

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-138**

**20-164 S-075**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 22-138

**Drug Name:** Lovanox (enoxaparin)

**Indication(s):** Reduce incidence of mortality and non-fatal myocardial re-infarction in patients with acute ST-segment elevation myocardial infarction receiving fibrinolytic therapy

**Applicant:** Sanofi Aventis

**Date(s):** November 17, 2006.

**Review Priority:** Priority

**Biometrics Division:** Biometrics I (HFD-710)

**Statistical Reviewer:** John Lawrence

**Concurring Reviewers:** Jim Hung.

**Medical Division:** Division of Cardiovascular and Renal Products (HFD-110)

**Clinical Team:** Khin U, Medical Reviewer  
Abraham Karkowsky, Clinical Team Leader

**Project Manager:** Meg Pease-Fry

**Keywords:**  
foreign clinical data, interim analysis

## Table of Contents

<b>1. EXECUTIVE SUMMARY .....</b>	<b>3</b>
1.1 CONCLUSIONS AND RECOMMENDATIONS .....	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES .....	3
1.3 STATISTICAL ISSUES AND FINDINGS .....	3
<b>2. INTRODUCTION .....</b>	<b>4</b>
2.1 OVERVIEW .....	4
2.2 DATA SOURCES .....	6
<b>3. STATISTICAL EVALUATION .....</b>	<b>6</b>
3.1 EVALUATION OF EFFICACY .....	6
3.2 EVALUATION OF SAFETY .....	8
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>9</b>
4.1 GENDER, RACE AND AGE .....	9
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS .....	9
<b>5. SUMMARY AND CONCLUSIONS .....</b>	<b>11</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	11
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	11

## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

There is strong evidence that enoxaparin is superior to unfractionated heparin in reducing the risk of myocardial re-infarction within 30 days in the population studied. There is also strong evidence that the risk of thrombolysis in myocardial infarction (TIMI) major hemorrhage within 30 days is higher in the enoxaparin treated group.

### **1.2 Brief Overview of Clinical Studies**

There is one double-blind Phase III study that compared enoxaparin with a control group treated with unfractionated heparin. Approximately twenty thousand patients with acute ST-segment elevation myocardial infarction receiving fibrinolytic therapy were randomized to one of the treatment arms. The primary endpoint is the number of subjects who died or had non-fatal myocardial re-infarction within 30 days of randomization.

### **1.3 Statistical Issues and Findings**

Approximately 9.9% = 1017/10256 of the subjects in the enoxaparin arm had a primary endpoint event (death and non-fatal myocardial re-infarction within 30 days). Approximately 12% = 1223/10223 of the subjects in the heparin arm had a primary endpoint event. This difference represents an estimated relative risk of 0.83 and is statistically significant ( $p=0.00003$ ). There were numerically more deaths at 30 days in the heparin group, but the difference was not statistically significant. Approximately 2.1% of the subjects in the enoxaparin arm had a major hemorrhagic episode within 30 days compared to approximately 1.4% in the heparin arm. This difference represents an estimated relative risk of 1.53 and is statistically significant ( $p<0.0001$ ).

**APPEARS THIS WAY ON ORIGINAL**

## 2. INTRODUCTION

### 2.1 Overview

There is one double-blind study that compared enoxaparin to heparin. A total of 20,506 patients were randomly assigned to receive enoxaparin or unfractionated heparin. The administration of enoxaparin varied according to subject's age and creatinine clearance (CrCl) as shown in Table 1 and the duration of treatment is 8 days. Heparin was administered via an initial IV bolus, followed by continuous IV infusion. The continuous IV infusion rate was determined for each subject according to the subject's blinded aPTT/ACT value. The duration of heparin treatment is 48 hours.

Table 1 Dosing plan.

	Subjects randomized to enoxaparin	Subjects randomized to UFH
<b>Initial iv bolus Drug A<sup>a</sup></b> (-15 min to +30 min relative to start of fibrinolytic therapy)	<p>Subjects &lt;75 years old</p> <p>Subjects ≥75 years old</p>	<p>Bolus A (enoxaparin) 30 mg iv</p> <p>No bolus A</p> <p>Bolus A (placebo)</p> <p>No bolus A</p>
<b>Initial iv bolus Drug B<sup>a</sup></b> (-15 min to +30 min relative to start of fibrinolytic therapy)	Bolus B (placebo)	Bolus B (UFH) 60 U/kg (max 4000 U) (1 vial contains 50,000 U/10 mL or 25,000 U/5 mL)
<b>sc injections Drug A</b>		
- First sc dose to be given within 15 min of iv bolus A)		
- sc injections to continue until hospital discharge, or Day 8, or until PCI, whichever comes first		
Subjects <75 years old	sc Drug A (enoxaparin) 1 mg/kg sc Q12h <sup>b</sup> (max of 100 mg/injection for each of first 2 injections)	sc Drug A (placebo)
Subjects ≥75 years old	sc Drug A (enoxaparin) 0.75 mg/kg sc Q12h <sup>b</sup> (max of 75 mg/injection for each of first 2 injections)	sc Drug A (placebo)
<b>iv continuous infusion Drug B<sup>a</sup></b>		
- Start of infusion within 15 min after iv bolus	Drug B (placebo)	Drug B (UFH) 12 U/kg/h (max 1000 U/h initially)
- The iv continuous infusion will be administered for a minimum of 48 hours, or until PCI (see Section 3.3.2.4)		Dilute concentration for infusion to 50 U/mL (eg, add 5 mL from vial to 495 mL of isotonic saline solution)

UFH = unfractionated heparin; iv = intravenous; sc = subcutaneous; PCI = percutaneous coronary intervention; Q12h = every 12 hours

<sup>a</sup> Only iv bolus injections (A and B) when UFH (24000 U) was administered within 3 hours prior to randomization. Therefore:

If < 4000 U of UFH was administered within 3 hours prior to randomization:

Subjects less than 75 years of age:

Will receive 2 initial iv boluses (bolus A and bolus B), repeated sc injections of Drug A and an iv continuous infusion of Drug B.

Subjects 75 years of age or older:

Will receive 1 iv bolus (bolus B only), sc injections of Drug A and an iv continuous infusion of Drug B.

If ≥4000 U of UFH was administered within 3 hours prior to randomization:

All subjects (regardless of age):

Will receive repeated sc injections of Drug A and an iv continuous infusion of Drug B (no initial iv boluses of A and B).

<sup>b</sup> Dose to be reduced to 1.0 mg/kg once daily, if creatinine clearance is determined to be ≤30 mL/min.

<sup>c</sup> Adjusted to an activated partial thromboplastin time of 1.5-2.0x control (Hemcocon<sup>®</sup> or local laboratory).

Source: Table 3, p. 29 of Study Report

The baseline demographics of the patients studied are in Table 2. There do not appear to be any significant differences between the groups with respect to these variables.

**Table 2** Summary of demographics and other baseline data.

	Treatment as randomized	
	Enoxaparin (N=10 256)	UFH (N=10 223)
Sex		
Male	7841 ( 76.5%)	7855 ( 76.8%)
Female	2415 ( 23.5%)	2368 ( 23.2%)
Age (years)		
NUMBER	10256	10223
MEAN	59.8	59.9
SD	11.90	11.95
MINIMUM	20	20
MAXIMUM	99	98
Age category		
< 65 years	6444 ( 62.8%)	6345 ( 62.1%)
[65-75) years	2571 ( 25.1%)	2587 ( 25.3%)
≥75 years	1241 ( 12.1%)	1291 ( 12.6%)
Race		
Caucasian	8935 ( 87.1%)	8920 ( 87.3%)
Black	23 ( 0.2%)	36 ( 0.4%)
Asian/Oriental	1007 ( 9.8%)	990 ( 9.7%)
Other	290 ( 2.8%)	277 ( 2.7%)
Missing	1	0
Creatinine clearance (mL/minute)		
< 30 mL/minute	115 ( 1.2%)	117 ( 1.3%)
≥ 30 mL/minute	9139 ( 98.8%)	9207 ( 98.7%)
Missing	1002	899
Previous or current smoker		
No	4321 ( 42.1%)	4320 ( 42.3%)
Yes	5933 ( 57.9%)	5895 ( 57.7%)
Missing	2	8
Systolic blood pressure		
NUMBER	10254	10222
MEAN	133.3	133.6
SD	20.76	20.82
MINIMUM	50	54
MAXIMUM	211	240
Diastolic blood pressure		
NUMBER	10254	10221
MEAN	80.5	80.5
SD	12.76	12.84
MINIMUM	20	23
MAXIMUM	127	149

Source: pp 63-64 of Study Report.

## 2.2 Data Sources

Electronic study reports and data sets (\\CDSESUB1\N22138\N\_000\2006-11-17)

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

Approximately 9.9% = 1017/10256 of the subjects in the enoxaparin arm had a primary endpoint event (death and non-fatal myocardial re-infarction within 30 days). Approximately 12% = 1223/10223 of the subjects in the heparin arm had a primary endpoint event. This difference represents an estimated relative risk of 0.83 with a 95% confidence interval of (0.766, 0.897) and is statistically significant ( $p=0.000003$ ). These numbers are from the Study Report and confirmed by the reviewer. The results for the primary endpoint and the two components are in Table 3. The components are analyzed in two different ways. The first counts all events, so if a subject had a myocardial re-infarction and subsequently died within 30 days, these would count as two events. The second analysis only counts the first event (e.g. only the myocardial re-infarction would be counted in the example given).

**Table 3** Analysis of primary 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

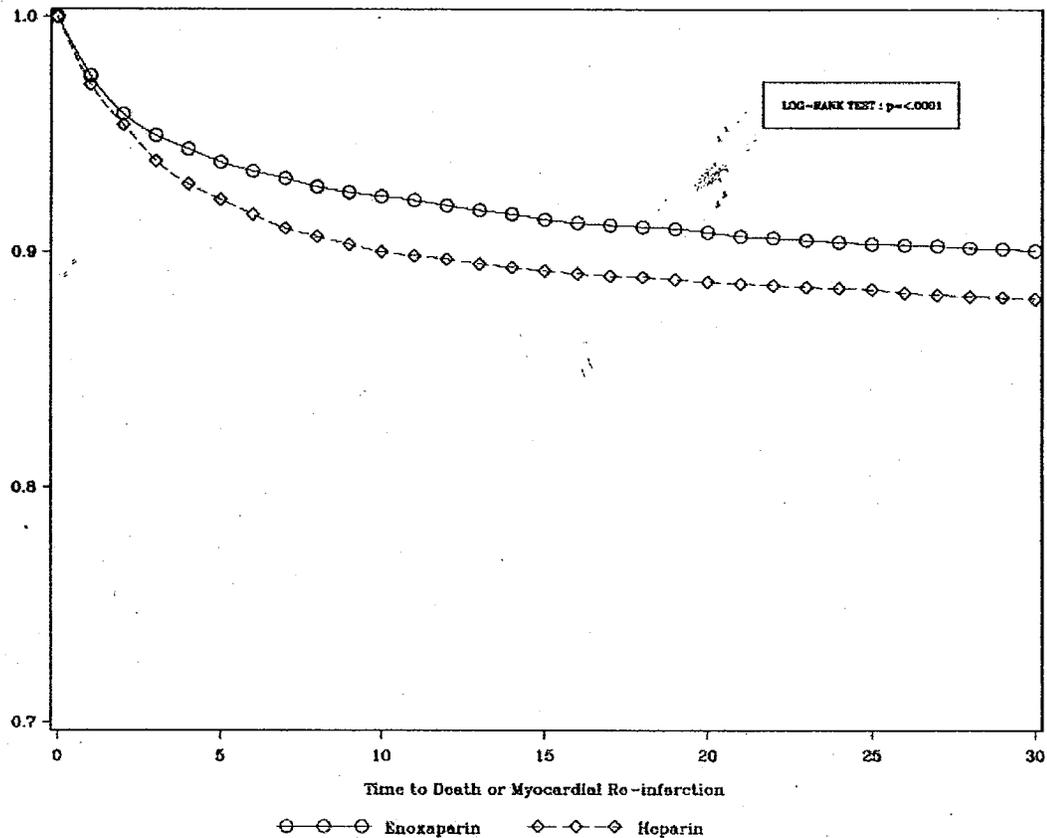
Source: Study Report, pp 77-79 and FDA analysis.

The Kaplan-Meier curves for the estimated proportion of subjects who survived each day without an event through 30 days appear in

Figure 1. The curves appear to diverge at about Day 3 and continue to separate further until about Day 6. The difference at Day 6 appears to persist through Day 30. Both curves appear to drop rapidly within the first 10 days, but stay more or less constant thereafter.

**APPEARS THIS WAY ON ORIGINAL**

**Figure 1** Kaplan-Meier estimates of event-free survival.



Source: Study Report p. 75

Three interim analyses were planned and an O'Brien-Fleming type boundary was used. The interim boundary was crossed at the third interim analysis, but the DMC apparently decided not to stop the study in order to obtain more information. The nominal alpha remaining at the final analysis is 0.0434.

There was one main secondary endpoint defined as the composite of death, myocardial re-infarction or myocardial ischemia leading to urgent revascularization. There were 1199/10256  $\approx$  11.7% events in the enoxaparin group and 1479/10223  $\approx$  14.5% events in the heparin group. This represents an estimated relative risk of 0.81 and is statistically significant ( $p < 0.0001$ ).

### 3.2 Evaluation of Safety

The safety population included a total of 20327 subjects (enoxaparin: 10176, heparin: 10151) who received at least 1 dose of study treatment. Approximately 2.1% of the subjects in the enoxaparin arm had a major hemorrhagic episode within 30 days compared to approximately 1.4% in the heparin arm. This difference represents an estimated relative risk of 1.53 and is statistically significant ( $p < 0.0001$ ). See medical review for more detailed safety review.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

The results for the primary endpoint in subgroups defined by gender, race and age appear in Table 4. Numerically, the difference between groups appeared to be smaller in subjects at least 75 years old and in non-Caucasian race, but the interaction p-values are not significant.

**Table 4** Results for primary endpoint in demographic subgroups

Baseline covariate subgroup	Enoxaparin n/N (%)	UFH n/N (%)	Relative Risk (95% CI)	p-value for interaction
Age (years)				
<75	709/9015 (7.9)	883/8932 (9.9)	0.80 (0.72-0.87)	0.1042
≥75	308/1241 (24.8)	340/1291 (26.3)	0.94 (0.82-1.08)	
Sex				
Male	646/7841 (8.2)	790/7855 (10.1)	0.82 (0.74-0.90)	0.9155
Female	371/2415 (15.4)	433/2368 (18.3)	0.84 (0.74-0.95)	
Race				
Caucasian	890/8935 (10.0)	1096/8920 (12.3)	0.81 (0.75-0.88)	0.1144
Non-Caucasian	127/1320 (9.6)	127/1303 (9.7)	0.99 (0.78-1.25)	

Source: Study Report p. 76

The results for TIMI major bleeding endpoint in subgroups defined by gender, race and age appear in Table 5. The risk of bleeding appears numerically to be increased in each subgroup.

**Table 5** Safety results for TIMI major bleeding in demographic subgroups (Safety population)

Baseline covariate subgroup	Enoxaparin n/N (%)	UFH n/N (%)	RR (95% CI)	p-value for interaction <sup>a</sup>
Age (years)				
<75	170/8944 (1.9)	101/8870 (1.1)	1.67 (1.31, 2.13)	0.1548
≥75	41/1232 (3.3)	37/1281 (2.9)	1.15 (0.74, 1.78)	
Sex				
Male	156/7777 (2.0)	105/7793 (1.3)	1.49 (1.16, 1.90)	0.7018
Female	55/2399 (2.3)	33/2358 (1.4)	1.64 (1.07, 2.51)	
Race				
Caucasian	181/8871 (2.0)	125/8875 (1.4)	1.45 (1.16, 1.82)	0.2036
Non-Caucasian	30/1304 (2.3)	13/1276 (1.0)	2.26 (1.18, 4.31)	

Source: Study Report p. 86

### 4.2 Other Special/Subgroup Populations

The results for the primary endpoint in subgroups defined by gender, race and age appear in Table 6. The difference between groups appeared to be smaller in subjects with TIMI risk score larger than 3 and the interaction p-value for that subgroup is significant. Less

than 200 subjects total were enrolled from North American sites. Consequently, there is not much information about any possible difference in efficacy between North American sites and other sites.

**Table 6** Results for primary endpoint in special subgroups

Baseline covariate subgroup	Enoxaparin n/N (%)	UFH n/N (%)	Relative Risk (95% CI)	p-value for interaction
<b>Fibrinolytic drug use</b>				
Streptokinase	213/2083 (10.2)	242/2056 (11.8)	0.87 (0.73-1.03)	0.5818
Fibrin-specific fibrinolytic drugs	801/8142 (9.8)	974/8141 (12.0)	0.82 (0.75-0.90)	
<b>Regions</b>				
North America	6/79 (7.6)	11/87 (12.6)	0.60 (0.23-1.55)	0.6400
Western Europe	201/2422 (8.3)	267/2426 (11.0)	0.75 (0.69-0.87)	
Other	810/7755 (10.4)	945/7710 (12.3)	0.85 (0.78-0.93)	
<b>TIMI risk score</b>				
0 to ≤3	335/6534 (5.1)	507/6519 (7.8)	0.66 (0.58-0.75)	<0.0001
>3	668/3605 (18.5)	700/3618 (19.3)	0.96 (0.87-1.05)	
<b>PCI in 30 days</b>				
Yes	247/2295 (10.8)	337/2421 (13.9)	0.77 (0.66-0.90)	0.2705
No	770/7961 (9.7)	866/7802 (11.4)	0.85 (0.78-0.93)	

Source: Study Report p. 76

The results for TIMI major bleeding endpoint in subgroups defined by gender, race and age appear in Table 7. The risk of bleeding appears numerically to be increased in each subgroup except subjects with PCI in the past 30 days. Although the number of events is small in this subgroup, the interaction test p-value is significant.

**Table 7** Safety results for TIMI major bleeding in special subgroups (Safety population)

Baseline covariate subgroup	Enoxaparin n/N (%)	UFH n/N (%)	RR (95% CI)	p-value for interaction <sup>a</sup>
<b>BMI (mg/kg<sup>2</sup>)</b>				
Male and BMI ≤30	162/7534 (2.2)	103/7640 (1.3)	1.59 (1.25, 2.04)	0.9463
Female BMI ≤28.6				
Male and BMI >30	40/2344 (1.7)	24/2204 (1.1)	1.57 (0.95, 2.59)	
Female BMI >28.6				
<b>Systolic blood pressure</b>				
<100 mmHg	10/377 (2.74)	6/342 (1.8)	1.51 (0.56 - 4.12)	0.9907
≥100 mmHg	201/9797 (2.17)	132/8808 (1.3)	1.52 (1.23 - 1.90)	
<b>Diastolic blood pressure</b>				
<110 mmHg	209/10084 (2.1)	138/10054 (1.4)	1.51 (1.22-1.87)	0.9992
≥110 mmHg	1/90 (1.1)	-/95/9207 (-)	- (-)	
<b>CrCl</b>				
≤30 mL/min	65/115 (5.2)	3/118 (2.5)	2.05 (0.53 - 8.01)	0.8806
>30 mL/min	188/9148 (2.1)	122/9210 (1.3)	1.55 (1.24 - 1.94)	
<b>PCI in 30 days</b>				
Yes	34/2261 (1.5)	42/2384 (1.8)	0.86 (0.55-1.34)	0.0043
No	177/7915 (2.2)	96/7757 (1.2)	1.81 (1.41-2.31)	

Source: Study Report p. 86

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

There is strong evidence that enoxaparin is superior to unfractionated heparin in reducing the risk of myocardial re-infarction within 30 days in the population studied. The difference in the event-free survival curves appears to emerge at about 3 days and persist for 30 days.

### **5.2 Conclusions and Recommendations**

There is strong evidence that enoxaparin is superior to unfractionated heparin in reducing the risk of myocardial re-infarction within 30 days in the population studied. There is also strong evidence that the risk of thrombolysis in myocardial infarction (TIMI) major hemorrhage within 30 days is higher in the enoxaparin treated group. There does not appear to be any particular subgroup that has an especially large treatment effect or especially small increased risk of bleeding.

**APPEARS THIS WAY ON ORIGINAL**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
John Lawrence  
3/13/2007 01:41:18 PM  
BIOMETRICS

James Hung  
3/15/2007 08:58:59 AM  
BIOMETRICS