenecteplase

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In addition, a new population PK analysis (Study POH0137) was conducted that included studies with obese and renally impaired subjects, patients undergoing PCI, and patients from the ENTIRE-TIMI 23 study and AMI-SK studies.

In the treatment of acute STEMI, a dosage regimen with an iv bolus of 30 mg administered at treatment initiation immediately followed by the first sc dose of 1 mg/kg has been used to allow steady-state conditions to be reached more rapidly. A study in healthy 50- to 68-year-old subjects (Study RP54563Q-142) showed that post-iv bolus mean anti-Xa plasma levels were 0.663 IU/mL (i.e., within the 0.5 to 1.1 IU/ml range representing steady-state) and were maintained in that range during the first 8-hour period after the combined iv and sc dosing. Steady-state conditions were reached on Day 1 for A_{max} and Day 2 for A_{min} . Similarly, the area under the concentration time curve (AUC) over the first dosing interval represented 84% of that at steady-state. For the secondary parameter of anti-IIa activity, post-injection values were about 70% higher than steady-state maximum values. Steady-state was then achieved immediately thereafter.

The population PK meta-analysis showed PK parameters very close to those observed in healthy subjects (Study POH0137) (Table 5). Body weight and renal function (as measured by $CrCl$ calculated with the Cockcroft-Gault formula) were the main covariates for enoxaparin (anti-Xa) clearance. Except for the impact of renal function, clearance only slightly decreased with increasing age and with decreasing hematocrit levels, both resulting in minor effects on AUC. There was no effect based on the gender of patients. Concomitant administration of TNK-tPA, streptokinase, or glycoprotein (GP) IIb/IIIa antagonists did not modify enoxaparin (anti-Xa) clearance. Inter-individual and intra-individual variability in enoxaparin clearance were moderate.

Table 5 Summary of enoxaparin anti-Xa clearance and exposure across studies

Dosing regimen	142	ENTIRE	AMI-SK	EXTRACT		TIMI 11A	POH0137
	Group B1			<75 years	≥75 years	Population mean	
	30 mg iv bolus + 1 mg/kg sc	30 mg iv bolus + 1 mg/kg sc	30 m iv bolus + 1 mg/kg sc	30 mg iv bolus + 1 mg/kg sc	0.75 mg/kg sc	30 mg iv bolus + 1 mg/kg or 1.25 mg/kg sc	Different doses iv + sc
Median enoxaparin anti-Xa Cl (L/h)	0.678	0.866	0.738	0.794	0.654	0.733	0.757
Median AUC(0-12) first day (IU·h/mL)	10.4	8.90		9.8	4.53		
Median AUC _τ (τ=12h) (IU·h/mL)	12.6	10.1	9.62	10.0	8.33		

anti-Xa = anti-factor Xa; TIMI = Thrombolysis in Myocardial Infarction; iv = intravenous; sc = subcutaneous; AUC = area under the curve

In study AMI-SK, a PK/PD analysis using a logistic regression model showed that in the univariate analyses, the parameters significantly correlated with any hemorrhage was age (strongest), $CrCl$ and enoxaparin clearance. In the multivariate analysis, age was the only covariate in the model.

In the ExTRACT PK substudy, the standard dosage regimen was 1 mg/kg sc every 12 hours with a 30 mg iv bolus, and a reduced dose of 0.75 mg/kg sc every 12 hours with no iv bolus was proposed in patients ≥75 years old. The enoxaparin (anti-Xa) clearance in these elderly patients was 17.6% lower than that observed in younger patients. In younger

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patients, the $AUC_{(0-12h)}$ on Day 1 represented 98% of the AUC_t , showing the adequacy of the iv bolus. The absence of the iv bolus and lower sc dose in ≥ 75 year-old patients led to an $AUC_{(0-12h)}$ on Day 1 that was 54% lower than that observed in younger patients. At steady-state, AUC_t in ≥ 75 year-old patients was 17% lower than that in the younger patients (Table 5). No obvious difference was observed in enoxaparin clearance according to the type of thrombolytics used. No conclusion could be drawn for patients with severe renal impairment who received 1 mg/kg once daily, due to the small number of such patients recruited in the PK substudy.

5.2 Pharmacodynamics

The sponsor submitted that apart from studies for anti-Xa activity used to estimate enoxaparin PK parameters, no pharmacodynamic parameters have been studied.

5.3 Exposure-Response Relationships

Please see section 7.2 for review related to exposure, and section 6.1.4.8 for review of relationship of duration of treatment with enoxaparin and UFH to the efficacy and safety endpoint events.

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6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The following STEMI indication (underlined) is proposed by the sponsor for insertion in the text for the current indications:

Lovenox® Injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in patients undergoing hip replacement surgery, during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Lovenox® Injection is indicated for:

- the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium;
- the out patient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

Lovenox® Injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

Lovenox® Injection is indicated for the treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

Rationale for the new indication

Despite current treatment with a regimen of a fibrinolytic agent, aspirin, and UFH, a substantial number of patients die or have another nonfatal myocardial infarction within 1 month after treatment^{2,4,5,6,7,8,9}. To reduce morbidity and mortality, enoxaparin contributes to prevention of re-occlusion of the infarct-related artery (IRA) by reducing thrombus formation through acceleration of the irreversible binding of antithrombin III to multiple clotting factors, including factors IIa and Xa.

Compared to UFH, enoxaparin – which is a low molecular weight heparin (LMWH) obtained by depolymerization of standard UFH – has a higher ratio of anti-factor Xa (anti-Xa) to anti-factor IIa (anti-IIa) activity and a reduced interaction with platelets. This high anti-Xa activity of enoxaparin was expected to be useful in the suppression of thrombus generation.

6.1.1 Methods

Please see Section 10 Appendix, 10.1 Review of Study Report on ExTRACT-TIMI 25 study for review of study protocol and amendments, study drug administration, enoxaparin and UFH dosing regimens, antithrombin therapy for patients requiring CABG, and patients requiring PCI (before, during and after PCI), study procedures and follow up, adjudication of endpoints, safety monitoring, study organization, etc.

6.1.2 General Discussion of Endpoints

For the ExTRACT-TIMI 25 study, the primary efficacy endpoint was the composite of death from any cause or non-fatal myocardial re-infarction in the first 30 days after randomization.

The main secondary endpoint was the composite of death from any cause, non-fatal re-myocardial infarction, or recurrent myocardial ischemia leading to urgent revascularization in the first 30 days. An additional secondary end point (net clinical benefit) was the composite of death from any cause, non-fatal reinfarction, or non-fatal disabling stroke.

The tertiary endpoints were:

- (i) the incidence of severe congestive heart failure alone or in combination with all-cause death and non-fatal myocardial re-infarction within 30 days after randomization, and
- (ii) the incidence of all-cause mortality, non-fatal myocardial re-infarction, non-fatal disabling stroke, and myocardial ischemia leading to urgent revascularization alone or in combinations at 48 hours and at 8 days after randomization.

At a meeting between the sponsor and FDA on 15-Dec-2001, the Agency provided the following suggestions regarding endpoints in the proposed ExTRACT-TIMI 25 study design:

- The primary efficacy endpoint should be assessed at 30 days. Assessments at 14 days and other time points may be secondary analyses. Time-to-event analyses may be of interest as secondary analyses.
- The definition of major hemorrhage must include a statement that intraocular, retroperitoneal and intracranial hemorrhages are always considered major hemorrhage.

Please see Section 10 Appendix, 10.1.1 Review of Study Report on ExTRACT-TIMI 25 study for detailed description of Study end point definitions (death, myocardial re-infarction, recurrent myocardial ischemia requiring urgent revascularization, recurrent severe myocardial ischemia, severe congestive heart failure, cardiogenic shock, stroke and bleeding events (using Thrombolysis In Myocardial Infarction (TIMI) hemorrhage classification¹³).

The sponsor maintained that all ischemic and clinically significant bleeding events were adjudicated in a blinded fashion by an independent clinical events committee (CEC) using prespecified definitions¹⁴.

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Table 6 summarizes the primary, secondary and tertiary efficacy endpoints and the corresponding time points for statistical analyses.

Table 6 ExTRACT-TIMI 25 study efficacy endpoints and corresponding time points

The Primary Efficacy Endpoint:			
The adjudicated combined double endpoint of death or re-infarction ^a at 30 days			
The First Secondary Efficacy Endpoint:			
The adjudicated combined triple endpoint of death, re-infarction ^a or ischemia leading to urgent revascularization at 30 days			
Other Secondary Efficacy Endpoints:			
The adjudicated combined triple endpoint of death, re-infarction ^a or disabling stroke at 30 days			
Tertiary Efficacy Endpoints:			
Incidence of	At 48 hours	At 8 days	At 30 days
The adjudicated combined double endpoint of death or re-infarction ^a	Tertiary	Tertiary	
The adjudicated combined triple endpoint of death, re-infarction ^a or ischemia leading to urgent revascularization	Tertiary	Tertiary	
The adjudicated combined triple endpoint of death, re-infarction ^a or disabling stroke	Tertiary	Tertiary	
The adjudicated combined triple endpoint of death, re-infarction ^a or severe CHF ^b			Tertiary
The adjudicated combined quadruple endpoint of death, re-infarction ^a , ischemia leading to urgent revascularization and disabling stroke	Tertiary	Tertiary	Tertiary
Each individual death, re-infarction ^a , ischemia leading to urgent revascularization and disabling stroke, as per CEC	Tertiary	Tertiary	Tertiary
Severe CHF ^b			Tertiary
Revascularization (CABG, PCI)			Tertiary

^aFor myocardial re-infarction to be considered part of the composite endpoint the myocardial infarction (MI) had to be distinct from the index event. An ST-depression in V1-V3 was considered equivalent to ST-segment elevation if the recurrent MI was suspected to be true posterior in location, and an increase in R-wave amplitude in V1-V3 was considered equivalent to Q-waves if the recurrent MI was suspected to be true posterior in location.

^b Severe CHF was defined as rales over more than 50% of the lung fields that did not clear with coughing or evidence of pulmonary edema on chest radiograph.

CHF = congestive heart failure; CEC = Clinical Events Committee; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention. [Source: Sponsor's Appendix B.1, Section 3.1.1]

For the six previous studies, the endpoints are different from the endpoints in the ExTRACT-TIMI 25 trial. Three of the 6 previous studies evaluated a clinical endpoint (ASSENT 3, ASSENT 3+ and TETAMI) and three others (ENTIRE, HART II and AMI-SK) evaluated a mechanistic endpoint.

In the ASSENT 3 and ASSENT 3+ studies, the primary efficacy endpoint was a composite of all-cause death, myocardial re-infarction, and ischemia at 30 days or in-hospital, quite similar to the primary efficacy endpoint in the ExTRACT-TIMI 25 study.

In the TETAMI study performed in *non-thrombolized* STEMI patients treated with enoxaparin or UFH and tirofiban, the primary efficacy endpoint was a composite of all-cause death, re-infarction and recurrent angina at Day 30 (which differed from that of the ExTRACT-TIMI 25 study).

The ENTIRE study was a *dose-finding study* of enoxaparin (in combination with half-dose tenecteplase (TNK-tPA, 0.27 mg/kg) and with full dose abciximab (bolus 0.25 mg/kg, infusion 0.125 µg/kg/min x 12 hours). The primary efficacy endpoint was TIMI grade 3

flow at 60 minutes in at least 60% of patients.

In the HART II and AMI-SK studies, the primary efficacy endpoint was TIMI flow grades of the infarct related artery (IRA) at 90 minutes (HART II) or Day 8 (AMI-SK).

The description of the primary efficacy endpoints in the ExTRACT-TIMI 25 trial and the 6 previous studies are shown in Table 2 and Table 3, and summarized in Table 7 below.

Table 7 Description of primary efficacy endpoints in the ExTRACT-TIMI 25 study and 6 previous studies

Enoxaparin study	Type of endpoint	Primary efficacy endpoint
EXTRACT	Clinical	Composite endpoint of all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization
ASSENT 3	Clinical	The composite endpoint of 30-day mortality or in-hospital re-infarction or in-hospital refractory ischemia
ASSENT 3+	Clinical	The composite endpoint of 30-day mortality or in-hospital re-infarction or in-hospital refractory ischemia
TETAMI	Clinical	The incidence of the death, re-infarction, or recurrent angina at Day 30 post-randomization
ENTIRE	Mechanistic	The percentage of patients who reached TIMI grade 3 flow in the IRA at 60 minutes post- TNK-tPA bolus measured by the core laboratory
HART II	Mechanistic	The reperfusion rate of the IRA at the 90-minute post-rt PA angiogram (TIMI grades 2 and 3 flow), as provided by a core laboratory
AMI-SK	Mechanistic	The percentage of patent IRAs (TIMI grade 3 flow) on the Day 8 angiogram provided by the core laboratory

rt-PA = recombinant tissue plasminogen activator; TIMI = Thrombolysis in Myocardial Infarction; IRA = infarct related artery; TNK-tPA = tenecteplase. Source: sponsor's Table 4 in Clinical Overview, page 22.

6.1.3 Study Design

Briefly, the ExTRACT-TIMI 25 study is a multi-national, randomized, double-blind, double-dummy, parallel group, clinical trial with an active control (UFH). A network of 850 sites in 47 countries was planned for the trial. Enrollment started in October 2002 with a projected sample size of 21000 patients. During 24-Oct-2002 through 01-Oct-2005, 20,506 patients underwent randomization at 674 sites in 48 countries (9 sites in the US).

Please see Section 10 Appendix, 10.1.1 Review of Study Report on ExTRACT-TIMI 25 study for detailed description of study design, maintenance of study blind and follow up.

Design of the 6 previous studies:

Briefly, four of these previous studies (ASSENT 3, ASSENT 3+, ENTIRE-TIMI 23 and HART II) were open-label. The remaining *two* (AMI-SK and TETAMI) were randomized, double-blind, placebo-controlled, parallel group studies.

The inclusion criteria for the 6 previous studies were similar.

The enoxaparin and UFH treatment regimens differed across studies due to the absence of an initial enoxaparin iv bolus or to the addition of a fibrinolytic medication administered either prior to and/or following enoxaparin sc administration.

A clinically important difference between the ExTRACT-TIMI 25 study and the previous 6

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studies is that in these previous 6 studies enoxaparin was administered without dose modifications for age or renal impairment.

Please also see Table 2 and Table 3, and Section 10 Appendix, 10.1.2 Review of Study Report on the 6 previous studies for details of study design.

The sponsor submits that due to differences in study designs and study endpoints, no integrated analyses were performed on efficacy and safety data from the ExTRACT-TIMI 25 study with efficacy and safety data from the 6 previous studies.

Brief account of statistical methods:

The sponsor submits that in the ExTRACT-TIMI 25 study, all efficacy analyses of endpoint events were based on adjudicated data from the independent Clinical Events Committee (CEC). The primary efficacy analysis compared the percentages of patients who had the composite endpoint of all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization between the 2 treatment groups (enoxaparin vs UFH) using a **Chi-square test** and based on the ITT patient population. A patient with multiple events was counted only once in the incidence-based analysis.

An independent Data Safety Monitoring Board reviewed **unblinded** results of the ExTRACT-TIMI 25 study at about 25%, 50%, and 75% of the total targeted primary events. Using a conservative approach, a penalty adjustment for the 3 major interim analyses was applied according to the Lan-DeMets Type O'Brien Fleming boundary with critical p-values of 0.00007209, 0.00348532, and 0.01906029, respectively. In order to maintain the overall significance level at 5%, the critical p-value at the final analysis was 0.04341996, as described in the sponsor's statistical analysis plan (SAP).

In the ASSENT 3 and ASSENT 3+ studies, both composite and single endpoints were analyzed as event rates and 95% CIs (two-sided) separately for each treatment group. An overall **Chi-square test** was performed to compare the 3 treatment groups.

In the TETAMI study, the primary composite endpoint was analyzed using a **Chi-square test**.

In the ENTIRE study, **Chi-square tests** were used to compare incidence rates of efficacy endpoints between the treatment groups; odds-ratios and 95% CIs were calculated.

In the HART II study, the primary efficacy analysis was a **non-inferiority test** on the patency rates using one-sided 95% CI, which was accepted if the lower limit of the CI did not exceed -10%.

In the AMI-SK study, the primary efficacy analysis was a between-group comparison of patency rates (TIMI flow grade 3) using a **Chi-square test**.

Sample size considerations

Sample size calculation for the ExTRACT-TIMI 25 study was based on the assumption that the 30-day event rate for the composite primary endpoint in the UFH group would be 10.50%, and that this rate would be reduced by 13.0% (absolute reduction of 1.37%) in the enoxaparin group (based on data from the ASSENT 3 study). Based on the assumed event rate and treatment effect, in order to have approximately at least 90% power at the overall 5.0% significance level (2-sided), the trial was to **enroll approximately 21,000 subjects to accrue a total number of 2080 events.** The sample size calculations also assumed that

there was no loss to follow-up in the 2 treatment groups. It appears that that this sample size was conservative for an event-based approach.

In the ASSENT 3 study, the sample size estimation was based on the estimation of the 95% CIs (two-sided) for each endpoint within 3 treatment groups, as well as of the 95% CIs (two-sided) for between-group comparisons. Approximately 2000 patients for each of 3 treatment arms were estimated for the ASSENT 3 study.

For the ASSENT 3+ study, no specific sample size estimation was performed due to its descriptive nature. During the course of the study, recruitment was extended from 1000 to 1600 patients.

In the ENTIRE study, a minimum of 35 evaluable patients (necessary to detect a lower patency rate than expected) was to be enrolled in each of the dose groups tested during the dose-finding phase of the study.

In the HART II study, in order to show non-inferiority between UFH and enoxaparin, a sample size of 198 patients per treatment arm (approximately 400 total) was selected with a significance level of 0.05 (one-sided) and an assumed patency rate of 80% for both treatment arms.

In the AMI-SK study, a sample size of 200 evaluable patients per treatment arm (400 total) was chosen to provide 80% power to demonstrate a 22% increase in patency rate with enoxaparin, assuming a rate of 60% at Day 8 for the placebo group (at the 5% level). A 10% rate of non-evaluable patients was estimated. However, 20% to 25% were non-evaluable due to angiographies that were not performed or assessable, or that were performed outside of the timeframe for assessment. The Steering Committee extended enrollment to a total of approximately 500 patients.

In the TETAMI study, sample size was calculated assuming a 25.5% overall event rate with respect to the primary efficacy endpoint in UFH-treated patients, and a 30% relative reduction in event rate with enoxaparin vs UFH. Assuming a type-I error of 5%, a sample size of 450 patients per treatment arm was expected to provide 80% power to demonstrate superiority of enoxaparin over UFH. After recruitment of 439 patients, a lower UFH event rate than expected was found; then, the sample size was increased to a total of 1224 to maintain sufficient power.

6.1.4 Efficacy Findings

6.1.4.1 Comparability of treatment groups in ExTRACT-TIMI 25 trial

Of 20,506 patients randomized (10,273 enoxaparin and 10,233 UFH) in the ExTRACT-TIMI 25 study, 27 (17 enoxaparin and 10 UFH) did not receive study drug and had no follow-up information. Thus, the ITT population was 20,479 (10,256 enoxaparin and 10,223 UFH) patients.

The demographic and baseline characteristics appear well-matched between the two treatment groups, with 76% male and 87.3% Caucasian patients.

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The baseline cardiovascular disease characteristics were also comparable between the enoxaparin and UFH treatment groups, with a history of a prior MI in 13.2% and 12.9%, prior PCI in 3.3% and 3.1%, prior CABG surgery in 1.3% and 1.2%, CHF in 3.2% and 3.1%, hypertension requiring drug treatment in 44.5% and 43.6%, diabetes mellitus in 15.2% and 15.0%, hypercholesterolemia in 18.3% and 18.2%, family history of coronary artery disease in 24.3% and 23.6%, chronic use of NSAIDs/ASA in 13.6% and 13.3%, and a prior coronary angiography showing $\geq 50\%$ stenosis in 5.5% and 5.3%, respectively.

These patients had prolonged (≥ 20 minutes) ischemic symptoms of rest ≤ 6 hours prior to randomization, with the mean time (\pm SD) from symptom onset to randomization being 3.26 ± 7.29 hours in the enoxaparin group, and 3.17 ± 1.39 hours in the UFH group. Only 126 (1.2%) patients in enoxaparin group and 115 (1.1%) patients in UFH group were randomized >6 hours after symptom onset.

Baseline ECG findings for MI were comparable between the 2 treatment groups (Table 8).

Table 8 Baseline ECG findings for MI in ExTRACT TIMI 25 study – ITT population

12-lead ECG findings for MI	Enoxaparin (N = 10,256)	UFH (N = 10,223)
Anterior alone	4356 (42.8%)	4428 (43.6%)
Non-anterior alone	5737 (56.4%)	5663 (55.8%)
Anterior + non-anterior	83 (0.8%)	66 (0.6%)
Missing	80 (0.8%)	66 (0.6%)
Left bundle-branch block		
No	10,164 (99.1%)	10,129 (99.1%)
Yes	92 (0.9%)	94 (0.9%)

Use of thrombolytic medication was comparable between the enoxaparin and UFH groups, being treated with streptokinase in 20.2% and 20.1%, TNK-tPA (tenecteplase) in 19.3% and 19.6%, Reteplase in 5.5% and 5.4%, and Alteplase in 55.0% and 54.8%, respectively, of patients. 3 patients in enoxaparin and 1 in UFH groups received no fibrinolytic therapy.

Concomitant medications prior to hospitalization were comparable between the enoxaparin and UFH groups, with aspirin in 94.8% and 95.4%, β -blockers (excluding eye drops) in 85.9% and 85.5%, ACE inhibitors in 78.5% and 77.8%, statins in 69.5% and 69.5%, clopidogrel in 27.2% and 28.7%, oral anticoagulants in 2.1% and 2.5%, and thrombolytics (other than those of index MI) in 4% and 0.5%, respectively, of patients.

A few patients who received thrombin agents were also comparable between the enoxaparin and UFH groups, having received ≥ 4000 U of UFH 3 hours prior to randomization in 15.9% and 15.7%, UFH 7 days to 3 hours prior to randomization in 0.8% and 0.8%, and low molecular weight heparin (other than study drug) within 7 days before randomization in 0.4% and 0.5%, respectively, of patients.

Less than 2% of treated patients did not receive the required enoxaparin or enoxaparin placebo bolus (326 of 20,327 patients) or the required UFH or UFH placebo bolus (367 of 20,327 treated patients).

The mean duration for enoxaparin or enoxaparin placebo sc injection was 6.6 days (median duration = 7 days) with 74.5% treated for ≥ 6 days. The mean duration of UFH or UFH placebo iv infusion was 53.7 hours (median duration = 48 hours) with 89.6% of the total population treated for ≥ 36 hours.

6.1.4.2 Primary and secondary efficacy endpoint findings in ExTRACT-TIMI 25 trial

In the ITT population, the rate of the primary efficacy endpoint (death or non-fatal myocardial re-infarction) was 9.9% in the enoxaparin group, as compared with 12.0% in the UFH group (17% reduction in relative risk, P<0.000003) (Table 9).

The time to clinical endpoint of death or non-fatal myocardial re-infarction (by log rank test, Figure 4A) also showed a statistically significant reduction in the enoxaparin group compared to the UFH treatment group (HR = 0.83, 95% CI 0.77 – 0.90, P<0.001).

The treatment benefits of enoxaparin became evident for non-fatal myocardial re-infarction at 48 hours, at which time there was a 33% reduction in the relative risk of non-fatal myocardial re-infarction, as compared with treatment with UFH (P = 0.002) (Table 9).

Table 9 Primary and Secondary Efficacy Outcomes*

Clinical Outcome	Enoxaparin (N = 10,256)	UFH (N = 10,223)	Relative Risk (95% CI)	P value§
<i>Number (percent)</i>				
Outcome at 48 hr				
Death or non-fatal myocardial re-infarction	478 (4.7)	531 (5.2)	0.90 (0.80 – 1.01)	0.08
Death	383 (3.7)	390 (3.8)	0.98 (0.85 – 1.12)	0.76
Non-fatal myocardial re-infarction	95 (0.9)	141 (1.4)	0.67 (0.52 – 0.87)	0.002
Urgent revascularization	74 (0.7)	96 (0.9)	0.77 (0.57 – 1.04)	0.90
Death, non-fatal MI or urgent revascularization	548 (5.3)	622 (6.1)	0.88 (0.79 – 0.98)	0.02
Outcome at 8 days				
Death or non-fatal myocardial re-infarction	740 (7.2)	954 (9.3)	0.77 (0.71 – 0.85)	<0.001
Death	559 (5.5)	605 (5.9)	0.92 (0.82 – 1.03)	0.15
Non-fatal myocardial re-infarction	181 (1.8)	349 (3.4)	0.52 (0.43 – 0.62)	<0.001
Urgent revascularization	145 (1.4)	247 (2.4)	0.59 (0.48 – 0.72)	<0.001
Death, non-fatal MI or urgent revascularization	874 (8.5)	1181 (11.6)	0.74 (0.68 – 0.80)	<0.001
Outcome at 30 days				
Death or non-fatal myocardial re-infarction	1017 (9.9)	1223 (12.0)	0.83 (0.77 – 0.90)	0.000003
Death	708 (6.9)	765 (7.5)	0.92 (0.84 – 1.02)	0.11
Non-fatal myocardial re-infarction	309 (3.0)	458 (4.5)	0.67 (0.58 – 0.77)	<0.001
Urgent revascularization	213 (2.1)	286 (2.8)	0.74 (0.62 – 0.88)	<0.001
Death, non-fatal MI or urgent revascularization	1199 (11.7)	1479 (14.5)	0.81 (0.75 – 0.87)	<0.001

Nonfatal myocardial re-infarction (MI) indicates that a patient had a recurrent MI and had not died by the time shown. Urgent revascularization denotes episodes of recurrent myocardial ischemia (without infarction) that drove the clinical decision to perform coronary revascularization during the same hospitalization. CI denotes confidence interval.
 § Pearson's Chi-square or Fisher's Exact test, as appropriate.

At 30 days, the mortality rate was 7.5% in the UFH group, as compared with 6.9% in the enoxaparin group (P = 0.11) (Table 9). Enoxaparin significantly reduced the rate of recurrent non-fatal myocardial reinfarction (3.0%, vs. 4.5% in the UFH group; 33% reduction in relative risk; P<0.001) (Table 9). Episodes of recurrent myocardial ischemia leading to urgent revascularization were significantly reduced, from 2.8% in the UFH group to 2.1% in the enoxaparin group (P<0.001) (Table 9).

As compared with UFH, enoxaparin also significantly reduced (by 17%) the incidence of the main composite secondary end point of death, non-fatal myocardial re-infarction, or urgent revascularization (11.7% vs. 14.5%, P<0.001) (Table 9 and Figure 4B). This efficacy outcome at 30 days was also already significant at day 2 and day 8 (Table 9).

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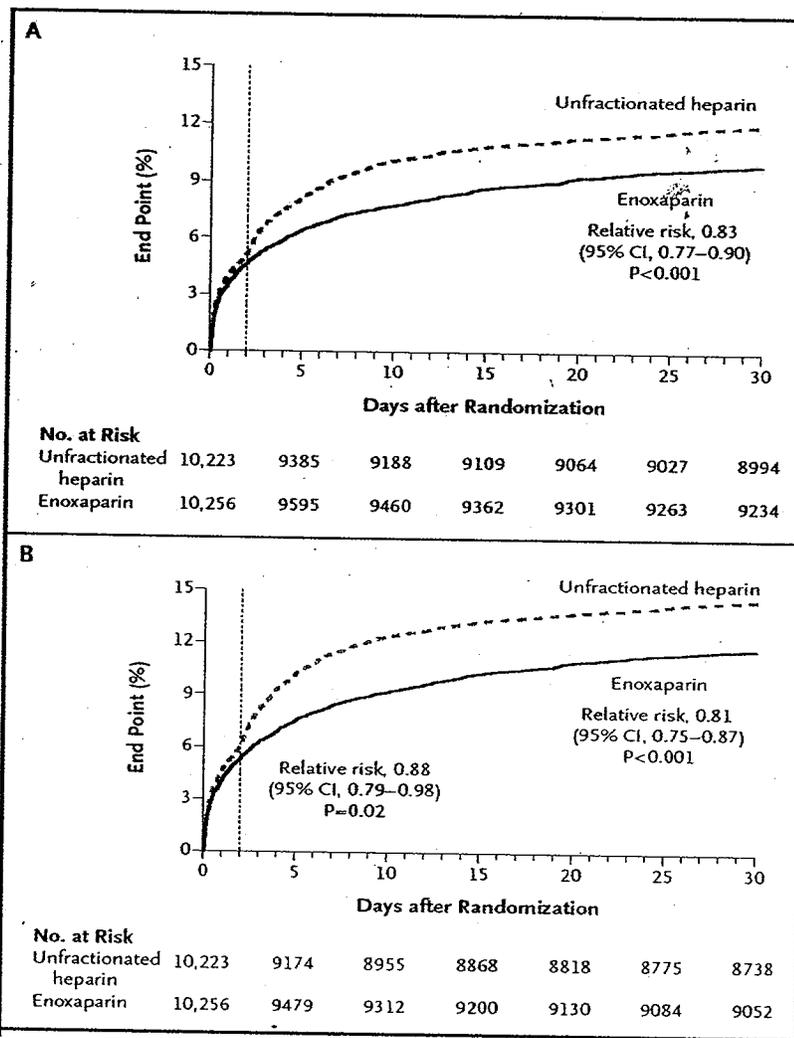


Figure 4 Cumulative Incidence of the Primary End Point (Panel A) and the Secondary End Point (Panel B).

In Panel A, the rate of the *primary end point* (death or nonfatal MI) at 30 days was significantly lower in the enoxaparin group than in the UFH group (9.9% vs. 12.0%, P < 0.001 by the log-rank test). The dashed vertical line indicates the comparison at day 2 (direct pharmacologic comparison), at which time a trend in favor of enoxaparin was seen.

In Panel B, the rate of the *main secondary end point* (death, nonfatal MI, or urgent revascularization) at 30 days was significantly lower in the enoxaparin group than in the UFH group (11.7% vs. 14.5%, P < 0.001 by the log-rank test). The difference was already significant at 48 hours (6.1% in the UFH group vs. 5.3% in the enoxaparin group, P = 0.02 by the log-rank test). The interval shown is the time (in 24-h intervals) from randomization to an event or the last follow-up visit. CI denotes confidence interval.

Cited from: Antmann et al¹⁴, NEJM 2006; 354: 1477-88.

My concern is that if patients adjudicated as having experienced myocardial re-infarction events were censored at the time of re-infarction, then any subsequent death(s) may not be known. In the data in Table 10 (reproduced below) from the Statistical Review by John Lawrence (which became available on 15-Mar-2007), the two components of the composite primary efficacy endpoints are counted in two ways: first, counting ALL events (so that if a subject had a myocardial re-infarction and subsequently died within 30 days,

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these would count as two events; and secondly counting only the first events (e.g., only the non-fatal myocardial re-infarction would be counted).

Table 10 Analysis of the composite primary efficacy endpoint and the individual components

Event	Enoxaparin (N=10256)	Heparin (N=10223)	Relative Risk	P-value
Death or myocardial re-infarction at 30 days	1017	1223	0.83	0.000003
Counting events after the primary endpoint				
Death at 30 days	708	765	0.92	0.11
Myocardial re-infarction at 30 days	352	508	0.69	<0.0001
Counting first event in the primary endpoint only				
Death at 30 days	665	715	0.93	0.15
Myocardial re-infarction at 30 days	352	508	0.69	<0.0001

From: Statistical Review by John Lawrence, 15-Mar-2007.

From the above table, I calculated that among the 10,256 STEMI patients treated with enoxaparin, 352 patients experienced the primary efficacy endpoint of non-fatal myocardial re-infarction. Of these patients, 43 (12.2%) subsequently died within 30 days. In the 10,223 STEMI patients treated with UFH, 508 patients experienced the primary efficacy endpoint of myocardial re-infarction, of which 50 (9.8%) subsequently died within 30 days.

To determine the interrelationship between these two components of the primary efficacy endpoint – non-fatal myocardial re-infarction during 30 days to deaths at 30 days – I requested for and received the following data from the sponsor on 16-Mar-2007 (Table 11).

Table 11 Relationship of myocardial re-infarction at 30 days to death 30 days (ITT population)

Myocardial re-infarction	Treatment group	N	RR enoxaparin vs UFH				HR enoxaparin vs UFH	
			n (%)	RR [95% C.I.]	RRR	P value ^a	HR [95% C.I.]	P value ^b
Absent	Enoxaparin	9904	665 (6.7)	0.91 [0.82-1.01]	0.09	0.0772	0.91 [0.82-1.01]	0.0792
	UFH	9715	715 (7.4)					
Present	Enoxaparin	352	43 (12.2)	1.24 [0.85-1.82]	-0.24	0.2705	1.25 [0.83-1.88]	0.2806
	UFH	508	50 (9.8)					

^aPearson's Chi-square or Fisher's Exact test, as appropriate; ^bLog rank test; ITT = intent-to-treat, UFH = unfractionated heparin, RR = relative risk, CI = confidence interval, RRR = relative risk reduction; HR = hazard ratio; N = Total number of patients in treatment group; n=number (%) of patients who died

Myocardial re-infarction during the first 30 days was associated with a higher risk of death, whether the patients received enoxaparin or UFH. However, the 95% confidence interval for the RR of death in patients who experienced myocardial re-infarction included the identity line; therefore no conclusion can be drawn from this small subset of patients about the relative benefit with enoxaparin treatment vs UFH. Also, the number of patients considered in this subset is imbalanced between the enoxaparin and the UFH groups reflecting the benefit already observed with enoxaparin in significantly reducing the rate of myocardial re-infarction.

In patients who did *not* experience a myocardial re-infarction, the rate of death was 6.7% in the enoxaparin group compared with 7.4% in the UFH group, corresponding to a 9% reduction in relative risk of death (Table 11) independent of the benefit observed with enoxaparin in significantly reducing the rate of myocardial re-infarction.

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In addition to a significant reduction in the primary efficacy endpoint events, there was also a significant reduction ($p < 0.0001$) in the first and main secondary efficacy variable (the composite of death, myocardial re-infarction or myocardial ischemia leading to urgent revascularization at 30 days) in the enoxaparin group vs the UFH group (Figure 5).

When disabling stroke at 30 days was added to the primary composite endpoint as another secondary efficacy variable, there was also a significant reduction ($p < 0.0001$) in the enoxaparin group compared with the UFH group (Figure 5).

The apparent beneficial effect of enoxaparin compared with UFH was also demonstrated in the tertiary efficacy endpoints, with a consistent trend toward decreased relative risk in the enoxaparin group (Figure 5).

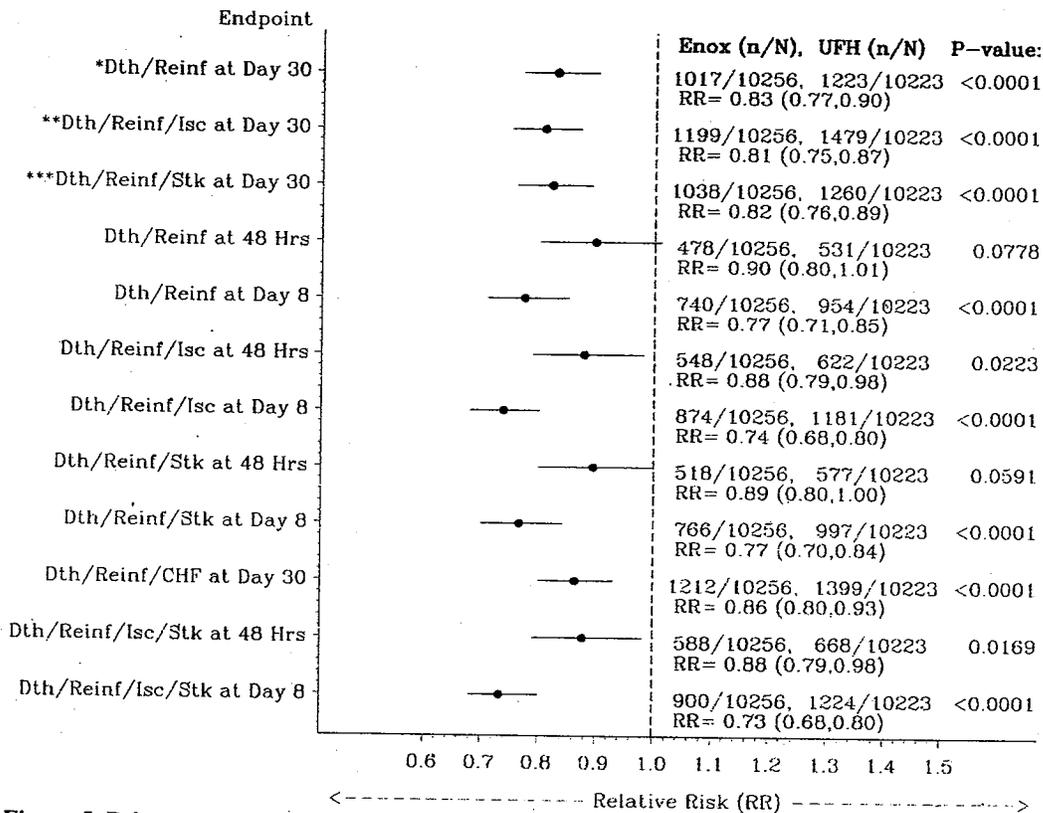


Figure 5 Primary, secondary and tertiary endpoints at 2, 8 and 30 days in ExTRACT-TIMI 25 study
Enox= enoxaparin; n= sample size; N= population size; UFH= unfractionated heparin; Dth= death; Reinf= myocardial re-infarction; RR= relative risk; Isch= myocardial ischemia leading to urgent revascularization; Stk= disabling stroke; CHF= severe congestive heart failure

6.1.4.3 Efficacy findings in subgroups of STEMI patients in the ExTRACT-TIMI 25 trial

The beneficial effect of enoxaparin on the primary end point was consistent across key prespecified sub-groups, and did not differ directionally from the overall effect on the whole study population (Figure 6). All treatment-by-subgroup interaction P-values were not significant at the 10% level.

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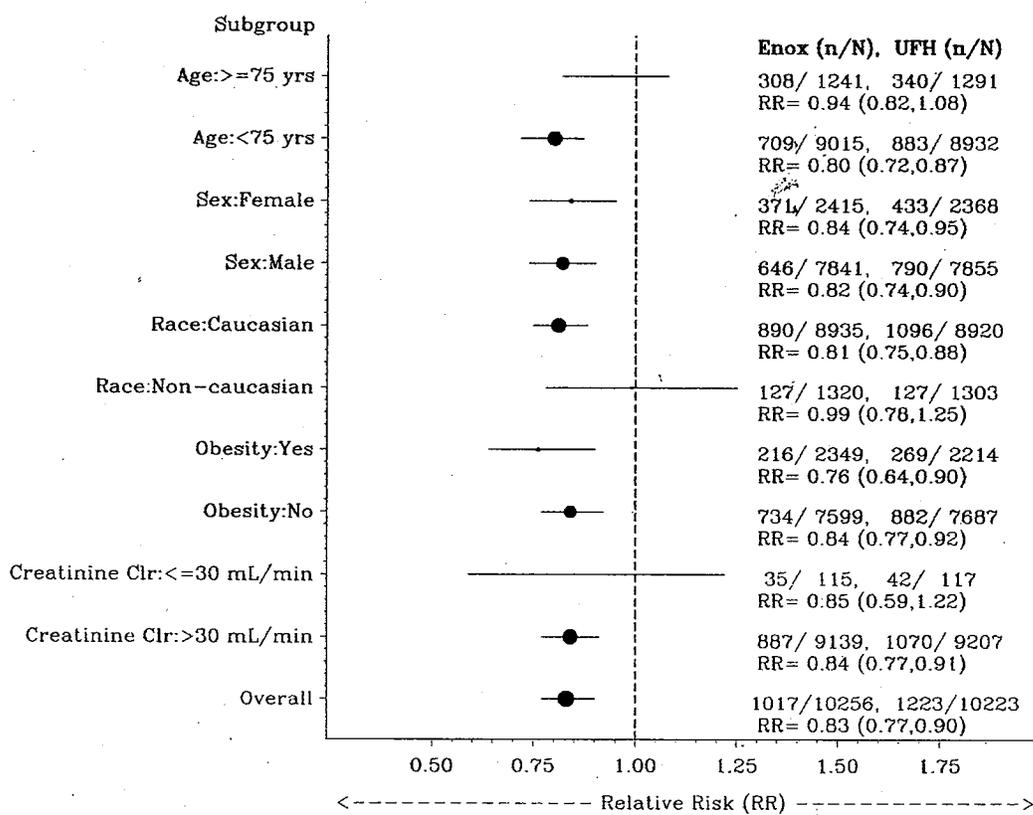


Figure 6 Drug-demographic and drug-disease subgroup analyses for the composite primary efficacy endpoint in the ExTRACT-TIMI 25 study – ITT population

Enox= enoxaparin; n= sample size; N= population size; UFH= unfractionated heparin; RR= relative risk; Clr = clearance

Elderly patients ≥75 years received a lower dose of 0.75 mg/kg sc q 12 hours without an initial IV bolus. The significant treatment benefit of enoxaparin compared with UFH did not differ directionally among elderly patients ≥75 years and those < 75 years old (Figure 6), despite empirical treatment with the low dose regimen of enoxaparin in elderly patients.

The ASSENT 3 study showed that in patients ≥75 years old, enoxaparin carries a risk of bleeding, and that the balance between effectiveness and safety may be less favorable in elderly patients at highest risk of bleeding¹⁵. These elderly patients at risk of bleeding are at increased risk of recurrent CV events and may therefore have the most to benefit from effective adjunctive antithrombotic therapies. In the ExTRACT-TIMI 25 trial, the reduced-dose regimen produced comparable incidences of TIMI major hemorrhages in patients ≥75 years and those <75 years (Please see Figure 13 in Section 7.1.2 of this review).

A very small proportion (enoxaparin 1.2%, UFH 1.3%) had a CrCl ≤30 ml/min indicative of severe impairment and received a lower dose of 30 mg single iv bolus plus a 1 mg/kg sc dose followed by 1 mg/kg sc/day. (1002 patients in enoxaparin group and 899 patients in UFH group had missing CrCl data, and could not be included in the data analysis.) With the exclusion of these 1901 patients in whom the CrCl data is not available, the significant treatment benefit of enoxaparin compared with UFH did not appear to differ directionally among patients with or without severe renal impairment despite treatment with the low dose regimen of enoxaparin for patients with severe renal impairment (Figure 6).

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Table 12 shows that in patients with Killip Class III/IV (severe heart failure or cardiogenic shock), the “beneficial” overall effect of enoxaparin was going in the wrong direction, but the number of patients with Killip Class III/IV were too small to make valid conclusions.

Table 12 Primary efficacy outcome in patients with Killip Class I/II and III/IV heart failure in ExTRACT-TIMI 25 study – ITT population

Killip Class	Enoxaparin n/N (%)	UFH n/N (%)	RR (95% CI)	p-value for interaction ^a
I/II	984/10,147 (9.7)	1195/10,114 (11.8)	0.82 (0.76 – 0.89)	0.0752
III/IV	33/100 (33.0)	28/107(26.2)	1.26 (0.83 – 1.93)	

^aWald test from logistic regression model. ITT= intent-to-treat; n= sample size; N=population size; RR= relative risk; CI = confidence interval.

In the ExTRACT study, the comparison of enoxaparin with UFH for the primary efficacy endpoint did not reveal a treatment by subgroup interaction for most subgroups including PCI in 30 days, type of fibrinolytic agent used, aspirin use, clopidogrel or ticlopidine use, or statin use through Day 8 or hospital discharge (Figure 7).

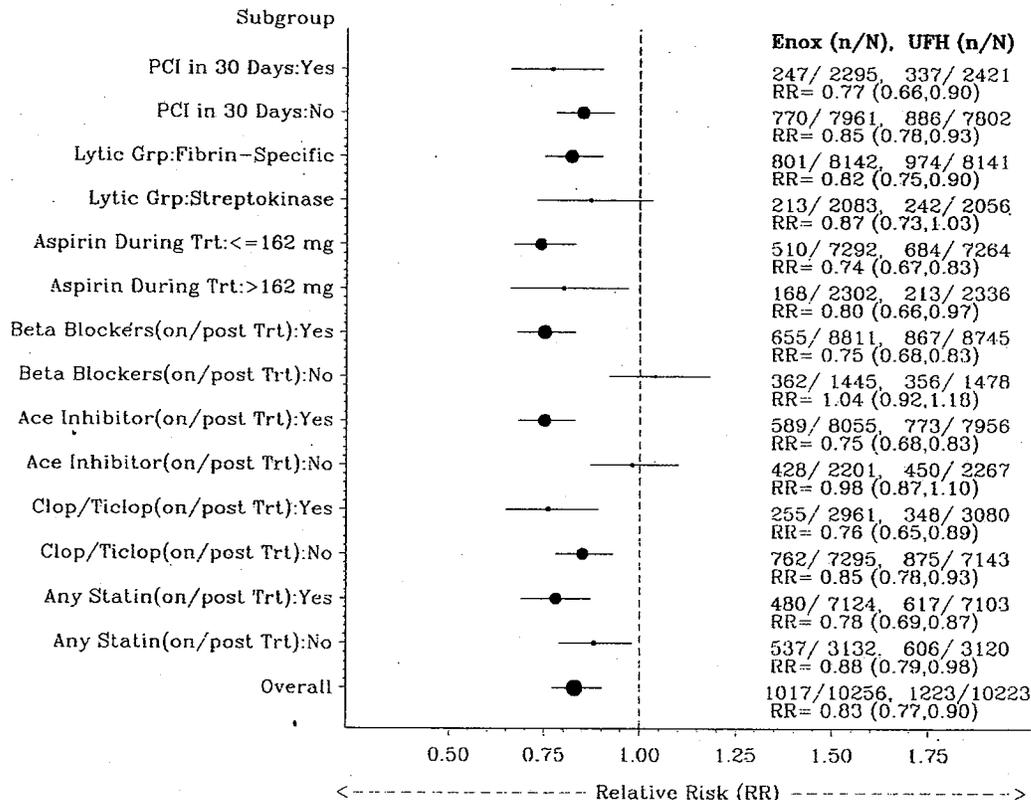


Figure 7 Drug-drug subgroup analyses for the composite primary efficacy endpoint in the ExTRACT-TIMI 25 study – ITT population

Enox= enoxaparin; n= sample size; N= population size; UFH= unfractionated heparin; RR= relative risk; PCI = percutaneous coronary intervention; Grp = group; Trt = treatment; Ace = angiotensin-converting enzyme; Clopidogrel/Ticlopidine = clopidogrel/ticlopidine

In the ExTRACT-TIMI 25 trial, 22.4% (2295 of 10,256) patients in the enoxaparin group and 23.7% (2421 of 10,223) patients in the UFH group underwent PCI within 30 days after randomization. The remaining patients were treated medically. There was a significant

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treatment benefit of enoxaparin as compared with UFH (Figure 7), in patients who underwent PCI within 30 days after randomization (23% reduction in relative risk) as well as those who were treated medically (15% reduction in relative risk).

The European Society of Cardiology recommends that even after successful thrombolysis, patients should routinely undergo coronary angiography and PCI, if applicable¹⁶. At present, there are no randomized trials of LMWH vs UFH in the setting of PCI for patients with STEMI with the exception of limited data below:

- A subgroup analysis of the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial comparing LMWH with UFH in non-ST-elevation acute coronary syndrome in patients treated with an early invasive strategy that excluded patients who switched to a different anticoagulant at the time of randomization suggested that LMWH was more effective than UFH for preventing myocardial infarction or death at 30 days¹⁷.
- The Safety and Efficacy of Enoxaparin in Elective Percutaneous Coronary Intervention (STEEPLE) trial demonstrates that in patients treated by elective PCI, enoxaparin appears to be as effective as, and safer than, UFH¹⁸.

However, most STEMI patients do not undergo primary or even delayed PCI¹⁹. In addition, this week's issue of New England Journal of Medicine published an article which suggested that the long-term survival {all-cause deaths and non-fatal myocardial infarction during a follow-up period of 2.5 to 7.0 years (median, 4.6 years)} in 1149 patients with stable coronary artery disease who underwent PCI and 1138 patients with stable coronary artery disease who received optimal medical therapy alone appear to be the same²⁰.

Thus, I think the ExTRACT-TIMI 25 trial results which showed that enoxaparin produced a significant benefit (reduction in deaths or re-infarction) in patients who underwent PCI as well as those who did not undergo PCI is of clinical relevance to most STEMI patients.

This significant treatment benefit of enoxaparin was also seen in STEMI patients regardless of the type of fibrinolytic treatment (streptokinase, TNK-tPA, reteplase or alteplase), and regardless of concomitant use or non-use of aspirin, clopidogrel or ticlopidine (Figure 7).

This significant treatment benefit of enoxaparin was also seen in patients regardless of concomitant medications these patients were taking for chronic coronary artery diseases, such as statins, with the exception of non-use of ACE inhibitors or β -blockers (Figure 7). The observations in patients not using ACE inhibitors or β -blockers may be biased due to the *post-hoc* nature of the analyses, and the relatively small size of the 2 subgroups of patients.

6.1.4.4 Tertiary efficacy composite endpoint findings in ExTRACT-TIMI 25 trial

Analyses of the tertiary composite endpoints (Table 13) also support the beneficial effect of enoxaparin compared with UFH.

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Table 13 Tertiary composite endpoints in the ExTRACT-TIMI 25 study – ITT population

Parameter	Incidence on enoxaparin n/N (%)	Incidence on UFH n/N (%)	RR enoxaparin versus UFH	95% CI of RR	p-value ^a
Death or myocardial re-infarction at 48 hours	478/10 256 (4.7%)	531/10 223 (5.2%)	0.90	[0.80 - 1.01]	0.0778
Death or myocardial re-infarction at Day 8	740/10 256 (7.2%)	954/10 223 (9.3%)	0.77	[0.71 - 0.85]	<0.0001
Death, myocardial re-infarction or myocardial ischemia leading to urgent revascularization at 48 hours	548/10 256 (5.3%)	622/10 223 (6.1%)	0.88	[0.79 - 0.98]	0.0223
Death, myocardial re-infarction or myocardial ischemia leading to urgent revascularization at Day 8	874/10 256 (8.5%)	1181/10 223 (11.6%)	0.74	[0.68 - 0.80]	<0.0001
Death, myocardial re-infarction or disabling stroke at 48 hours	518/10 256 (5.1%)	577/10 223 (5.6%)	0.89	[0.80 - 1.00]	0.0591
Death, myocardial re-infarction or disabling stroke at Day 8	766/10 256 (7.5%)	997/10 223 (9.8%)	0.77	[0.70 - 0.84]	<0.0001
Death, myocardial re-infarction or severe CHF at Day 30	1212/10 256 (11.8%)	1399/10 223 (13.7%)	0.86	[0.80 - 0.93]	<0.0001
Death, myocardial re-infarction, myocardial ischemia leading to urgent revascularization, or disabling stroke at 48 hours	588/10 256 (5.7%)	668/10 223 (6.5%)	0.88	[0.79 - 0.98]	0.0169
Death, myocardial re-infarction, myocardial ischemia leading to urgent revascularization, or disabling stroke at Day 8	900/10 256 (8.8%)	1224/10 223 (12.0%)	0.73	[0.68 - 0.80]	<0.0001
Death, myocardial re-infarction, myocardial ischemia leading to urgent revascularization, or disabling stroke at Day 30	1220/10 256 (11.9%)	1516/10 223 (14.9%)	0.80	[0.75 - 0.86]	<0.0001

^aPearson's Chi-square or Fisher's Exact test, as appropriate. ITT= intent-to-treat; n= sample size; N=population size; RR= relative risk; CI = confidence interval; CHF= congestive heart failure.

6.1.4.5 Relationship between efficacy and safety endpoints in ExTRACT-TIMI 25 trial

That enoxaparin has an AE profile (TIMI major hemorrhages and ICH, in Table 14) not very different from UFH is not very comforting, because UFH has a worse AE profile than placebo. Comparing enoxaparin against a drug that has a worse safety outcome than placebo makes risk evaluation difficult in the absence of data for comparison with placebo.

Table 14 Bleeding during hospitalization/at 7 days in randomized heparin trials

Bleeding Outcome	Total N	UFH, n/N (%)	Control, n/N (%)	OR (95% CI)*
Minor bleeding	1022	101/516 (19.6%)	63/506 (12.5%)	1.72 (1.22–2.43)
Major bleeding	1231	26/622 (4.2%)	21/609 (3.4%)	1.21 (0.67–2.18)
Bleeding Outcome	Total N	LMWH, n/N (%)	Placebo, n/N (%)	OR (95% CI)*
Minor bleeding†	1272	97/641 (15.1%)	33/631 (5.2%)	3.24 (2.12–4.91)‡
Major bleeding	16842	94/8421 (1.1%)	35/8421 (0.4%)	2.70 (1.83–3.99)
Bleeding Outcome	Total N	LMWH, n/N (%)	UFH, n/N (%)	OR (95% CI)*
Minor bleeding	6393	739/3242 (22.8%)	612/3151 (19.4%)	1.26 (1.12–1.43)
Major bleeding	7093	117/3591 (3.3%)	89/3502 (2.5%)	1.30 (0.98–1.72)

*No statistical heterogeneity for any bleeding outcome unless indicated otherwise. †The CREATE study did not report minor bleeding. ‡P for heterogeneity 0.003. (From: Circulation 2005; 112:3855-67)²³

The American College of Cardiology and the American Heart Association (ACC/AHA) Practice Guidelines introduced the concept of “Net Clinical Benefit” to estimate the

STEMI patient's underlying risk without treatment, the expected benefit (reduction in mortality), and the risk (life-threatening hemorrhage, particularly intracranial hemorrhage) of fibrinolytic therapy¹. The sponsor proposed similar analyses of "Net Clinical Benefit" to obtain a perspective of the benefit and risk of treatment with enoxaparin vs UFH.

Table 15 Net Clinical Benefit at 30 Days* in ExTRACT-TIMI 25 study

Clinical Outcome	Enoxaparin (N = 10,256)	UFH (N = 10,223)	Relative Risk (95% CI)	P value	Absolute Risk Difference (%)
<i>Number (percent)</i>					
Death, nonfatal MI, or nonfatal disabling stroke	1038 (10.1)	1260 (12.3)	0.82 (0.76 – 0.89)	<0.001	2.2%
Death, nonfatal MI, or nonfatal major bleeding	1128 (11.0)	1305 (12.8)	0.86 (0.80 – 0.93)	<0.001	1.8%
Death, nonfatal MI or nonfatal intracranial hemorrhage	1040 (10.1)	1250 (12.2)	0.83 (0.77 – 0.90)	<0.001	2.1%

* The composite end points listed were calculated in a hierarchical fashion in the order shown, and equivalent weight was assigned to each of the three elements. CI = confidence interval, MI = myocardial infarction; UFH = unfractionated heparin.

As shown in Table 15, these "Net Clinical Benefit" endpoints are composites of efficacy and different aspects of safety endpoints (non-fatal disabling stroke, non-fatal major bleeding, and non-fatal intracranial hemorrhage). The relative risks of the three net-clinical-benefit composite endpoints were significantly lower at 30 days in the enoxaparin group than in the UFH group. The range of Absolute Risk Differences (reductions in the absolute event rates) was 1.8 to 2.2% percentage points, corresponding to reductions in the relative risk of 14 to 18% (P < 0.001 for all comparisons, Table 15).

To obtain a more detailed perspective of the STEMI patients who experienced major TIMI hemorrhages and ICH in the context of patients who experienced the composite primary efficacy endpoint events of death and non-fatal myocardial re-infarction, I prepared Venn-diagrams for patients treated with enoxaparin (Figure 8) and those treated with UFH (Figure 9).

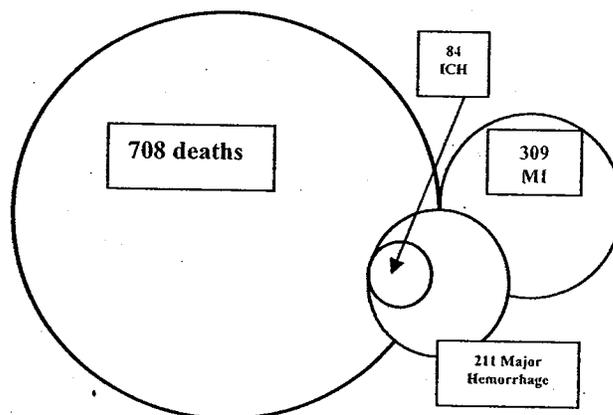


Figure 8 Primary Efficacy and Safety Outcome in STEMI patients on Enoxaparin – ExTRACT-TIMI 25 study

Number of ENOX patients who reached primary efficacy endpoint	= 1017
Number of ENOX patients who reached primary efficacy endpoint + No. with nonfatal major hemorrhage	= 1128
Number of ENOX patients who had non-fatal major hemorrhage only (1128 – 1017 =)	= 111
Number who had both primary efficacy endpoint and major hemorrhage together (211 hemorrhage – 111)	= 100
Number of ENOX patients who reached primary efficacy endpoint + No. nonfatal with ICH	= 1040
Number of ENOX patients who had nonfatal ICH only (1040 – 1017 =)	= 23
Number of ENOX patients who had both primary efficacy endpoint and ICH together (84 ICH – 23)	= 61

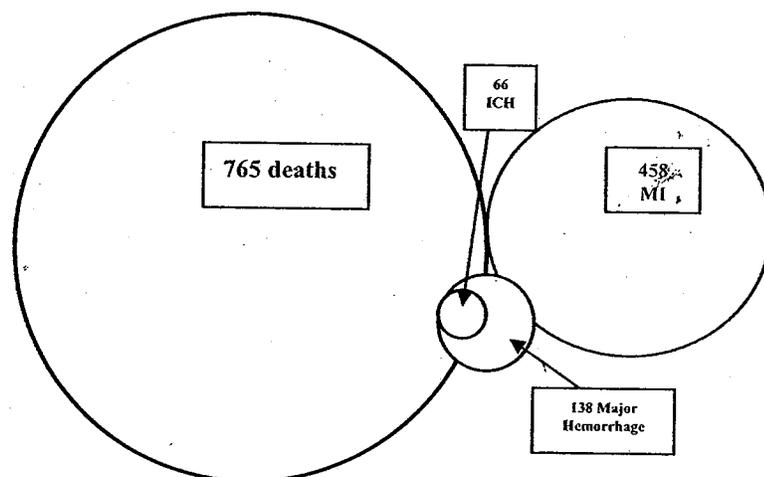


Figure 9 Primary Efficacy and Safety Outcome in STEMI patients on Unfractionated Heparin – ExTRACT-TIMI 25 study

Number of UFH patients who reached primary efficacy endpoint	= 1223
Number of UFH patients who reached primary efficacy endpoint + No. with nonfatal major hemorrhage	= 1305
Number of UFH patients who had nonfatal major hemorrhage only (1305 – 1223 =)	= 122
Number who had <u>both</u> primary efficacy endpoint and major hemorrhage <u>together</u> (138 hemorrhage – 122)	= 16
Number of UFH patients who reached primary efficacy endpoint + No. with nonfatal ICH	= 1250
Number of UFH patients who had nonfatal ICH only (1250 – 1223 =)	= 27
Number of UFH patients who had <u>both</u> primary efficacy endpoint and ICH <u>together</u> (66 ICH – 27)	= 39

In STEMI patients treated with enoxaparin in the ExTRACT-TIMI 25 trial,

Number of enoxaparin patients who reached primary efficacy endpoint (Table 9)	= 1017
No. enoxaparin patients with primary eff. endpoint+ No. with major hemorrhage (Table 15)	= 1128
∴ No of enoxaparin patients who had non-fatal major hemorrhage only (1128 – 1017)	= 111
Total number of enoxaparin patients who had a TIMI major hemorrhage (Table 35)	= 211
∴ No. who had <u>both</u> primary efficacy endpoint and major hemorrhage <u>together</u> (211 – 111)	= 100
No. enoxaparin patients who reached primary efficacy endpoint + No. with ICH (Table 15)	= 1040
∴ Number of enoxaparin patients who had nonfatal ICH only (1040 – 1017)	= 23
Total number of enoxaparin patients who had ICH (Table 35)	= 84
∴ No. who had <u>both</u> primary efficacy endpoint and ICH <u>together</u> (84 – 23)	= 61

In STEMI patients treated with UFH in the ExTRACT-TIMI 25 trial,

Number of UFH patients who reached primary efficacy endpoint (Table 9)	= 1223
No. of UFH patients with primary efficacy endpoint+ No. with major hemorrhage (Table 15)	= 1305
∴ Number of UFH patients who had nonfatal major hemorrhage only (1305 – 1223)	= 122
Total number of UFH patients who had a TIMI major hemorrhage (Table 35)	= 138
∴ No who had <u>both</u> primary efficacy endpoint and major hemorrhage <u>together</u> (138– 122)	= 16
No. of UFH patients who reached primary efficacy endpoint + No. with ICH (Table 15)	= 1250
∴ Number of UFH patients who had nonfatal ICH only (1250 – 1223)	= 27
Total number of UFH patients who had ICH (Table 35)	= 66
∴ No. UFH patients who had <u>both</u> primary efficacy endpoint and ICH <u>together</u> (66– 27)	= 39

The findings in the Venn-diagrams are described below and summarized in Table 16.

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While there are more TIMI major hemorrhages overall in the enoxaparin group (see Table 35, in section 7.1.2 of this review), for patients who experienced non-fatal TIMI major hemorrhages alone, there were *more* patients in the UFH group. In a similar manner, for patients who experienced non-fatal ICH alone, there were *more* patients in the UFH group.

In the UFH group, patients who experienced non-fatal TIMI major hemorrhages or non-fatal ICH constitute a relatively larger proportion of the patients who experienced the safety endpoint (88.4% and 40.9%, respectively), compared to 52.6% and 27.6%, respectively, of patients who experienced the safety endpoint in the enoxaparin group (Table 16).

Table 16 Occurrence of safety and efficacy endpoints together in ExTRACT-TIMI 25 study

Safety and efficacy endpoint	Enoxaparin (N = 10,256)	UFH (N = 10,223)
TIMI major hemorrhages†	211	138
Non-fatal TIMI major hemorrhage <i>alone</i> ‡	111 (52.6%)	122 (88.4%)
TIMI major hemorrhage and a primary efficacy endpoint event <i>together</i>	100 (47.4%)	16 (11.6%)
Intracranial hemorrhage (ICH)†	84	66
Non-fatal ICH <i>alone</i> ‡	23 (27.4%)	27 (40.9%)
ICH and a primary efficacy endpoint event <i>together</i>	61 (72.6%)	39 (59.1%)

† From safety endpoint data in Table 35; ‡ Calculated from data in (Table 15 – Table 9);

§ Calculated from data in {Table 35 – (Table 15 – Table 9)}

On 26-Jan-2007, I requested the sponsor for data in the ExTRACT-TIMI 25 trial to evaluate the relationship of TIMI major hemorrhage and intracranial hemorrhage (ICH) at 30 days to the primary efficacy endpoint events. On 09-Mar-2007, the sponsor provided the following data.

Table 17 Relationship of TIMI major hemorrhage at 30 days to composite primary efficacy endpoint events at 30 days (ITT population)

TIMI Major hemorrhage	Treatment group	N	RR enoxaparin vs UFH				HR enoxaparin vs UFH	
			n (%)	RR [95% C.I.]	RRR	P value ^a	HR [95% C.I.]	P value ^b
<i>Composite primary efficacy endpoint at 30 days</i>								
Absent	Enoxaparin	10045	917 (9.1)	0.79 [0.73-0.86]	0.21	<0.0001	0.78 [0.71-0.85]	<0.0001
	UFH	10085	1167 (11.6)					
Present	Enoxaparin	211	100(47.4)	1.17 [0.91-1.50]	-0.17	0.2106	1.19 [0.86-1.16]	0.2771
	UFH	138	56 (40.6)					
<i>Deaths at 30 days</i>								
Absent	Enoxaparin	10045	628 (6.3)	0.87 [0.79-0.97]	0.13	0.0109	0.87 [0.78-0.97]	0.0115
	UFH	10085	721 (7.1)					
Present	Enoxaparin	211	80 (37.9)	1.19 [0.88-1.60]	-0.19	0.2498	1.22 [0.84-1.76]	0.2892
	UFH	138	44 (31.9)					
<i>Myocardial re-infarction at 30 days</i>								
Absent	Enoxaparin	10045	289 (2.9)	0.65 [0.56-0.75]	0.35	<0.0001	0.64 [0.55-0.74]	<0.0001
	UFH	10085	446 (4.4)					
Present	Enoxaparin	211	20 (9.5)	1.09 [0.55-2.16]	-0.09	0.8043	1.14 [0.56-2.33]	0.7198
	UFH	138	12 (8.7)					

^aPearson's Chi-square or Fisher's Exact test, as appropriate; ^bLog rank test; TIMI = Thrombolysis in Myocardial Infarction, ITT = intent-to-treat, UFH = unfractionated heparin, RR = relative risk, CI = confidence interval, RRR = relative risk reduction; HR = hazard ratio; N = Total number of patients in treatment group; n = number (%) of patients who had the event

In Table 17; TIMI major hemorrhage was consistently associated with a higher risk of death (4 to 6 times) and myocardial re-infarction (2 to 4 times) whether the patients received enoxaparin or UFH.

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The 95% C.I. for the RR of events in patients who experienced TIMI major hemorrhage included the identity line, suggesting that no conclusion could be drawn in the small subsets of patients to compare the relative risk of enoxaparin treatment vs UFH.

The 95% CI for the RR of events in patients who did *not* experience a TIMI major hemorrhage was below the identity line, with a significant relative risk reduction for enoxaparin for all comparisons, indicating the benefit with enoxaparin treatment in the absence of a TIMI major hemorrhage.

In this context, we need to take into consideration the shorter duration of enoxaparin treatment in patients who experienced TIMI major hemorrhage (mean duration of enoxaparin treatment in patients who experienced TIMI major is 3.47±2.83 days vs 6.68±2.39 days in other enoxaparin-treated patients). (Please see also Table 21 and Table 22 showing the relationship of efficacy and safety endpoint events to the duration of enoxaparin and UFH treatment.)

Intracranial hemorrhage (ICH) represents a clinically important component of TIMI major hemorrhages. In Table 18, ICH was consistently associated with a higher risk of death (8 to 10 times more), whether the patients received enoxaparin or UFH. The 95% C.I. for the RR of events in patients who experienced ICH included the identity line, suggesting that no conclusion could be drawn in this subgroup of patients to compare the relative benefit of enoxaparin treatment vs UFH.

The 95% CI for the RR of events in patients who did *not* experience ICH was consistently below the identity line, with a significant relative risk reduction, further suggesting the beneficial effect with enoxaparin treatment in the absence of ICH.

Table 18 Relationship of intracranial hemorrhage at 30 days to composite primary efficacy endpoint events at 30 days (ITT population)

Intracranial hemorrhage	Treatment group	N	RR enoxaparin vs UFH				HR enoxaparin vs UFH	
			n (%)	RR [95% C.I.]	RRR	P value ^a	HR [95% C.I.]	P value ^b
<i>composite primary efficacy endpoint at 30 days</i>								
Absent	Enoxaparin	10172	956 (9.4)	0.81 [0.74-0.87]	0.19	<0.0001	0.80 [0.73-0.87]	<0.0001
	UFH	10157	1184 (11.7)					
Present	Enoxaparin	84	61 (72.6)	1.23 [0.97-1.56]	-0.23	0.0810	1.41 [0.94-2.11]	0.0790
	UFH	66	39 (59.1)					
<i>Deaths at 30 days</i>								
Absent	Enoxaparin	10172	650 (6.4)	0.89 [0.80-0.99]	0.11	0.0275	0.89 [0.80-0.99]	0.0282
	UFH	10157	728 (7.2)					
Present	Enoxaparin	84	58 (60.9)	1.23 [0.95-1.59]	-0.23	0.1013	1.40 [0.93-2.12]	0.0928
	UFH	66	37 (56.1)					
<i>Myocardial re-infarction at 30 days</i>								
Absent	Enoxaparin	10172	306 (3.0)	0.67 [0.58-0.77]	0.33	<0.0001	0.66 [0.57-0.76]	<0.0001
	UFH	10157	456 (4.5)					
Present	Enoxaparin	84	3 (3.6)	1.18 [0.20-6.85]	-0.18	1.0000	1.47 [0.24-8.86]	0.6723
	UFH	66	2 (3.0)					

^aPearson's Chi-square or Fisher's Exact test, as appropriate; ^bLog rank test; ITT = intent-to-treat, UFH = unfractionated heparin, RR = relative risk, CI = confidence interval, RRR = relative risk reduction; HR = hazard ratio; N = Total number of patients in treatment group; n = number (%) of patients who had the event

In this context of subgroup analyses made through post-randomization, we would need to take into consideration the shorter duration of enoxaparin treatment in patients who experienced ICH (mean duration of enoxaparin treatment in patients who experienced ICH is 2.13+/-2.02 days vs 6.65+/-2.41 days in enoxaparin-treated patients).

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In addition, there was a significant interaction between treatment and whether or not the patients experienced ICH within 30 days (Table 19). The 95% confidence interval for the RR of the primary endpoint events in patients who experienced ICH included the identity line; thus, no conclusion could be drawn in this subgroup of patients about the relative benefit with enoxaparin treatment vs UFH.

Table 19 Death or myocardial re-infarction at Day 30 per ICH status (ITT population)

ICH at 30 days	Treatment group	N	Deaths or re-infarction at Day 30		
			N _d (%)	HR 95% C.I.	P value*
Present	Enoxaparin	84	61 (72.6)	1.23 [0.97-1.56]	0.0163
	UFH	66	39 (59.1)		
Absent	Enoxaparin	10172	956 (9.4)	0.81 [0.74-0.87]	
	UFH	10157	1184 (11.7)		

*Wald test from logistic regression model; ICH = intracranial hemorrhage, ITT = intent-to-treat, UFH = unfractionated heparin, CI = confidence interval N = Total number of patients in treatment group; N_d = number (%) of patients who died; HR = hazard ratio

6.1.4.6 Supportive findings

In the ExTRACT-TIMI 25 trial, I found support for the clinical benefit of enoxaparin in STEMI patients from intrinsic findings in the results of the study as well as from extrinsic findings.

The intrinsic findings within the ExTRACT-TIMI 25 trial are:

- the results in the subgroups that did not differ directionally from the overall results for the whole study population,
- the positive findings in the results of the composite secondary efficacy endpoints,
- the positive findings in the results of the composite tertiary efficacy endpoints, and
- the positive results from the “net clinical benefit” evaluation using composites of efficacy and different aspects of safety endpoints (non-fatal disabling stroke, non-fatal major bleeding, and non-fatal intracranial hemorrhage).

An extrinsic finding in partial support of the benefit of enoxaparin is from the primary efficacy endpoint findings in the 6 previous studies of enoxaparin. Of these 6 previous studies, three studies (ASSENT 3, ASSENT 3+ and TETAMI) evaluated clinical endpoints:

- The ASSENT 3 study found a statistically significant ($p = 0.0001$) reduction in the primary efficacy endpoint of a composite of 30-day death or in-hospital re-infarction or in-hospital refractory ischemia (please see Appendix Section 10.1.2.1, Table 55);
- The ASSENT 3+ study found a reduction in the primary efficacy endpoint of a composite of 30-day death or in-hospital re-infarction or in-hospital refractory ischemia (please see Appendix Section 10.1.2.2, Table 58), which was not statistically significant ($P = 0.08$);
- The TETAMI study showed that enoxaparin did not significantly reduce the 30-day incidence of death, myocardial re-infarction and recurrent angina compared with UFH in *non-thrombolized* STEMI patients (please see Appendix Section 10.1.2.6, Table 67 and Table 68).

Another extrinsic finding in support of the efficacy findings in the ExTRACT-TIMI 25 study is the CLARITY-TIMI 28 trial²¹ (LMWH = 1429, UFH = 1431) in which clopidogrel vs placebo was administered to patients in addition to aspirin. Of patients who received

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LMWH, 85% received enoxaparin, and the remaining 15% received nadroparin, dalteparin, tinzaparin or certoparin. The CLARITY-TIMI 28 trial showed that treatment with LMWH was associated with a significantly *lower* rate of

- a closed infarct-related artery or death or myocardial infarction before angiography (13.5% vs 22.5%, adjusted odds ratio (OR) = 0.76, $p = 0.027$), and
- cardiovascular death or myocardial re-infarction through 30 days (6.9% vs 11.5%, adjusted OR = 0.68, $p = 0.030$).

The lower event rates in the LMWH-treated patients were observed in patients allocated to clopidogrel and in those who underwent PCI. Rates of TIMI major bleeding through 30 days (1.6% vs 2.2%, $p = 0.27$) and ICH (0.6% vs 0.8%, $p = 0.37$) were comparable in the LMWH and UFH groups.

Patients who received *both* clopidogrel and LMWH, in addition to a standard fibrinolytic and aspirin, had a high rate of infarct-related artery patency (90.9%) and low rates of cardiovascular death (3.2%), myocardial re-infarction (3.0%) and major bleeding (1.8%).

The CLARITY-TIMI 28 trial showed that in patients with STEMI receiving fibrinolytic therapy, use of LMWH and other standard therapies including aspirin and clopidogrel is associated with improved angiographic outcomes and lower rates of adverse cardiovascular events.

It is likely that three factors may have contributed to the treatment differences observed in the ExTRACT-TIMI 25 trial:

- (i) a superior antithrombotic effect of enoxaparin (which the sponsor would like to attribute to),
- (ii) a longer duration of treatment with enoxaparin, (Because of ease of subcutaneous injection, enoxaparin was administered for the duration of the index hospitalization; this extended treatment duration most likely contributed to a more sustained anti-thrombotic effect.)
- (iii) a possible rebound increase in thrombotic events after the discontinuation of UFH (This post-heparin rebound thrombosis may occur regardless of the duration of the infusion²², and there are no treatment strategies to reduce this rebound thrombosis.)

I do not think it is possible, from the data collected in the ExTRACT-TIMI 25 trial, to determine the relative contribution of each of these 3 factors to the results observed.

6.1.4.7 Efficacy endpoint findings of ExTRACT-TIMI 25 trial in the context of clinical trials of antithrombin agents in STEMI patients

Table 20 shows the relative risk reduction (RRR) and absolute risk difference (ARD) for death at 30 days and non-fatal myocardial re-infarction at 30 days in the ExTRACT-TIMI 25 trial in the context of the RRR and ARD for death and myocardial re-infarction observed in a meta-analysis of clinical trials of antithrombin agents²³. It appears that the RRR and ARD values in the ExTRACT-TIMI 25 trial fall close to the point estimates and within the confidence intervals of the clinical trials of LMWH vs UFH.

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Table 20 Relative risk reduction and absolute risk difference in ExTRACT-TIMI 25 trial in comparison to other trials of anti-thrombin agents

Clinical Endpoint Event	Odd Ratio	C.I.	RRR	ARD
UFH vs Placebo trials				
*Death during hospitalization	1.04	0.62 [†] – 1.78	-4%	-0.23%
*Re-infarction during hospitalization	1.08	0.58 [†] – 1.99	-8%	-0.45%
LMWH vs Placebo trials				
†Death at 30 days	0.86	0.78 – 0.95	14%	1.41%
†Re-infarction at 30 days	0.76	0.62 – 0.93	24%	0.63%
†Death during hospitalization or 7 days	0.90	0.80 – 0.99	10%	0.86%
†Re-infarction during hospitalization or 7 days	0.72	0.58 – 0.90	28%	0.59%
LMWH vs UFH trials				
#Death at 30 days	0.94	0.77 – 1.14	6%	0.42%
#Re-infarction at 30 days	0.65	0.50 – 0.84	35%	1.87%
#Death during hospitalization or 7 days	0.92	0.74 – 1.13	8%	0.48%
#Re-infarction during hospitalization or 7 days	0.57	0.45 – 0.73	43%	2.15%
Enoxaparin vs UFH (ExTRACT-TIMI 25 trial)				
§Death at 30 days	0.92	0.84 – 1.02	8%	0.57%
§Re-infarction at 30 days	0.67	0.58 – 0.77	33%	1.47%
§Death during hospitalization or 8 days	0.92	0.82 – 1.03	8%	0.47%
§Re-infarction during hospitalization or 8 days	0.52	0.43 – 0.62	48%	1.65%

CI= confidence interval; RRR= relative risk reduction; ARD= absolute risk difference; *Results from 4 studies: DUCCS, ECSG, ISIS-2 Pilot, OSIRIS; †Results from 3 studies: AMI-SK, BIOMACS II, CREATE; ‡Results from 3 studies: AMI-SK, CREATE, FRAMI; #Results from 6 studies: ASSENT 3, ASSENT 3 Plus, ENTIRE-TIMI 23, HART II and BAIRD; §ExTRACT-TIMI 25 study. (Calculated from: Circulation 2005; 112:3855-67)²³

In general, LMWH compared with iv UFH reduced the risk of myocardial re-infarction by 33% ~ 43% with no reduction in death. This reduction in the risk of re-infarction with LMWH vs UFH is also consistent with the findings in clinical trials of UFH vs placebo (no reduction in re-infarction) and LMWH vs placebo (24% ~ 28% reduction in re-infarction).

It is interesting to find that in Table 20, LMWH provides an even greater reduction in re-infarction in the active comparator trials (i.e., vs UFH; 33% ~ 43% reduction), than when LMWH is compared with placebo (24% ~ 28%). The following are possible explanations:

- First, I do not think one can assume that UFH is worse than placebo with regard to re-infarction; the comparisons between UFH and placebo were on small numbers of patients only, and therefore they were severely underpowered (Please see Table 46 in Section 8.6, Literature Review).
- Secondly, a larger effect size in the LMWH vs UFH compared to LMWH vs placebo as shown in Table 20 could have been due to a diagnostic suspicion bias because all of the trials comparing LMWH with placebo were double-blind (Please see Table 47 in Section 8.6, Literature Review) whereas all of the LMWH vs UHF trials referred to in the meta-analysis were open-label (Please see Table 51 in Section 8.6, Literature Review). The confidence intervals for point estimates from the pooled analyses of these two groups of trials overlap; thus, the apparent difference in the results for re-infarction could be due to chance.
- Third, UFH vs control trials were conducted during 1987-1994, and LMWH vs placebo trials were conducted during 1997-2005. Substantial changes in the way myocardial re-infarction is diagnosed could have limited the ability of earlier trials to reliably detect a treatment effect.
- Fourth, LMWH vs placebo trials involved the use of first-generation thrombolytic

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agents (streptokinase), whereas direct comparisons between LMWH and UFH were performed primarily in patients treated with more fibrin-specific thrombolytic agents (such as tenecteplase, alteplase, and, in the ExTRACT-TIMI 25 trial, reteplase also).

6.1.4.8 Efficacy and safety endpoint findings in ExTRACT-TIMI 25 trial in relation to the duration of treatment with enoxaparin and UFH

Table 21 shows the frequencies of efficacy and safety endpoint events according to the duration of treatment with enoxaparin for STEMI patients in the enoxaparin-treated group.

Table 21 Efficacy and safety endpoint events in relation to the duration of enoxaparin treatment in ExTRACT-TIMI 25 trial – ITT population

Duration (Days) of enoxaparin treatment	Total patients in group N	Primary efficacy endpoint n (%)	Secondary efficacy endpoint n (%)	Deaths n (%)	Non-fatal MI n (%)	Urgent revascularization n (%)	Disabi stroke n (%)	ICH n (%)	TIMI major hemorrhage n (%)
≤1 day	991	450 (45.4)	487 (49.1)	395 (39.9)	55 (5.5)	84 (8.5)	No data	No data	99 (10.0)
>1 – 2 days	317	87 (27.4)	99 (31.2)	69 (21.8)	18 (5.7)	23 (7.5)	No data	No data	30 (9.5)
>2 – 3 days	433	60 (13.9)	77 (17.8)	35 (8.1)	25 (5.8)	32 (7.4)	No data	No data	12 (2.8)
>3 – 4 days	579	45 (7.8)	58 (10.0)	33 (5.7)	1 (2.1)	21 (3.6)	No data	No data	10 (1.7)
>4 – 5 days	745	50 (6.7)	63 (8.5)	27 (3.6)	23 (3.1)	25 (3.4)	No data	No data	11 (1.5)
>5 – 6 days	668	43 (6.4)	56 (8.4)	23 (3.4)	20 (3.0)	17 (2.5)	No data	No data	9 (1.3)
>6 – 7 days	2876	120 (4.2)	148 (5.1)	60 (2.1)	60 (2.1)	40 (1.4)	No data	No data	16 (0.6)
>7 – 8 days	3338	129 (3.9)	169 (5.1)	46 (1.4)	83 (2.5)	51 (1.5)	No data	No data	21 (0.6)
>8 days	126	10 (7.9)	12 (9.5)	3 (2.4)	7 (5.6)	5 (4.0)	1 (0.8)	No data	1 (0.8)
Missing	95	14 (14.7)	20 (21.1)	10 (10.5)	4 (4.2)	10 (10.5)	No data	No data	1 (1.1)
Not received	10311	1232 (11.9)	1489 (14.4)	772 (7.5)	460 (4.5)	466 (4.5)	98 (1.0)	66 (0.6)	130 (1.3)

ITT = intent-to-treat; Enox = enoxaparin, MI = myocardial infarction, TIMI = Thrombolysis in Myocardial Infarction
N = total number of patients in treatment group; n = number of patients who reached an endpoint event

The rates of both the efficacy and the safety endpoint events were highest in patients who received enoxaparin treatment for only 2 days or less, suggesting that this subset of population probably required interruption of treatment following either a non-fatal myocardial re-infarction or a TIMI major hemorrhage (including ICH). It is possible that some of these patients who stopped enoxaparin within 2 days might have had an urgent revascularization performed subsequent to discontinuation of enoxaparin treatment.

On the other hand, the majority of patients who received enoxaparin treatment for a longer – protocol-specified – duration showed lower event rates, both for efficacy and for major safety endpoints, suggesting that the benefits with enoxaparin are observed when treatment is given per protocol.

Table 22 shows the frequencies of efficacy and safety endpoints events according to the duration of treatment with UFH for STEMI patients in the UFH-treated group:

The rates of both efficacy and safety endpoint events were highest in patients who received UFH treatment for only 1 day or less, indicating a subset of the patient population who interrupted treatment following either a non-fatal myocardial re-infarction or a TIMI major hemorrhage (including ICH). Subsequent to this UHF study drug discontinuation, an urgent revascularization may have been performed, or an open-label treatment may have been used, similar to that discussed (above) for patients who received enoxaparin treatment for only 2 days or less in the enoxaparin-treated group.

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Table 22 Efficacy and safety endpoint events in relation to the duration of UFH treatment in ExTRACT-TIMI 25 trial – ITT population

Duration (Days) of UFH treatment	Total patients in group N	Primary efficacy endpoint n (%)	Secondary efficacy endpoint n (%)	Deaths n (%)	Non-fatal MI n (%)	Urgent revascularization n (%)	Disabling stroke n (%)	ICH n (%)	TIMI major hemorrhage n (%)
≤1 day	903	431 (47.7)	464 (51.4)	359 (39.8)	72 (8.0)	103 (11.4)	56 (6.2)	46 (5.1)	75 (8.3)
>1 – 2 days	3712	309 (8.3)	389 (10.5)	180 (4.8)	129 (3.5)	129 (3.5)	22 (0.6)	11 (0.3)	22 (0.6)
>2 – 3 days	4239	298 (7.0)	377 (8.9)	148 (3.5)	150 (3.5)	140 (3.3)	11 (0.3)	6 (0.1)	26 (0.6)
>3 days	1241	162 (13.3)	216 (17.4)	61 (4.9)	101 (8.1)	83 (6.7)	6 (0.5)	3 (0.2)	13 (1.0)
Missing	49	8 (16.3)	13 (26.5)	5 (10.2)	3 (6.1)	5 (10.2)	0	0	2 (4.1)
Not received	10335	1032 (10.0)	1219 (11.8)	720 (7.0)	312 (3.0)	314 (3.0)	82 (0.8)	84 (0.8)	211 (2.0)

ITT = intent-to-treat; UFH = unfractionated heparin; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; ICH = intracranial hemorrhage; N = total number of patients in treatment group; n = number of patients who reached an endpoint event

In contrast to enoxaparin-treated patients (Table 21), patients who received UFH treatment for >3 days showed **higher** rates of efficacy endpoints (Table 22). If the lack of continued anti-thrombin therapy (when UFH was stopped at 48 hours) might have contributed to a relative increase in the efficacy endpoint events, then it is difficult to understand why patients who continued to receive UFH for a longer duration had increase rates of primary and secondary endpoint events. This finding appears to support the duration of UFH treatment (48 hours) for STEMI as recommended by the current ACC/AHA guidelines¹.

6.1.4.9 Findings at long-term follow-up (6 months and 1 year)

Most subjects in each treatment group completed the follow-up period (except those who died before 12 months, Table 23).

Table 23 Summary of subject completion status at 12 months – ITT population

Study treatment completion status ^a	Treatment randomized		
	All N=20 479 (%)	Enoxaparin N=10 256 (%)	UFH N=10 223 (%)
Number of subjects			
Completed 12-month follow-up	18 160 (88.7)	9098 (88.7)	9062 (88.6)
Discontinued study ^b	2312 (11.3)	1155 (11.3)	1157 (11.3)
Primary reason for discontinuation from 12-month follow-up period			
Lost to follow-up	107 (4.6)	57 (4.9)	50 (4.3)
Death ^c	2115 (91.5)	1055 (91.3)	1060 (91.6)
Subject did not wish to continue	25 (1.1)	10 (0.9)	15 (1.3)
Other reason	61 (2.6)	31 (2.7)	30 (2.6)

^aDenominator used for the following calculations: completed study and discontinued study;

^bDenominator used for the following calculations: primary reasons for discontinuation

^cDeath counts relative to disposition at 12 months represent the primary reason for discontinuation only.

ITT = intent-to-treat; N = population size; UFH = unfractionated heparin

For patient outcomes at follow up based on the patient's status following treatment in the first 30 days, the sponsor submitted that the *post-hoc* analyses required that time zero be reset beyond the 30-day period. This would introduce bias since the patient populations at the non-randomized time zero had already been influenced by the earlier beneficial effects observed with enoxaparin. In this case, the enoxaparin group would be enriched with a larger number of higher risk patients who had survived in the first 30 days.

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The sponsor also presented 6-month and 1-year survival data as Kaplan-Meier curves on all randomized patients, which is probably less biased. I will present these Kaplan-Meier curves first, followed by analyses of the endpoint-specific follow-up data.

There was a statistically significant difference ($p = 0.0111$, log-rank test, HR = 0.92) in favor of the enoxaparin group vs the UFH group with respect to *time to death or myocardial re-infarction at 12 months* as assessed by survival analysis (log-rank test) (Figure 10 and Table 24). The separation of the 2 survival curves in Figure 10, observed at 30 days after randomization, was maintained throughout the 12-month follow-up period.

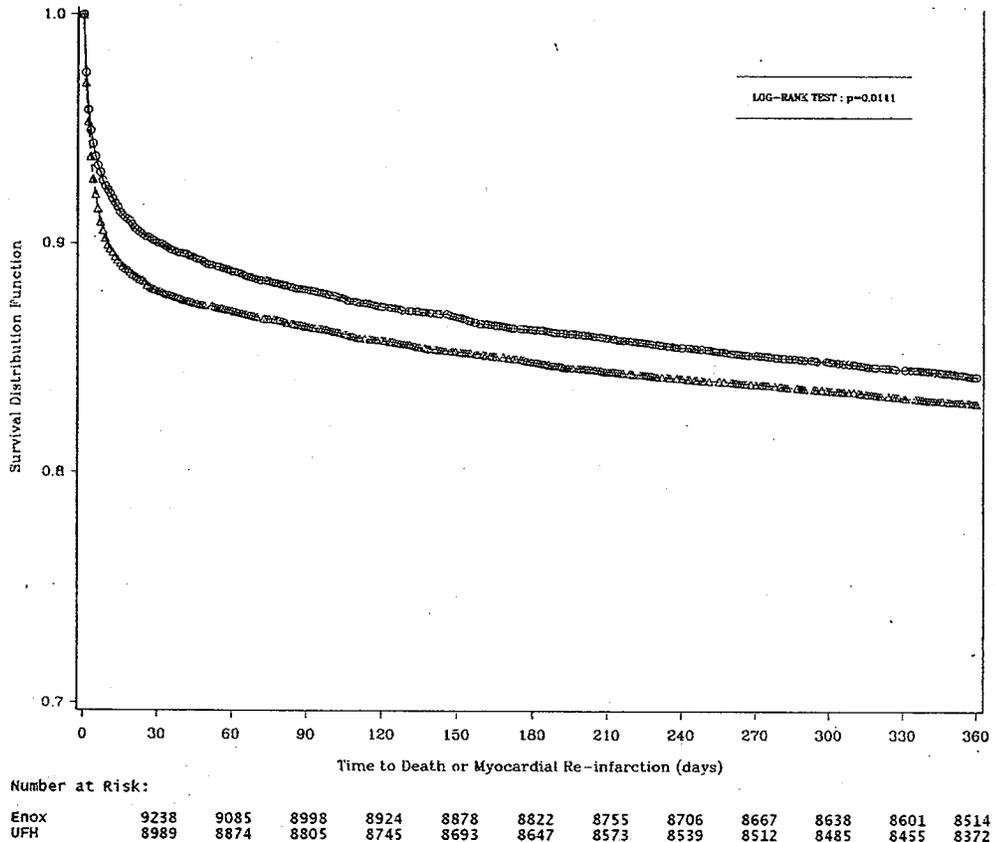


Figure 10 Kaplan-Meier plot - death or myocardial re-infarction at 12 months - ITT population

ITT = intent-to-treat; Enox = enoxaparin; UFH = unfractionated heparin

Table 24 Time to main clinical endpoint at 6 and 12 months - ITT population

Parameter	Enoxaparin		UFH		Enox vs UFH hazard ratio	95% CI of HR	p-value ^a
	N	n	N	n			
Death or myocardial re-infarction, 6 month	10 256	1403	10 223	1545	0.89	[0.83 - 0.96]	0.0020
Death or myocardial re-infarction, 12 months	10 256	1614	10 223	1732	0.92	[0.86 - 0.98]	0.0111

^alog-rank test; ITT = intent to treat population; UFH = unfractionated heparin; Enox = enoxaparin, vs = versus, N = population size; n = sample size; CI = confidence interval; HR = hazard ratio

There was a statistically significant difference ($p = 0.0069$, log-rank test, HR = 0.91) in favor of the enoxaparin group compared with the UFH group with respect to time to death,

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myocardial re-infarction or disabling stroke at 12 months as assessed by survival analysis (log-rank test) (Figure 11 and Table 25).

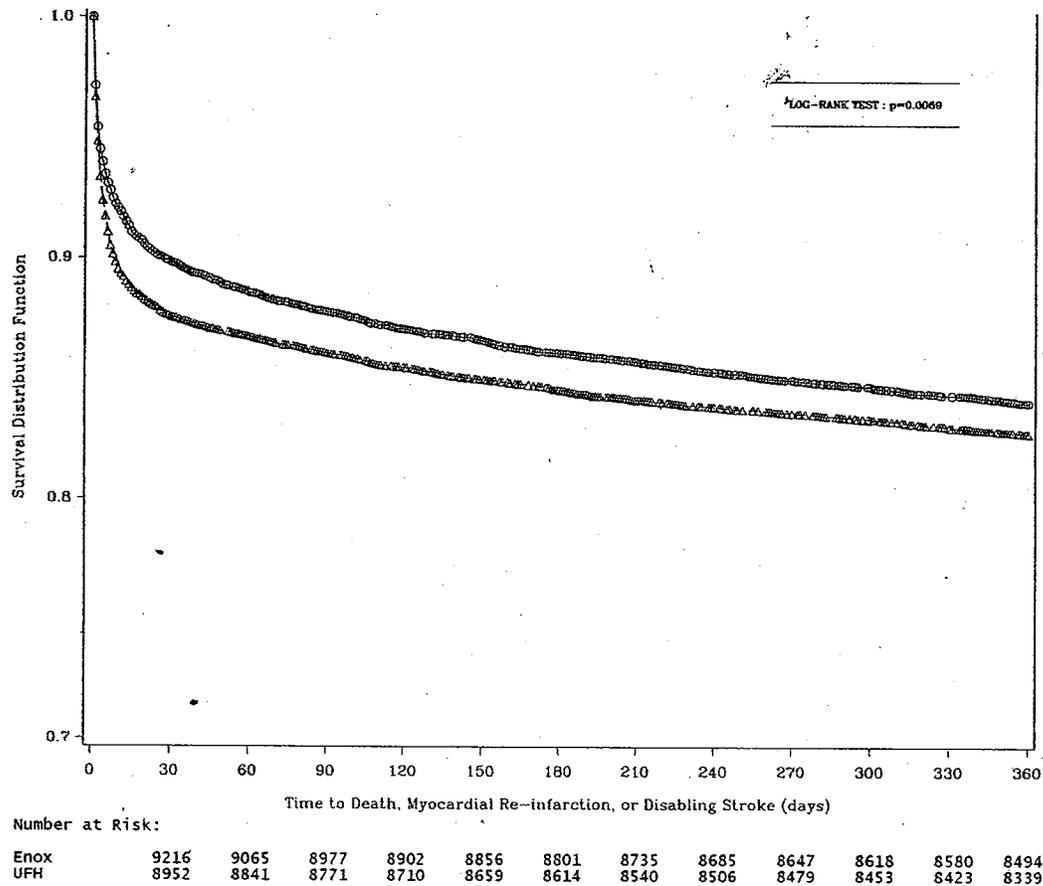


Figure 11 Kaplan-Meier plot – death, myocardial re-infarction or disabling stroke at 12 months - ITT population

ITT = intent-to-treat; Enox = enoxaparin; UFH = unfractionated heparin

Table 25 Time to clinical endpoint of death, re-infarction or disabling stroke at 6 and 12 months - ITT population

Parameter	Enoxaparin		UFH		Enox vs UFH Hazard ratio	95% CI of HR	p-value ^a
	N	n	N	n			
Death or myocardial re-infarction, or disabling stroke, 6 months	10 256	1425	10 223	1578	0.89	[0.83 - 0.95]	0.0010
Death or myocardial re-infarction, or disabling stroke, 12 months	10 256	1638	10 223	1765	0.91	[0.85 - 0.98]	0.0069

^alog-rank test; ITT = intent to treat population; UFH = unfractionated heparin; Enox = enoxaparin, vs = versus, N = population size; n = sample size; CI = confidence interval; HR = hazard ratio

A Kaplan-Meier plot for all-cause death at 12 months in Figure 12 shows that the two survival curves are quite close at 1-3 months, and stay close together for the remainder of the year.

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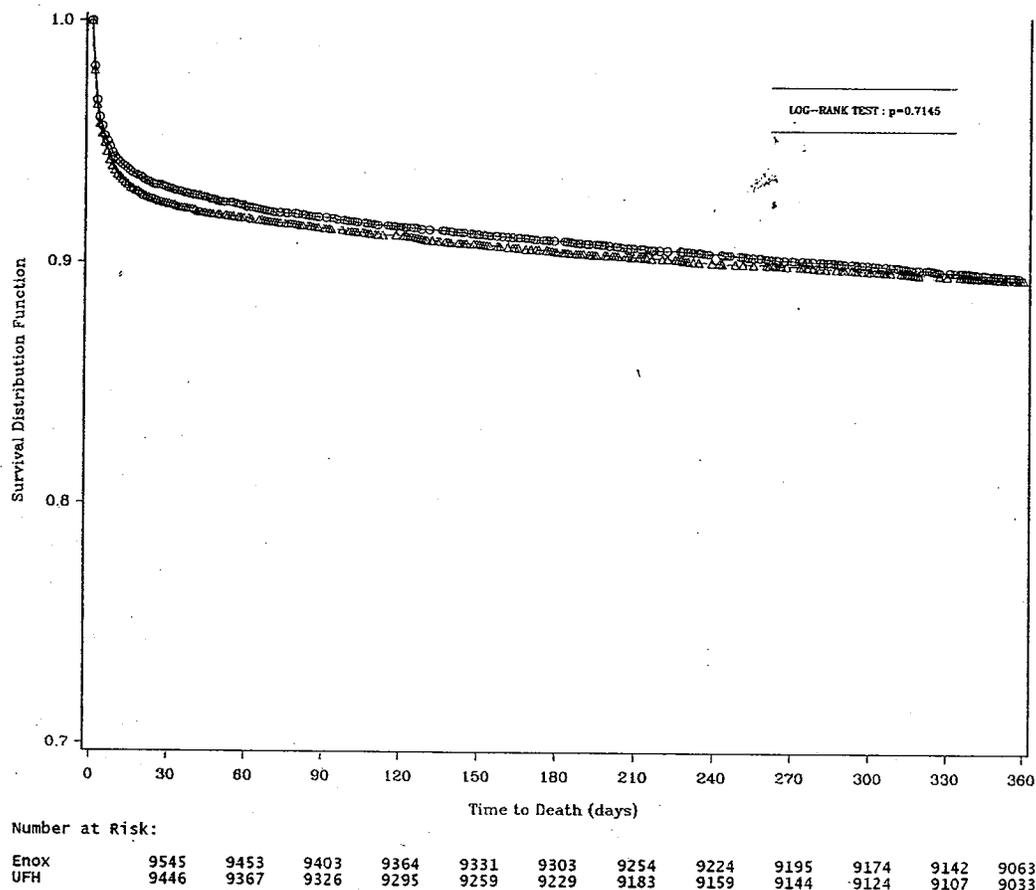


Figure 12 Kaplan-Meier plot – death at 12 months - ITT population
 ITT = intent-to-treat; Enox = enoxaparin; UFH = unfractionated heparin

Table 26 Time to individual endpoint components at 6 and 12 months (ITT population)

Parameter	Enoxaparin		UFH		Enox vs UFH Hazard ratio	95% CI of HR	p-value ^a
	N	n	N	n			
Death, 6 months	10 256	923	10 223	968	0.95	[0.87 – 1.04]	0.2360
Death, 12 months	10 256	1075	10 223	1085	0.98	[0.90 – 1.07]	0.7145
Myocardial re-infarction, 6 months	10 256	572	10 223	681	0.82	[0.74 – 0.92]	0.0006
Myocardial re-infarction, 12 months	10 256	666	10 223	775	0.84	[0.76 – 0.94]	0.0013
Disabling stroke, 6 months	10 256	93	10 223	108	0.86	[0.65 – 1.13]	0.2732
Disabling stroke, 12 months	10 256	112	10 223	115	0.97	[0.75 – 1.26]	0.8121
Re-hospitalization, 6 months	10 256	2361	10 223	2233	1.05	[0.99 – 1.12]	0.0788
Re-hospitalization, 12 months	10 256	2873	10 223	2742	1.05	[0.99 – 1.10]	0.0849

^alog-rank test ITT = intent to treat population; UFH = unfractionated heparin; Enox = enoxaparin, N = population size; n = sample size; CI = confidence interval; HR = hazard ratio

Table 26 shows the Kaplan-Meier failure rate estimates for the composite endpoint of death, myocardial re-infarction, or disabling stroke at 6 and 12 months.

Significant treatment differences in favor of enoxaparin were seen with respect to *time to*

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myocardial re-infarction at 6 months ($p = 0.0006$) and 12 months ($p = 0.0013$). The differences between treatment groups with respect to *time to death or disabling stroke alone* were not significant. The above analyses included ALL randomized patients from randomization to 6 or 12 months. Thus, the advantage that enoxaparin had on deaths and myocardial re-infarction during the 30 days could obscure any difference in long term outcome of these patients.

I took a different perspective on the above follow up data:

- first by evaluating long term outcome on all surviving patients (i.e., removing all deaths in the first 30 days), and
- secondly by evaluating long term outcome on patients who did not experience a primary efficacy endpoint event (i.e., removing the advantage that enoxaparin had on deaths and myocardial re-infarction during the 30 days).

The primary efficacy endpoint events at 6 months and 12 months follow up in all surviving patients (i.e., excluding all deaths during the first 30 days) are shown in Table 27.

Table 27 Efficacy endpoints at 6 and 12 months follow up in patients surviving at 30 days (ITT population)

Event at	Treatment group	N	Deaths			Myocardial re-infarction			Disabling stroke		
			n (%)	HR [95% C.I.]	P value ^a	n (%)	HR [95% C.I.]	P value ^a	n (%)	HR [95% C.I.]	P value ^a
Six month	Enoxaparin	9548	215 (2.3)	1.05 [0.87-1.28]	0.5899	226 (2.4)	1.20 [0.99-1.46]	0.0653	12 (0.1)	0.99 [0.45-2.21]	0.9833
	UFH	9548	203 (2.1)			187 (2.0)			12 (0.1)		
Twelve month	Enoxaparin	9548	367 (3.8)	1.14 [0.98-1.33]	0.0831	326 (3.4)	1.13 [0.96-1.32]	0.1415	32 (0.3)	1.67 [0.95-2.95]	0.0721
	UFH	9548	319 (3.4)			288 (3.0)			19 (0.2)		

^aLog rank test; ITT = intent-to-treat, UFH = unfractionated heparin, CI = confidence interval, HR = hazard ratio; N = Total number of patients in treatment group; n=number (%) of patients who had the event

The sponsor contended that the above post-hoc analyses may be biased (because of the earlier effect on deaths observed with enoxaparin and UFH, thereby apparently enriching the enoxaparin group with a larger number of higher risk patients).

I think it is interesting to note that the separation in survival curves seen for the composite endpoint (Figure 10) and for deaths, myocardial re-infarction or disabling stroke (Figure 11) is not supported (by the findings in Table 27) when deaths within the first month were excluded from follow up data.

The primary efficacy endpoint events at 6 months and 12 months follow-up in patients who did not experience a primary efficacy endpoint event (i.e., removing the advantage that enoxaparin had on deaths and myocardial re-infarction during the 30 days) are shown in Table 28.

Table 28 Efficacy endpoints at 6 and 12 months follow up in patients who did not experience a primary efficacy endpoint event at 30 days (ITT population)

Event at	Treatment group	N	Deaths			Myocardial re-infarction		
			n (%)	HR [95% C.I.]	P value ^a	n (%)	HR [95% C.I.]	P value ^a
Six month	Enoxaparin	9239	207 (2.2)	1.13 [0.92-1.38]	0.2396	219 (2.4)	1.24 [1.02-1.52]	0.0317
	UFH	9000	179 (2.0)			172 (1.9)		
Twelve month	Enoxaparin	9239	349 (3.8)	1.18 [1.01-1.38]	0.0337	313 (3.4)	1.15 [0.98-1.36]	0.0885
	UFH	9000	288 (3.2)			266 (3.0)		

^aLog rank test; ITT = intent-to-treat, UFH = unfractionated heparin, CI = confidence interval, HR = hazard ratio; N = Total number of patients in treatment group; n = number (%) of patients who had the event

There is a statistically significant excess of deaths at 12 months, and a statistically significant excess of myocardial re-infarction at 6 months among patients in the enoxaparin group who did *not* experience a primary efficacy endpoint event during the first month. The sponsor attributed this finding to the biased nature of the *post-hoc* analysis that does not take into account the early benefit favoring enoxaparin, and that there was a larger number of patients in the enoxaparin subgroup than in the UFH subgroup (Table 28).

The data in Table 28 suggests that after the early benefit observed during the first 30 days with enoxaparin, there was no further reduction in myocardial re-infarction and no survival benefit at 6 months and 12 months, respectively. This data suggests that the beneficial effect of enoxaparin over UFH in STEMI patients is probably limited to the first 30 days.

The sponsor suggested also that patients who died between Day 30 and Month 12 in the enoxaparin-treated group were older (65.7 years ± 11.70 standard deviation (SD) vs 59.8 years ± 11.93 SD in the overall population) and at higher risk (TIMI score 4.3 ± 2.15 SD vs 2.9 ± 2.07 SD in the overall population). However, the two treatment groups were well-matched with regard to demographics at enrollment, including age and TIMI score.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

The ExTRACT-TIMI 25 trial was a large trial (20,506 patients) with relatively large numbers of events. The trial demonstrates a clinical benefit (reduction in the composite primary efficacy endpoint of deaths and non-fatal myocardial re-infarction) with a very high statistically significant “p” value. The primary efficacy findings in support of the proposed indication are as follows:

At 30 days,

- the rate of the primary efficacy endpoint (death or non-fatal myocardial re-infarction) was 9.9% in the enoxaparin group vs 12.0% in the UFH group (17% reduction in the relative risk, P<0.000003, Table 9),
- the all-cause death rate was 6.9% in the enoxaparin group vs 7.5% in the UFH group

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(8% reduction in relative risk; P = 0.11, Table 9), and

- the rate of non-fatal myocardial re-infarction was 3.0% in the enoxaparin group vs. 4.5% in the UFH group (33% reduction in the relative risk; P<0.001, Table 9).

The time-to-composite-endpoint (of death or non-fatal myocardial re-infarction) also showed a statistically significant reduction in the enoxaparin group compared to the UFH treatment group (HR = 0.83, 95% CI 0.77 – 0.90, P<0.001; Figure 4A).

The treatment benefit of enoxaparin became evident at 48 hours, and was significantly positive at Day 8 and at Day 30 (Table 9 and Figure 4A).

The robustness of this clinical benefit of treatment with enoxaparin is supported by:

- consistent positive findings across pre-specified subgroups of
 - age (<75 years vs ≥75 years, Figure 6),
 - both male and female gender (Figure 6),
 - presence of obesity (Figure 6),
 - presence of severe renal function impairment (Figure 6),
 - treatment with PCI or medical treatment (Figure 7),
 - type of fibrinolytic agent used (Figure 7),
 - concomitant medications with the exception of non-use of β-blockers (Figure 7) and
 - Killip Class I/II heart failure {with the exception of severe heart failure or cardiogenic shock (Killip Class III/IV; Table 12)};
- positive findings in the composite secondary efficacy endpoint (Figure 4B and Table 9) and
- positive findings in the tertiary composite endpoints (Table 13).

A review of randomized clinical trials that evaluated the effects of anti-thrombin therapy in patients with STEMI showed that risk reduction for death and myocardial re-infarction with UFH was observed only in patients who were *not* routinely receiving aspirin; for patients treated with aspirin, UFH failed to demonstrate a similar reduction in mortality^{10,23}. (Please see Table 46 and Figure 17 in section “8.6 Literature Review” of this review.)

I think the finding in the ExTRACT-TIMI 25 trial (where aspirin use was 94.8% and 95.4% in enoxaparin and UFH groups, respectively) that enoxaparin produced a “statistically significant” reduction in relative risks of clinical events (all-cause death and non-fatal myocardial re-infarction at 30 days) compared to UFH can be regarded as showing that enoxaparin is better than placebo. This finding in the ExTRACT-TIMI 25 trial cannot be construed as showing that enoxaparin is better than a proven “efficacious” treatment.

The beneficial effect of enoxaparin on death and myocardial re-infarction appears to be limited to 30 days post-randomization:

- First, the Kaplan-Meier curves for death at 12 month for the enoxaparin and UFH treatment groups appear to run *closely* together (Figure 12). This observation is also found in the long-term results of the ASSENT 3 study (please see Figure 23 in Section 10.1 Appendix, subsection 10.1.2.1 ASSENT 3 Study).
- Secondly, despite the sponsor’s contention that the separation of the survival curves for

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(a) death and myocardial re-infarction at 12 month (Figure 10), and (b) death, myocardial re-infarction and disabling stroke at 12 month (Figure 11) was maintained over the 12-month period, this effect appears to be due mainly to the beneficial effect of enoxaparin observed during the first 30 days. Analysis of clinical events at 6-months and 12-months showed an excess of deaths and myocardial re-infarction when:

- (i) deaths at day 30 post-randomization were excluded (Table 27), and
- (ii) patients who experienced the composite primary efficacy endpoint of death or myocardial re-infarction at 30 days were excluded (Table 28).

In conclusion, it appears from an efficacy perspective that the ExTRACT-TIMI 25 trial shows a statistically significant relative risk reduction (RRR) and the absolute risk difference (ARD) in myocardial re-infarction or deaths during the first 30 days of treatment in STEMI patients treated with a regimen of sc enoxaparin compared to the standard therapy of 48 hours of UFH as adjunctive antithrombin therapy to support fibrinolysis. This beneficial effect of enoxaparin on death and myocardial re-infarction appears to be limited to 30 days post-randomization, which should be mentioned in the labeling.

Thus, I recommend an **approval** consideration of enoxaparin as an adjunct for antithrombin treatment of patients with STEMI based on a large, simple trial in which clinically relevant benefits were observed with enoxaparin over UFH (a comparator drug, which has not been shown to have a beneficial effect over placebo in this population of STEMI patients who routinely receive aspirin).

APPEARS THIS WAY ON ORIGINAL

7. INTEGRATED REVIEW OF SAFETY

The data supporting the use of enoxaparin in patients with acute STEMI are provided by the safety results of 1 pivotal study (ExTRACT-TIMI 25) and 6 supportive studies: ASSENT 3, ASSENT 3+, ENTIRE-TIMI 23, HART II, AMI-SK, and TETAMI studies. The overall safety population is shown in Table 29.

Table 29 Safety populations of clinical trials of enoxaparin in patients with STEMI

Study	Enoxaparin-treated patients ^a	UFH-treated patients ^b	Placebo-treated patients
ASSENT 3	2019	3970	--
ASSENT 3+	818	821	--
ENTIRE	324	159	--
HART II	191	189	--
AMI-SK	252	--	239
TETAMI	544	554	--
Sub-total	4128	5673	239
ExTRACT	10,176	10,151	
Patients ≥75 years	1232	1281	
Severe renal dysfunction ^c	115	118	
Total Safety population	14,304	15,824	239

UFH = unfractionated heparin; sc = subcutaneous; iv = intravenous

^a Enoxaparin-treated patients include any patient who received at least 1 dose of sc enoxaparin (0.3, 0.75, or 1.0 mg/kg), ± initial enoxaparin 30 mg iv bolus, and ± sc/iv bolus fibrinolytic medication or ± placebo.

^b UFH-treated patients include any patient who received at least 1 dose of sc UFH (initial 60U/kg iv bolus or various doses followed by continuous infusion adjusted to aPTT), and ± iv bolus/sc fibrinolytic medication or ± placebo. Some patients in ASSENT 3 were treated with UFH + abciximab.

^c Severe renal dysfunction = CrCl ≤30 mL/min calculated with the Cockcroft and Gault formula

The cut-off date for data inclusion in this submission is 27 January 2006, when the 30-day database for the ExTRACT study was locked.

7.1 Methods and Findings

The sponsor made no integration of safety data from the ExTRACT study and the 6 previous studies; the reason provided was substantial differences in study design characteristics of the 6 previous studies (e.g., double-blind vs open-label, treatment regimens, primary safety endpoints, and/or major bleeding definitions). However, the sponsor performed pooled analysis with respect to a few variables by first pooling the data from the different studies and then performing the computations as if the data were from a single study.

From the sponsor's perspective, a comparative assessment of the total major bleeding in the 2 treatment groups was the focus of the safety analysis, with also a review of the key subgroups relative to the major bleeding. In addition, the rate of fatal bleeding (bleeding as primary cause of death) was assessed between the 2 groups. A review of TIMI major bleeding, particularly in elderly patients, was also performed.

In the ExTRACT study, the primary safety endpoint was the TIMI major hemorrhage

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within 30 days after randomization (Please see Table 53 in Section 10 Appendix, subsection 10.1.1 Review of ExTRACT-TIMI 25 Study). The sponsor used the Fisher's Exact test to evaluate differences between the treatment groups for this primary safety endpoint. Subgroup analyses were also performed for the primary safety endpoint (demographic, geographic, prognostic groups and use of different thrombolytic agents), but the study was not powered to detect treatment differences within these subgroups. AEs, SAEs, events that led to discontinuation of study drug, protocol-defined cardiac AEs (PDCAEs) and hemorrhagic AEs were identified as safety variables.

In the 6 previous studies, the primary safety endpoints varied widely (Table 30). However, the methodology used to collect AEs in the 6 previous studies was consistent with that used in the ExTRACT study.

Table 30 Primary safety endpoints in the 6 previous studies

Study	Type of statistics	Primary safety endpoint
ASSENT 3	Descriptive	A primary safety endpoint was not specifically identified; however, an efficacy plus safety composite endpoint (of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia or in-hospital ICH or in-hospital major bleedings [other than ICH]) was identified
ASSENT 3+	Descriptive	A primary safety endpoint was not specifically identified; however, an efficacy plus safety composite endpoint (of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia or in-hospital ICH or in hospital major bleedings [other than ICH]) was identified
ENTIRE	Descriptive	The incidence of TIMI major hemorrhage (including hemorrhagic strokes) at Day 30
HART II	Descriptive	The incidence of Aventis major hemorrhages at 30 days
AMI-SK	Descriptive	The incidence of Aventis major hemorrhages as per CEC, including hemorrhagic stroke, at Day 30
TETAMI	Descriptive	The incidence of Aventis major hemorrhages (including hemorrhagic strokes) at 30 days

ICH = intracranial hemorrhage; TIMI = Thrombolysis in Myocardial Infarction; CEC = Clinical Events Committee;
Aventis major hemorrhage = Clinically overt hemorrhage that resulted in (a) death or (b) transfusion of at least 2 units of packed red blood cells or whole blood, or (c) $\geq 30\text{g/L}$ decrease of hemoglobin, or (d) was retroperitoneal, intracranial or intra-ocular (confirmed by radiological exams or autopsy) or required surgical intervention or decompression of a closed space to stop or control bleeding (e.g., cardiac tamponade)

On 21-Mar- 2007 the sponsor submitted a 120-day safety update report, with a cut-off date of 19-Jan-2007 when the database for the 6-month and 12-month follow-up was locked. The sponsor also submitted that no new additional data were received for this indication in the NDA after 19-Jan-2007. Taking into account that AEs were not reported after the initial 30-day period of observation, and that no specific safety information or AEs were collected at 6-month and 12-month, and that there is no ongoing study or other completed study in the claimed indication during this period, the sponsor was merely providing information to complete/reconcile AEs of 12 patients that were reported as not completely reconciled at the time of the 30-day database lock, and provided narratives as required. The data in this 120-day safety update report does not change the safety review of the NDA.

7.1.1 Deaths

Death was one of the individual components of the composite primary efficacy endpoint and the composite secondary efficacy endpoints. The efficacy aspects of deaths including the relationship of deaths to myocardial re-infarction, TIMI major hemorrhages and ICH,

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and to the duration of treatment with enoxaparin or UFH, are presented in section 6.1.4 of this review.

The following is a review of the safety aspects of deaths in this NDA. The total deaths for this study are presented for the ITT population instead of the safety population.

Deaths in the ExTRACT-TIMI 25 study

In the ExTRACT study, the incidence of all-cause death at 30 days in the safety population (calculated as part of the primary efficacy endpoint) was 7.5% in the UFH group compared with 6.9% in the enoxaparin group (Table 31).

Table 31 Total deaths at 30 days in ExTRACT-TIMI 25 study (Safety population)

	Treatment as Randomized	
	Enoxaparin (N=10,176) (%)	Heparin (N=10,151) (%)
Total deaths at Day 30	708 (6.9%)	765 (7.5%)

In the ITT population, too, the incidence of all-cause death remains the same (Table 32), with the majority of deaths ((8% to 98.7%) being due to a cardiovascular cause. The incidence of non-cardiovascular death at 30 days in the ExTRACT study (Table 32) was numerically higher in the enoxaparin group (2.0%) versus the UFH group (1.3%).

Table 32 Cardiovascular and non-cardiovascular deaths at 30 days in ExTRACT-TIMI 25 study (ITT population)

Primary Cause of Death	All (N=20,479)	Treatment as Randomized	
		Enoxaparin (N=10,256)	Heparin (N=10,223)
No. of subjects with Event	1473 (7.2%)	708 (6.9%)	765 (7.5%)
Cardiovascular cause of death	1449 (98.4%)	694 (98.0%)	755 (98.7%)
Non-cardiovascular cause of death	24 (1.6%)	14 (2.0%)	10 (1.3%)

Ref: Sponsor's data table C.2.1.7 in Appendix C.2.1)

Table 33 AEs resulting in deaths at 30 days in ExTRACT-TIMI 25 study (Safety population)

Primary Cause of Death	All (N=20,327)	Treatment as Randomized	
		Enoxaparin (N=10,176)	Heparin (N=10,151)
No. of subjects without AEs resulting in death	18,886 (92.9%)	9479 (93.2%)	9407 (92.7%)
No. of subjects with AEs resulting in death	1441 (7.1%)	697 (6.8%)	744 (7.3%)
No. of subjects with Non-hemorrhagic AEs not resulting in death	18,970 (93.3%)	9533 (93.7%)	9437 (93.0%)
No. of subjects with Non-hemorrhage AEs resulting in death	1357 (6.7%)	643 (6.3%)	714 (7.0%)
No. of subjects with Hemorrhage AEs not resulting in death	20,200 (99.4%)	10,096 (99.2%)	10,104 (99.5%)
No. of subjects with Hemorrhagic AEs resulting in death	127 (0.6%)	80 (0.8%)	47 (0.5%)
All cardiac disorders	1217 (6.0%)	579 (5.7%)	638 (6.3%)
Cardiac tamponade	22 (0.1%)	12 (0.1%)	10 (0.1%)
Cerebral hemorrhage	76 (0.4%)	46 (0.5%)	30 (0.3%)
Cerebrovascular accident	37 (0.2%)	15 (0.1%)	22 (0.2%)
Hemorrhagic stroke	4 (0.0%)	2 (0.0%)	2 (0.0%)
Subarachnoid hemorrhage	1 (0.0%)	1 (0.0%)	--

Ref: Sponsor's data table C.3.1.19 in Appendix C.3.1)

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In the safety population, the incidence of death due to an AE was 6.8% in the enoxaparin group (697 of 10,176) and 7.3% in the UFH group (744 of 10,151), the incidence of hemorrhage AEs resulting in death was 0.8% in the enoxaparin group (80 of 10,176) compared to 0.5% (47 of 10,151) in the UFH group (Table 33).

The most frequently reported AE leading to death, excluding all cardiac disorder preferred terms, was cerebral hemorrhage (enoxaparin: 0.5%; UFH: 0.3%; Table 33).

Deaths associated with TIMI major bleeding in ExTRACT-TIMI 25 study

A total of 37.9% of patients in the enoxaparin group and 31.9% in the UFH group who had a major bleeding episode died (P = 0.25).

In patients who had a major bleeding episode, the mortality rate at 30 days was 0.8% in the enoxaparin group (80 of 10,176) and 0.4% in the UFH group (44 of 10,151; P = 0.001).

Among the 80 deaths among patients who had a major bleeding episode in the enoxaparin group, the primary cause was considered to be hemorrhagic in 56 (70%), cardiovascular in 19 (24%), non-cardiovascular in 4 (5%), and unknown in 1 (1%).

Among the 44 deaths among patients who had a major bleeding episode in the UFH group, the primary cause was considered to be hemorrhagic in 34 (77%), cardiovascular in 9 (20%), and non-cardiovascular in 1 (2%).

Reviewer's comments: There is a statistically significant (P < 0.0001) increase in TIMI major hemorrhage (see section 7.1.2 below and Table 35), which is accompanied by an increase in (i) deaths associated with hemorrhagic AEs (not statistically significant) and (ii) deaths associated with intracranial hemorrhage (not statistically significant). It appears that these hemorrhage-associated deaths are seen more frequently in patients on enoxaparin. These increase in risk are *clinically* significant and substantial.

Deaths in the 6 previous studies

In the 6 previous studies, a total of 248 (5.9%) patients in the enoxaparin groups and 377 (6.2%) patients in the UFH groups died before Day 30 of the study (Table 34).

Table 34 Total deaths through Day 30 in the 6 previous studies (safety population)

Study	Enoxaparin-treated patients		UFH-treated patients	
	N	n (%)	N	n (%)
Deaths within 30 days:				
*ASSENT 3	2040	109 (5.4)	4055	255 (6.3)
*ASSENT 3+	818	61 (7.5)	821	49 (6.0)
*ENTIRE	324	10 (3.1)	159	5 (3.1)
*HART II	196	9 (4.5)	197	10 (5.0)
AMI-SK	252	17 (6.7)	239	17 (7.0)
TETAMI	604	42 (7.0)	620	41 (6.6)
Total Safety population	4234	248 (5.9)	6091	377 (6.2)

* open-label studies

Reviewer's comments: This lack of difference in the incidence of deaths between the enoxaparin and UFH treatment groups is not reassuring because four of the studies that enrolled the majority of patients were open-label.

7.1.2 Other Serious Adverse Events

In the ExTRACT-TIMI 25 study, the incidence of *hemorrhagic* SAEs was higher in the enoxaparin group (2.9%, 291 of 10,176) compared with UFH group (1.6%, 164 of 10,151). The incidence of *non-hemorrhagic* SAEs was slightly higher in the UFH (13.5%, 1369 of 10,151) group compared with the enoxaparin (12.1%, 1235 of 10,176) group.

For the 6 previous studies, there are substantial differences in data collection and definitions of events in each study. For example, in the ASSENT 3 study, SAEs were categorized according to the relatedness to study drug, and in the ASSENT 3+ study, SAEs were analyzed according to 3 phases of the study: pre-hospital, pre/in-hospital, and 30-day follow up.

The relationship between TIMI major hemorrhage or intracranial hemorrhage (ICH) at 30 days and the composite primary efficacy endpoint and its components in the ExTRACT-TIMI 25 study are discussed earlier in section 6.1.4.5 Relationship between efficacy and safety endpoints, Table 17, Table 18, and Table 19.

TIMI major and minor bleeding in ExTRACT-TIMI 25 Study (Table 35)

The rates of TIMI major bleeding (including intracranial hemorrhage) at 30 days were 1.4% in the UFH group and 2.1% in the enoxaparin group (absolute increase of 0.7 percentage point and 53% increase in the relative risk, P<0.001) (Table 35).

The respective rates of TIMI minor bleeding and the composite of TIMI major or minor bleeding were 0.8 and 1.5 percentage points higher in the enoxaparin group than in the group given UFH (relative risk, 1.41 and 1.47, respectively) (Table 35).

Table 35 Safety endpoint events in the ExTRACT-TIMI 25 study (safety population)

Clinical Outcome	Enoxaparin (N = 10,176)	UFH (N = 10,151)	Relative Risk (95% CI)	P value
<i>Number (percent)</i>				
Outcome at 48 hr				
TIMI major bleeding (including ICH)	146 (1.4)	101 (1.0)	1.44 (1.12 – 1.86)	0.004
ICH	68 (0.7)	56 (0.6)	1.21 (0.85 – 1.72)	0.29
TIMI minor bleeding	159 (1.6)	122 (1.2)	1.30 (1.03 – 1.64)	0.028
TIMI major or minor bleeding	301 (3.0)	219 (2.2)	1.37 (1.15 – 1.63)	<0.001
Outcome at 8 days				
TIMI major bleeding (including ICH)	185 (1.8)	124 (1.2)	1.49 (1.19 – 1.87)	<0.001
ICH	81 (0.8)	62 (0.6)	1.30 (0.94 – 1.81)	0.11
TIMI minor bleeding	236 (2.3)	162 (1.6)	1.45 (1.19 – 1.77)	<0.001
TIMI major or minor bleeding	415 (4.1)	279 (2.7)	1.48 (1.28 – 1.72)	<0.001
Outcome at 30 days				
TIMI major bleeding (including ICH)	211 (2.1)	138 (1.4)	1.53 (1.23 – 1.89)	<0.0001†
ICH	84 (0.8)	66 (0.7)	1.27 (0.92 – 1.75)	0.14
TIMI minor bleeding	260 (2.6)	184 (1.8)	1.41 (1.17 – 1.70)	<0.001
TIMI major or minor bleeding	464 (4.6)	315 (3.1)	1.47 (1.28 – 1.69)	<0.001

* Safety events were assessed in the treated population. There were 15 patients in the safety population who were treated with study drug without undergoing randomization. Bleeding was assessed according to the TIMI criteria. † Fisher's exact test

Hemorrhagic events (TIMI classification) for the 6 previous studies:

The incidence of TIMI major hemorrhages up to Day 30 for each of the 6 previous studies is summarized by study in Table 36.

TIMI major hemorrhages were not evaluated in the ASSENT 3 and ASSENT 3+ studies. In

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the remaining four studies, the rates of TIMI major bleeding was higher with enoxaparin compared to UFH treatment. In the ENTIRE study, particularly, the rate of TIMI major bleeding was much higher with enoxaparin (5.6%) compared with UFH (1.9%).

Table 36 Incidence of TIMI major hemorrhages up to Day 30 in the 6 previous studies – Safety population

Previous enoxaparin study	Enoxaparin-treated patients ^a		UFH-treated patients	
	N	n (%)	N	n (%)
Any TIMI Major Hemorrhage:				
ASSENT 3 Study			Not defined in this study	
ASSENT 3+ Study			Not defined in this study	
ENTIRE Study	324	18 (5.6)	159	3 (1.9)
HART II Study	196	8 (4.1)	197	6 (3.0)
AMI-SK Study ^b	252	4 (1.6)	239	2 (0.8)
TETAMI Study	600	9 (1.5)	616	8 (1.3)
Total TIMI major hemorrhages in 6 previous studies	1372	39 (2.8)	1211	19 (1.8)

^a Includes all patients treated with enoxaparin, regardless of treatment regimen or route of administration.

^b Placebo-treated patients in the AMI-SK study, not UFH-treated patients. TIMI = Thrombolysis in Myocardial Infarction; N = population size; n = sample size; UFH = unfractionated heparin

Sites of TIMI major and minor hemorrhage

Cerebral hemorrhage (enoxaparin: 0.7%, 73 of 10,176, UFH: 0.6%, 61 of 10,151) and gastrointestinal hemorrhage (enoxaparin: 0.5%, 48 of 10,176, UFH: 0.1%, 15 of 10,151) were the most frequently reported sites of TIMI major hemorrhage at 30 days (Table 37). This higher incidence of TIMI major hemorrhage in the enoxaparin group compared to the UFH group appears to be due largely to a higher incidence of gastrointestinal hemorrhage in the enoxaparin group (Table 37).

Table 37 Sites of TIMI major hemorrhage in ExTRACT-TIMI 25 study

Sites of TIMI major hemorrhage	All (N=20,327)	Treatment as Randomized	
		Enoxaparin (N=10,176)	Heparin (N=10,151)
Cerebral hemorrhage	134 (0.7%)	73 (0.7%)	61 (0.6%)
Gastrointestinal hemorrhage	63 (0.3%)	48 (0.5%)	15 (0.1%)
Post procedural hemorrhage	23 (0.1%)	13 (0.1%)	10 (0.1%)
Vessel puncture site hemorrhage	18 (0.1%)	7 (0.1%)	11 (0.1%)
Catheter site hemorrhage	14 (0.1%)	8 (0.1%)	6 (0.1%)
Hematoma	13 (0.1%)	8 (0.1%)	5 (0.1%)

Source: Sponsors data listings in Appendix C 3.1, Table C.3.1-10 and Table C.3.1-11.

For TIMI minor hemorrhage, injection site hemorrhage, hematoma and injection site bruising, followed by hematuria and hemoptysis were more frequently seen in the enoxaparin group than in the UFH group (Table 38).

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Table 38 Sites of TIMI minor hemorrhage in ExTRACT-TIMI 25 study

Sites of TIMI minor hemorrhage	All (N=20,327)	Treatment as Randomized	
		Enoxaparin (N=10,176)	Heparin (N=10,151)
Gastrointestinal hemorrhage	81 (0.4%)	43 (0.4%)	38 (0.4%)
Injection site hemorrhage	53 (0.3%)	39 (0.4%)	14 (0.1%)
Hematoma	38 (0.2%)	24 (0.2%)	14 (0.1%)
Hematuria	37 (0.2%)	24 (0.2%)	13 (0.1%)
Catheter site hemorrhage	29 (0.1%)	14 (0.1%)	15 (0.1%)
Injection site bruising	26 (0.1%)	23 (0.2%)	3 (0.0%)
Hemoptysis	14 (0.1%)	10 (0.1%)	4 (0.0%)
Gingival bleeding	13 (0.1%)	7 (0.1%)	6 (0.1%)
Post procedural hemorrhage	13 (0.1%)	7 (0.1%)	6 (0.1%)

Source: Sponsors data listings in Appendix C 3.1, Table C.3.1-10 and Table C.3.1-11.

Intracranial hemorrhage in ExTRACT-TIMI 25 study

The rates of intracranial hemorrhage at 30 days were 0.8% (84 of 10,176) in the enoxaparin group and 0.7% (66 of 10,151) in the UFH group (P = 0.1443; Table 35).

Among patients who had a nonfatal intracranial hemorrhage, 46.2% (12 of 26) in the enoxaparin group and 62.1% (18 of 29) in the UFH group had a significant permanent neurologic disability (P = 0.24).

Intracranial hemorrhage events in the 6 previous studies:

The incidence of intracranial hemorrhage events up to Day 30 for 5 of the 6 previous studies was low in both treatment groups: 1.4% (38 of 3306) in the enoxaparin group and 0.9% (47 of 5312) in the UFH groups, with no statistical differences between treatment groups (Table 39).

Table 39 Incidence of intracranial hemorrhage up to Day 30 in the 6 previous studies – Safety population

Previous enoxaparin study	Enoxaparin-treated patients ^a		UFH-treated patients ^b	
	N	n (%)	N	n (%)
Any ICH:				
ASSENT 3 ^c	2040	18 (0.9)	4055	38 (0.9)
ASSENT 3+ ^c	818	18 (2.2)	821	8 (1.0)
ENTIRE	324	Not specifically recorded	159	Not specifically recorded
HART II	196	2 (1.0)	197	2 (1.0)
AMI-SK	252	0 (0.0)	239	1 (0.4)
TETAMI	600	Not specifically recorded	616	Not specifically recorded
Total incidence of ICH ^d	3306	38 (1.4)	5312	47 (0.9)

UFH = unfractionated heparin; N = population size; n = sample size; ICH = intracranial hemorrhage

^a Includes all patients treated with enoxaparin, regardless of treatment regimen or route of administration.

^b Includes placebo-treated patients from the AMI-SK study, and patients from ASSENT 3 who were treated with UFH + full dose TNK-tPA (Group A) and UFH + half dose TNK-tPA + abciximab (Group C).

^c Data are for intent-to-treat population.

^d Excluded patients from the ENTIRE and TETAMI studies since ICH was not evaluated in these studies.

In the ASSENT 3+ study, the incidence of in-hospital ICH events was significantly higher (p = 0.0470) in the enoxaparin group (2.2%; 18 of 818) compared with the UFH group (1.0%; 8 of 821). In the enoxaparin group, there was an age-related significant increase of ICH in patients >75 years, while no such influence of age was seen in the UFH group, and

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there was no difference between the treatment groups for the subset of patients ≤ 75 years. A subgroup analysis of the ASSENT 3+ study showed that the age-related increased event rates in the enoxaparin group were not related to concomitant treatment with TNK-tPA.

Subgroup analyses for TIMI major hemorrhage by enoxaparin and UFH treatment group in populations of subjects (including age, sex, race, obesity status and Creatinine Clearance) showed no significant “treatment-by-subgroup interaction” (Figure 13), although for most subgroups the incidences appear to be higher in patients treated with enoxaparin.

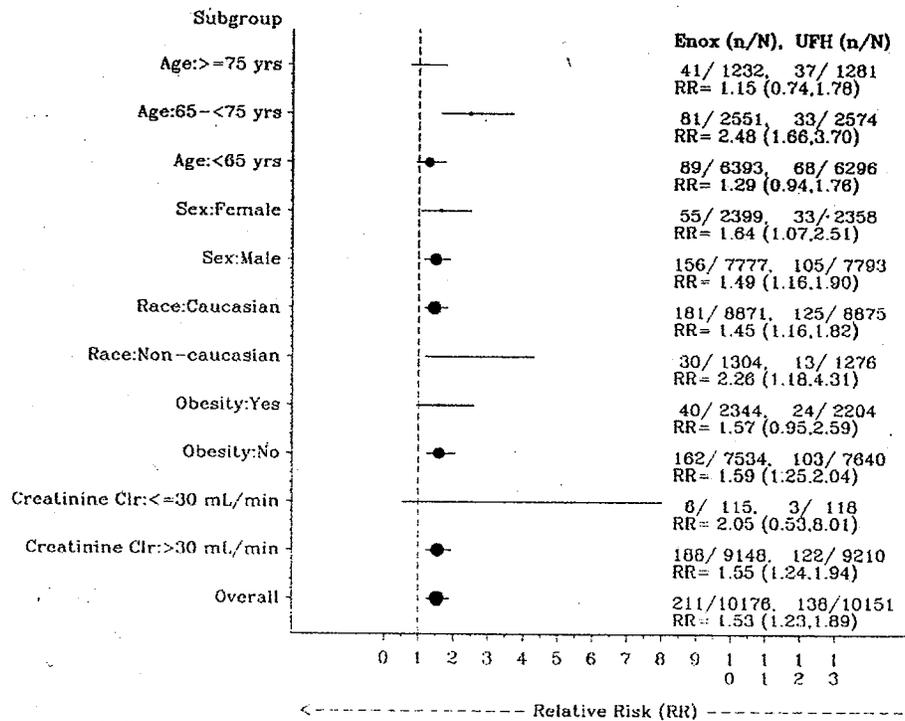


Figure 13. Drug-demographic and drug-disease subgroup analyses for the primary safety variable (TIMI major hemorrhage) in the ExTRACT-TIMI 25 study – Safety population
 Enox = enoxaparin; n = sample size; N = population size; UFH = unfractionated heparin; RR = relative risk; Clr = clearance

In the subgroup comparison for patients by treatment (PCI, type of fibrinolytic agent, use of aspirin, β -blockers, ACE inhibitors, clopidogrel/ticlopidine and statins), no significant treatment by subgroup interaction was identified (Figure 14). The exception was the “PCI at 30 days” subgroup, in which the patients who underwent PCI did *not* show an excess of TIMI major bleeding.

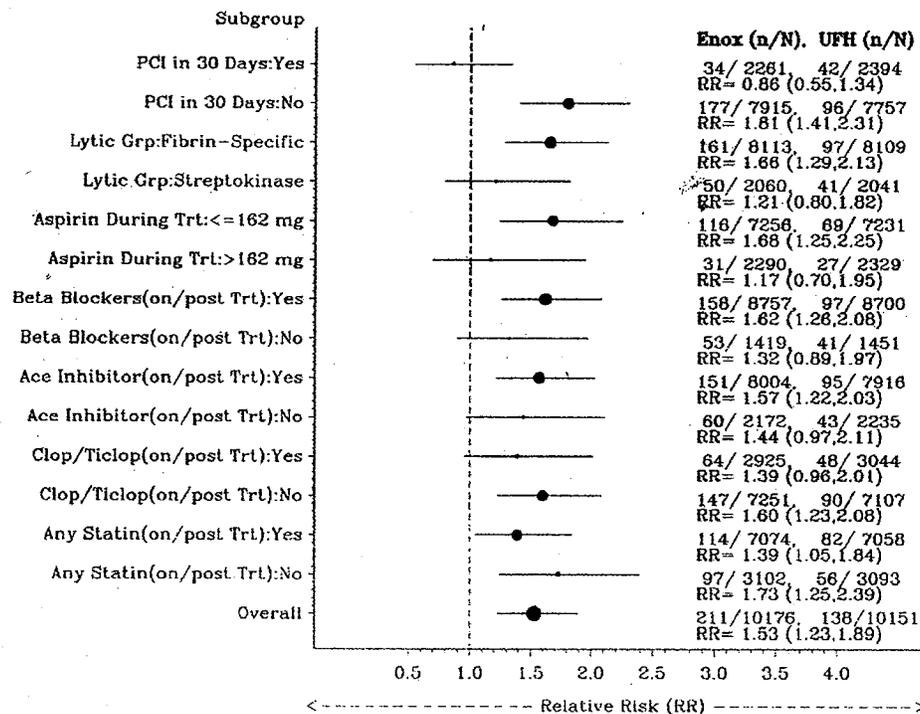


Figure 14 Drug-drug subgroup analyses for the primary safety variable (TIMI major hemorrhage) in the ExTRACT-TIMI 25 study – Safety population

Enox = enoxaparin; n = sample size; N = population size; UFH = unfractionated heparin; RR = relative risk; PCI = percutaneous coronary intervention; Grp = group; Trt = treatment; Ace = angiotensin-converting enzyme; Clop/Ticlopl = clopidogrel/ticlopidine

Reviewer's comments: The TIMI hemorrhage classification was introduced more than a decade ago during the thrombolytic era, before stents, GP IIb/IIIa inhibitors, clopidogrel, bivalirudin and LMWH became available. PCI paired with pharmacotherapy of atherothrombosis have changed the clinical presentation of bleeding events, for example, with specific and well-recognized bleeding features following clopidogrel, dipyridamole, etc.

I think that the TIMI hemorrhage classification could under-diagnose the bleeding risk associated with enoxaparin, particularly because a TIMI major hemorrhage requires an overt bleeding with a decrease in hemoglobin $\geq 5\text{g/dl}$ (i.e., a 5 pint bleeding).

A recently proposed new classification²⁴ called “BleedScore (Heart Drug Research, LLC, Wilmington, Delaware) uses a cumulative expression of events by adding points (depending on the severity of hemorrhage) to a resulting score, the accrued points being in an open-ended scale, which may provide a more realistic assessment of bleeding risk for the evaluation of modern antithrombotic and antiplatelet therapies in patients with STEMI.

7.1.3 Dropouts and Other Significant Adverse Events

Overall, the proportion of patients who discontinued treatment was similar in both enoxaparin (17.6%; 1790 of 10,256) and UFH (18.0%; 1830 of 10,223) treatment groups. From the efficacy analyses, I found that in the ITT population, the most frequent single reason for discontinuation was adverse event (AE) in both the enoxaparin (34.1%; 610 of 1790) and UFH (24.2%; 443 of 1830) groups. The numbers of patients discontinued

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appear to be lower for both treatment groups than those reported in the safety analyses (Table 40), which show that the incidence of AEs leading to permanent discontinuation of study drug in the ExTRACT-TIMI 25 study was higher in the enoxaparin group (8.1%; 825 of 10,176, or 17.3%; 825 of 4786 patients with AEs) compared with the UFH group (6.8%; 689 of 10,151, or 14.7%; 689 of 4692 patients with AEs).

Table 40 Overview of adverse events in the ExTRACT study through Day 30 – Safety population

	Treatment as received	
	Enoxaparin N=10 176 (%)	UFH N=10 151 (%)
Number of patients		
Patients with any AE	4786 (47.0)	4692 (46.2)
Patients with SAEs	1427 (14.0)	1466 (14.4)
– Patients with non-hemorrhagic SAEs	1235 (12.1)	1369 (13.5)
Patients with an SAE with an outcome of non-cardiovascular death	14 (0.1)	10 (0.1)
Patients who permanently discontinued study drug due to AEs	825 (8.1)	689 (6.8)
– Hemorrhagic AEs	491 (4.8)	217 (2.1)
– Non-hemorrhagic AEs	398 (3.9)	508 (5.0)

N = population size; UFH = unfractionated heparin; AE = adverse event; SAE = serious adverse event

7.1.3.1 Overall profile of dropouts

Not applicable.

7.1.3.2 Adverse events associated with dropouts

In the ExTRACT-TIMI 25 study, an increase in discontinuations due to AEs in the enoxaparin group was primarily due to the increase in hemorrhagic events (Table 40) which were reported in a greater number of patients in the enoxaparin group (4.8%; 491 of 10 176) compared with the UFH group (2.1%; 217 of 10 151).

On the other hand, the incidence of non-hemorrhagic AEs leading to permanent discontinuation was higher in the UFH (5.0%; 508 of 10,151) group compared with the enoxaparin (3.9%; 398 of 10,176) group (Table 40).

7.1.3.3 Other significant adverse events

The sponsor considered thrombocytopenia as a significant AE of greatest interest to this study population (because of the issue of heparin-induced thrombocytopenia).

In the ExTRACT study, thrombocytopenia (defined as a platelet count of $\leq 50\ 000/\mu\text{L}$ [$50 \times 10^3/\text{mm}^3$ or $50 \times 10^9/\text{L}$]) was reported in similar proportions of patients in both treatment groups when identified as

- An AE (enoxaparin: 2.2%, 221 of 10,176, UFH: 2.6%, 269 of 10,151), and
- a SAE (enoxaparin: 0.2%, 18 of 10,176, UFH: 0.2%, 18 of 10,151).

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Thrombocytopenia led to discontinuation of the study drug in 8 of 10,176 (0.1%) patients in the enoxaparin group and 18 of 10,151 (0.2%) in the UFH group.

One patient in each treatment group died following an event of thrombocytopenia.

In the 6 previous studies: The incidence of thrombocytopenia up to Day 30 in each of the 6 previous studies is summarized by study in Table 41. In the ASSENT 3, ASSENT 3+, and AMI-SK studies, the incidence of thrombocytopenia was similar between the enoxaparin groups and the UFH groups. In the ENTIRE study, the incidence of thrombocytopenia was greater in the enoxaparin groups (3.4%) than in the UFH groups (1.9%).

Table 41 The incidence of thrombocytopenia up to Day 30 in the 6 previous studies – Safety population

Previous enoxaparin study	Enoxaparin-treated patients ^a		UFH-treated patients ^b	
	Total patients	N (%)	Total patients	N (%)
Any thrombocytopenia:				
ASSENT 3 ^c	2040	24 (1.9)	4055	91 (2.2)
ASSENT 3+ ^c	818	9 (1.1)	821	6 (0.7)
ENTIRE	324	11 (3.4)	159	3 (1.9)
HART II	196	Not evaluated	197	Not evaluated
AMI-SK	252	4 (1.6)	239	3 (1.3)
TETAMI	600	Not evaluated	620	Not evaluated
Total incidence of thrombocytopenia ^d	3434	48 (1.4)	5274	103 (2.0)

^a Includes all patients treated with enoxaparin, regardless of treatment regimen or route of administration.

^b Includes placebo-treated patients from the AMI-SK study, and patients from ASSENT 3 who were treated with UFH + full dose TNK-tPA (Group A) and UFH + half dose TNK-tPA + abciximab (Group C).

^c Data are for intent-to-treat population. ^d Excludes patients from the HART II and TETAMI studies since thrombocytopenia was not evaluated in these studies. UFH=unfractionated heparin; N = population size

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

7.1.5.3 Incidence of common adverse events

As shown in (Table 40), the incidence of AEs was comparable between treatment groups in the ExTRACT-TIMI 25 study: 4786 (47.0%) patients in the enoxaparin group and 4692 (46.2%) patients in the UFH group experienced at least 1 AE through Day 30 of the study.

Adverse events in the 6 previous studies: For the 6 previous studies, the sponsor submitted that comparisons of AEs is complicated by differences in collection methods, calculation methodology, and definitions of events in each study. For example:

- In the ASSENT 3 study, summaries of patients who experienced bleeds were presented rather than summaries of hemorrhagic and non-hemorrhagic AEs.

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- In ASSENT 3+, AEs were analyzed according to 3 phases of the study: pre-hospital, pre/in-hospital, and 30-day follow-up, and summaries of AEs were not presented.
- In the ENTIRE study, the incidence of AEs leading to treatment discontinuation was higher with enoxaparin (0.11%) compared with UFH (0.06 %). The sponsor explained that such discontinuations occurred at lower rates in the 2 enoxaparin Standard Lytic groups (AEs: 3.7%, 10.1%; SAEs: 3.7%, 3.8%) compared with the 3 enoxaparin Combination Reperfusion Therapy groups (AEs: 14.6%, 20.8%, 10.3%; SAEs: 12.5%, 11.7%, 7.7%), which are not therapy regimens used in standard practice (Please see section 10.1.2.3 for design of ENTIRE study and efficacy and safety findings).

7.1.5.4 Common adverse event tables

At 30 days, the incidence of hemorrhagic AEs in the ExTRACT-TIMI 25 study was higher in the enoxaparin group (22.1%) compared with the UFH group (15.7%) (Table 42).

Table 42 Number (%) of subjects with hemorrhagic adverse events at 30 days by system organ class - Safety population

Adverse event (MedDRA System Organ Class and Preferred Term)	Treatment received	
	Enoxaparin (N=10 176)	UFH (N=10 151)
Number of subjects without hemorrhagic AE at 30 days	7926 (77.9%)	8557 (84.3%)
Number of subjects with hemorrhagic AE at 30 days	2250 (22.1%)	1594 (15.7%)
Gastrointestinal disorders	425 (4.2%)	344 (3.4%)
Gastrointestinal haemorrhage	206 (2.0%)	143 (1.4%)
Gingival bleeding	182 (1.8%)	163 (1.6%)
General disorders and administration site conditions	1322 (13.0%)	914 (9.0%)
Catheter site haemorrhage	139 (1.4%)	115 (1.1%)
Injection site bruising	360 (3.5%)	104 (1.0%)
Injection site haemorrhage	372 (3.7%)	195 (1.9%)
Vessel puncture site bruise	444 (4.4%)	450 (4.4%)
Vessel puncture site haemorrhage	189 (1.9%)	143 (1.4%)
Renal and urinary disorders	204 (2.0%)	138 (1.4%)
Haematuria	203 (2.0%)	138 (1.4%)
Respiratory, thoracic and mediastinal disorders	174 (1.7%)	118 (1.2%)
Vascular disorders	235 (2.3%)	120 (1.2%)
Haematoma	207 (2.0%)	97 (1.0%)

Notes: Subjects with multiple reports of the same MedDRA Preferred Term are counted only once within each Preferred Term and once within each organ class. Adverse events non-serious, non-hemorrhagic, non-protocol defined cardiac adverse events, and not related to study medication are not reported in the CRF. Adverse events present in < 1% of both treatment groups are excluded from this table. MedDRA = Medical Dictionary for Drug Regulatory Activities; UFH = unfractionated heparin; N = population size; AE = adverse event

For the 5 system organ classes (SOCs) in which the incidence of events was $\geq 1\%$ of subjects in either group, more subjects in the enoxaparin group compared with the UFH group had at least 1 AE (Table 42).

In the enoxaparin group the most frequently reported hemorrhagic AEs were vessel puncture site bruise (4.4% vs 4.4% in the UFH group) and injection site hemorrhage (3.7% vs 1.9% in the UFH group) (Table 42).

The incidence of non-hemorrhagic AEs in the ExTRACT-TIMI 25 study was higher in the

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UFH group (39.1%) compared with the enoxaparin group (35.6%) (Table 43).

Table 43 Number (%) of subjects with non-hemorrhagic adverse events at 30 days by system organ class - Safety population

Adverse event (MedDRA System Organ Class and Preferred Term)	Treatment received	
	Enoxaparin N=10 176 (%)	UFH N=10 151 (%)
Number of subjects without non-hemorrhagic AE at 30 days	6554 (64.4)	6178 (60.9)
Number of subjects with non-hemorrhagic AE at 30 days	3622 (35.6)	3973 (39.1)
Blood and lymphatic system disorders	268 (2.6)	304 (3.0)
Thrombocytopenia	221 (2.2)	269 (2.6)
Cardiac disorders	2977 (29.3)	3352 (33.0)
Atrial fibrillation	362 (3.6)	375 (3.7)
Atrioventricular block	136 (1.3)	171 (1.7)
Atrioventricular block complete	167 (1.6)	181 (1.8)
Cardiac arrest	128 (1.3)	159 (1.6)
Cardiac failure	485 (4.8)	483 (4.8)
Cardiogenic shock	507 (5.0)	504 (5.0)
Intracardiac thrombus	72 (0.7)	140 (1.4)
Myocardial infarction	388 (3.8)	561 (5.5)
Myocardial ischaemia	536 (5.3)	677 (6.7)
Myocardial rupture	120 (1.2)	141 (1.4)
Pericarditis	179 (1.8)	184 (1.8)
Ventricular fibrillation	230 (2.3)	281 (2.8)
Ventricular tachycardia	469 (4.6)	457 (4.5)
General disorders and administration site conditions	161 (1.6)	161 (1.6)
Infections and infestations	165 (1.6)	151 (1.5)
Nervous system disorders	116 (1.1)	171 (1.7)

Note: Subjects with multiple reports of the same MedDRA Preferred Term are counted only once within each Preferred Term and once within each organ class. Adverse events non-serious, non-hemorrhagic, non-protocol defined cardiac adverse events, and not related to study medication are not reported in the CRF; MedDRA = Medical Dictionary for Drug Regulatory Activities; N = population size;

For these non-hemorrhagic AEs (incidence: $\geq 1\%$ of subjects in either group) in the ExTRACT-TIMI 25 study, cardiac disorders were more common in the UFH (33.0%) group compared with the enoxaparin (29.3%) group (Table 43).

The most frequently reported AE was myocardial ischemia (enoxaparin: 5.3%; UFH: 6.7%) (Table 43). The incidence of non-hemorrhagic AEs in other SOCs did not show any large differences between the 2 treatment groups.

7.1.7 Laboratory Findings

In the ExTRACT-TIMI 25 study, a greater number of patients in the UFH (4.2%) group had a shift in hemoglobin values from normal at baseline to low on Day 8 compared with the enoxaparin (3.5%) group. The proportion of the patients with a decrease in hemoglobin (≥ 3 g/dL) reported as a pre-defined clinically abnormal (PCA) value was slightly higher in

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the enoxaparin (9.73%) group compared with the UFH group (5.28%).

Similarly, a slightly greater number of patients in the UFH (3.5%) group also had a shift in hematocrit values from normal at baseline to low on Day 8 compared with the enoxaparin (3.3%) group. The proportion of the patients with a decrease in hematocrit reported as a PCA was however similar and low in both treatment groups.

The changes in platelet count values were similar in both treatment groups from baseline through to Day 8 with no evidence of significant differences between the 2 groups. An evaluation of the platelet count at the Day 30 visit (Table 44) showed clinically significant values in a low and similar proportion of patients in both enoxaparin (0.2%) and UFH (0.2%) treatment groups.

Table 44 Thrombocytopenia up to Day 30 in ExTRACT-TIMI 25 Study (Safety population)

Thrombocytopenia Reported as	Enoxaparin (N = 10,176)	UFH (N = 10,151)
AE	221 (2.2%)	269 (2.6%)
SAE	28 (0.2%)	18 (0.2%)

Clinical laboratory evaluations for the 6 previous studies

In the ASSENT 3 and ASSENT 3+ studies no systematic laboratory measurements were performed on patients. Hemoglobin and platelet counts were measured in the ENTIRE, HART II, AMI-SK, and TETAMI studies; the laboratory safety data did not show any signal for safety concerns.

Table 45 Thrombocytopenia up to Day 30 in 6 previous studies

Previous enoxaparin study	Enoxaparin-treated patients ^a		UFH-treated patients ^b	
	Total patients	N (%)	Total patients	N (%)
Any thrombocytopenia:				
ASSENT 3 ^c	2040	24 (1.9)	4055	91 (2.2)
ASSENT 3+ ^c	818	9 (1.1)	821	6 (0.7)
ENTIRE	324	11 (3.4)	159	3 (1.9)
HART II	196	Not evaluated	197	Not evaluated
AMI-SK	252	4 (1.6)	239	3 (1.3)
TETAMI	600	Not evaluated	620	Not evaluated
Total incidence of thrombocytopenia ^d	3434	48 (1.4)	5274	103 (2.0)

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The sponsor submitted that comparable vital signs, physical findings, and ECG data were

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collected in the 6 previous studies; however, these data were collected at different post-baseline time points, and could not be reconciled with the data in the ExTRACT study.

The sponsor stated also that the vital signs, physical findings, and other observations related to safety for the ExTRACT study only were submitted in the NDA. These vital signs (including supine heart rate, systolic and diastolic BP), physical examinations, and ECG data were collected at baseline and at prespecified time points.

At hospital discharge or Day 8, both treatment groups showed a very similar mean decrease from baseline in diastolic BP (mean change [\pm SD] enoxaparin: -8.3 [\pm 14.62]; UFH: -8.4 [\pm 14.66]), pulse rate (enoxaparin: -5.0 [\pm 17.46]; UFH: -5.1 [\pm 17.21]), and systolic BP (enoxaparin: -15.8 [\pm 22.94]; UFH: -16.5 [\pm 22.64]) from baseline.

Analysis of PCAs (pre-defined clinically abnormal findings) for vital signs showed similar proportion of patients in both treatment groups with PCAs for decreases in diastolic BP (decrease \geq 25 mmHg), pulse rate (decrease \geq 20 bpm), and systolic BP (decrease \geq 40 mmHg). The sponsor's shift analysis of vital sign parameters at hospital discharge/Day 8 did not show any evidence of differences between the 2 treatment groups.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Drug abuse potential: The sponsor submitted that based on the pharmacological activity of enoxaparin in animals and in man, there is no potential for drug abuse, and that no case reports of drug abuse are recorded in their post-marketing global pharmacovigilance database.

Withdrawal phenomenon: The sponsor submitted that there is no evidence to suggest that a rebound effect could occur after withdrawal from enoxaparin treatment.

7.1.16 Overdose Experience

The sponsor submitted that there were 295 cases of overdose reported to the sponsor from the launch of the product in 1987 to May 2006, and that the most frequent reaction reported was bleeding.

7.1.17 Postmarketing Experience

The sponsor estimates that during the last 5 years, a total of 93 million patients were exposed (including all indications). The Global Pharmacovigilance and Epidemiology at Sanofi-Aventis received 8951 reports. These reports were reviewed routinely on an ongoing monitoring basis and they were also collectively reviewed with similar reports in detail for evaluation of possible signals. The sponsor submits that no particular clinical safety findings were identified.

Among the reactions reviewed in depth, a comprehensive analysis of all forms of hemorrhage (the most frequent reaction reported) was performed in each Periodic Safety Update Report (PSUR). The data analyzed did not suggest any change for the established

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safety profile despite an increase in exposure.

During the review period of the bridging report (Summary Safety Update Report covering the period 03-Apr-2001 to 03-Apr-2006), 81 cases involving a drug interaction with enoxaparin were reported. The majority of the alleged drug interactions reported during this period involved enoxaparin in combination with other drugs that affect hemostasis. The enoxaparin CCDS states that "agents which affect hemostasis should be discontinued prior to enoxaparin sodium therapy unless strictly indicated." No new interaction findings in addition to the information included in the current version of the CCDS for enoxaparin was identified.

An analysis of pregnancy AEs including congenital malformations during enoxaparin therapy was included in the PSUR No. 15 issued by the company in June 2006. No safety signal was identified.

The sponsor submits that it has performed continuous safety monitoring of enoxaparin since the first marketing authorization, and that no new safety findings were identified in the Summary Safety Update Report up to the cut-off date of this report (i.e., 03-Apr-2006).

Most recently, a review of a 120-day safety update report (with a cut-off date of 19-Jan-2007 when the database for the 6-month and 12-month follow-up was locked) submitted by the sponsor on 21-Mar-2007 identified no new safety findings.

7.2 Adequacy of Patient Exposure and Safety Assessments

The ExTRACT-TIMI 25 study and the 6 previous enoxaparin studies in patients with STEMI are the sources of clinical safety data.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The ExTRACT-TIMI 25 study provides safety data for 20,327 patients with STEMI (10,176 exposed to enoxaparin, and 10,151 to UFH) who received at least 1 dose of study treatment.

There were a few discrepancies in randomization: 15 subjects were not randomized prior to receiving treatment. Among the 10,176 subjects who received enoxaparin, 10,152 were randomized to enoxaparin, 16 were randomized to UFH, and 8 were not randomized. Among the 10,151 who received UFH, 10,130 were randomized to UFH, 14 were randomized to enoxaparin, and 7 were not randomized.

The majority (82%) of patients in each group completed the assigned treatment regimen. 17.6% (1790 of 10,256) patients in enoxaparin group and 18% (1830 of 10,223) patients in UFH group discontinued, most frequently due to a hemorrhagic AE (34.1% in enoxaparin group vs 24% in UFH group) or PCI-related reasons (48.5% (128 of 525) patients in enoxaparin group and 51.5% (136 of 625) patients in UFH group).

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The Sponsor also provided safety data for 10,040 randomized patients with STEMI (4128 enoxaparin patients, 5673 UFH patients, and 239 placebo patients) from 6 previously conducted studies. A majority (58%) of patients in each of the 6 studies completed the assigned treatment. Hemorrhagic events were the most frequent AEs that resulted in treatment discontinuation in all of these studies.

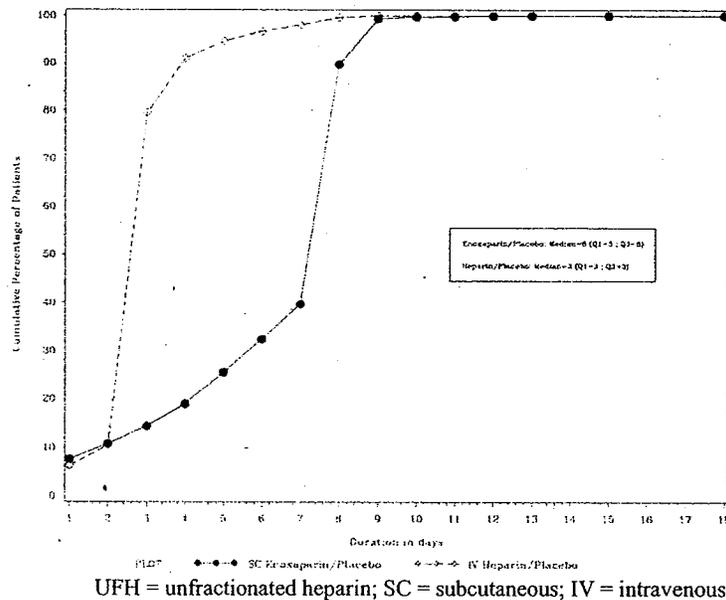
7.2.1.3 Extent of exposure (dose/duration)

In the ExTRACT-TIMI 25 study, the mean duration of exposure to enoxaparin/placebo sc injection was similar in both treatment groups. A majority of subjects in both treatment groups (enoxaparin: 74.9%; UFH: 74.1%) had received enoxaparin/placebo sc injection for ≥ 6 days.

The mean duration of exposure to UFH/placebo infusion was similar in both treatment groups. A majority of subjects in both treatment groups (enoxaparin: 89.6%; UFH: 89.5%) had received UFH/placebo infusion for ≥ 36 hours.

The cumulative duration curve after treatment with sc enoxaparin/placebo versus iv UFH/placebo (Figure 15) shows that the median duration of exposure to enoxaparin/placebo (8 days) was longer than the median duration of exposure to UFH/placebo (3 days).

Figure 15 Cumulative duration curve of sc enoxaparin/placebo and iv UFH/placebo



8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The following is the dosing regimen and administration for the treatment of acute STEMI:

In patients with acute STEMI, the recommended dose of enoxaparin is a single iv bolus of 30 mg plus a 1 mg/kg sc dose followed by 1 mg/kg administered sc every 12 hours (maximum 100 mg for the first two doses only, followed by 1 mg/kg dosing for the remaining doses).

For treatment of acute STEMI in geriatric patients ≥ 75 years of age, these elderly patients received 0.75 mg/kg SC every 12 hours *without* an initial IV bolus.

For treatment of acute STEMI in patients with severe renal impairment (creatinine clearance < 30 mL/minute) the recommended dose is a single iv bolus of 30 mg plus a 1 mg/kg sc dose followed by 1 mg/kg administered sc *once daily*.

When administered in conjunction with a thrombolytic (fibrin-specific or non-fibrin specific) agent, enoxaparin should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy.

All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated.

The recommended duration of enoxaparin treatment is 8 days or until hospital discharge, whichever comes first.

For patients managed with Percutaneous Coronary Intervention (PCI): If the last enoxaparin sc administration was given < 8 hours before balloon inflation, no additional dosing is needed. If the last enoxaparin sc administration was given more > 8 hours before balloon inflation, an iv bolus of 0.3 mg/kg of enoxaparin injection should be administered.

Dose justification for the ExTRACT study

The same dosing regimen used in patients with unstable angina and NSTEMI^{25,26}, were used in the STEMI indication (i.e., an initial 30 mg iv bolus of enoxaparin immediately followed by 1 mg/kg sc every 12 hours).

After sc injection of enoxaparin, the maximum plasma levels of anti-Xa activity are only reached 3 to 5 hours later, and it can take several sc administrations to reach steady-state.

The addition of the iv bolus to the sc regimen produces effective plasma anti-Xa activities quickly (0.663 ± 0.229 IU/mL anti-Xa at 5 minutes after injection) and early overall exposure near steady-state conditions (mean maximum value of $1.164 [\pm 0.170]$ IU/mL), anti-Xa reached from 2 to 4 hours after treatment initiation). This was shown in a supportive PK study in healthy 50- to 68-year-old subjects (Study RP54563Q-142). Steady state conditions were reached on Day 1 for maximum activity (AUC, A_{\max}) and Day 2 for minimum activity (A_{\min}).

The dose regimen consisting of a 30-mg iv bolus at initiation immediately followed by 1

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mg/kg sc twice daily, which was used in the ExTRACT study, demonstrated that exposure during the first dosing interval was already 98% of that at steady-state.

Dosing rationale for dose adaptations of enoxaparin:

Weight. Weight is significantly related to enoxaparin (anti-Xa) clearance (coefficient of variation of 46% in the basic model with no covariates) as shown in the population PK analysis of the TIMI 11A study submitted by the sponsor. Variation in body weight within the 5th and 95th percentiles (58 kg to 117 kg) would result in a change in anti-Xa clearance between 14% and 21%. Using a weight-adjusted dosage regimen shows that there was no change in AUC with weight changes, indicating that the weight-base dose adjustment is appropriate to account for the effect of weight on enoxaparin (anti-Xa) clearance.

Age (Elderly patients). Age may have an independent effect on bleeding risk (AMI-SK) with an altered PK/PD relationship. Therefore, a reduced dose of 0.75 mg/kg sc every 12 hours was proposed in patients ≥ 75 years old. The anti-IIa activity after an iv injection is higher than after sc administration, and with the 30 mg bolus + 1 mg/kg sc it was about 70% higher than the A_{max} at steady-state; therefore, the initial bolus was not administered in the elderly population. The reduced exposure obtained in elderly in the ExTRACT study was consistent with expected pharmacokinetics in that population and provided a better safety profile.

Renal impairment. Renal function is the main covariate affecting enoxaparin AUC in cases of weight-adjusted dosing. Impaired renal function, as estimated by CrCl, results in a proportional decrease in enoxaparin anti-Xa clearance (Study DMPK/FR/2249)²⁷. This appears as a factor explaining an increased risk of bleeding in case of severe renal impairment (CrCl < 30 mL/min)²⁸. Using the population PK model, a simulation of an administration of a dose-regimen of 1 mg/kg once daily in patients with severe renal impairment demonstrates that this would lead to an exposure at steady state that is similar to that at a dose of 1 mg/kg twice daily in healthy subjects with value of 16.9 and 21.2 IU*h/mL, respectively. Peak levels at steady-state would be similar to those achieved with the approved dosage regimens in healthy subjects, while A_{min} at steady-state would still be higher than that observed for a dose of 1.5 mg/kg once daily in healthy subjects with value of 0.303 compared to 0.165 IU/mL²⁸.

This dose adjustment has now been implemented in enoxaparin labeling in several countries, including the US.

Percutaneous coronary intervention (PCI). In the Collet study²⁹, 293 patients underwent a coronary angiography within 8 hours of sc injection (1 mg/kg every 12 hours) and in 132 patients angiography was followed by immediate PCI. Favorable efficacy results were observed and anti-Xa activity within 2 to 8 hours after the last sc dose was 0.98 ± 0.03 IU/mL, with 97.6% of values above 0.5 IU/mL. However, after this 8-hour period, the level of anticoagulation might not be sufficient to perform a PCI.

Pharmacokinetic modeling (based on study RPR54563Q-142 data) predicted that in patients undergoing intervention 8 to 12 hours after a last 1 mg/kg sc dose at steady state, an additional iv bolus of 0.3 mg/kg at the start of PCI would raise and maintain the anti-Xa level, between 0.6 and 1.8 IU/mL.

The RP54563Q-266 (PEPCI) study³⁰ evaluated the PK of this regimen (iv bolus of 0.3