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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00077844
		Study Code:	XRP4563_4001
Generic drug name:	enoxaparin	**Date:**	13 September 2007

Title
An international phase 2-3, stratified, randomized, open-label, parallel-group clinical trial to evaluate the safety and efficacy of a single intravenous bolus of enoxaparin versus intravenous unfractionated heparin in patients undergoing non-emergent Percutaneous Coronary Intervention

Investigator(s), study site(s)
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124 centers in 9 countries: Australia and New Zealand (6 sites), Belgium (5 sites), Canada (14 sites), France (13 sites), Germany (12 sites), Italy (7 sites), Spain (11 sites), USA (56 sites).

Study duration and dates
First subject enrolled on 13 January 2004 and the last subject completed on 16 February 2005

Phase II-III

Objectives
Primary: To determine the safety of intravenous enoxaparin (0.50 mg/kg and 0.75 mg/kg) compared to intravenous unfractionated heparin (UFH) in patients undergoing non-emergent percutaneous coronary intervention (PCI), as assessed by measuring the incidence of non-coronary artery bypass graft (CABG) major and minor bleeding up to 48 hours following the index PCI.

*Secondary:*The main secondary endpoint was an efficacy endpoint assessed by the percentage of subjects that were treated with intravenous enoxaparin who reached target anti-factor X activated (anti-Xa) level compared to the percentage of subjects that were treated with intravenous UFH who reached target activated clotting time (ACT) level, both at the beginning and end of procedure.

The other secondary endpoints included the following:

1. The composite event rate of non-CABG major bleeding [up to 48 hours (H48) following the index PCI], all-cause mortality, non-fatal myocardial infarction (MI), and urgent target vessel revascularization (UTVR) (by either PCI or CABG) at Day 30 following the index PCI.
2. The composite event rate of all-cause mortality and non-fatal MI at Day 30.
3. The time to event, defined as the time between index PCI and date of all-cause mortality, non-fatal MI, or UTVR at Day 30, whichever occurred first.

Study design
This was a multicenter, multinational prospective, open-label, randomized, 3-arm parallel-group investigation designed to evaluate the safety and efficacy of a single intravenous (IV) bolus of enoxaparin

0.50 mg/kg and 0.75 mg/kg compared to intravenous ACT-adjusted UFH in patients undergoing non-emergent PCI. Randomization was stratified according to planned GpIIb/IIIa inhibitor use. All patients received aspirin and/or a thienopyridine. Study treatment was administered after sheath placement and immediately prior to the PCI. Hospital discharge was scheduled 48 hours after PCI, and follow-up duration was 30 days.

Number of subjects planned
A total of 3532 patients including 1072 in the enoxaparin 0.50 mg/kg group and 1230 in each of the enoxaparin 0.75 mg/kg and UFH groups.

Inclusion criteria
Male or non-pregnant female =18 years of age; undergoing non-emergent single or multiple sites/vessels PCI during the same procedure; PCI to be performed with a femoral approach; informed consent obtained in writing at enrollment into the study.

Treatments
Commercially available enoxaparin was used, according to locally registered product presentationin prefilled syringes and vials. Enoxaparin was diluted in dextrose water 5% (DW5) or 0.9% normal saline solution, and the necessary volume was sampled according to the dose allocated by randomization (0.50 mg/kg or 0.75 mg/kg) and weight for each patient.
Commercially available sodium heparin was used. An initial IV bolus of 50 to 70 IU/kg was administered to achieve a target ACT of 200-300 seconds for patients receiving GpIIb/IIIa inhibitors, and an initial IV bolus of 70 to 100 IU/kg was administered to achieve a target ACT of 300-350 seconds for patients not receiving GpIIb/IIIa inhibitor.

Study endpoints
Primary safety endpoint of the study was the composite of non-CABG major and minor bleeding up to H48 after index PCI.
Main secondary efficacy endpoint was the success rate of achieving ACT target range of 300-350 seconds for patients not receiving concomitant GpIIb/IIIa inhibitor or 200-300 seconds for patients receiving concomitant GpIIb/IIIa inhibitor for UFH, anti-Xa target range of 0.5 to 1.8 IU/mL for enoxaparin both at the beginning and end of procedure.
Other Secondary efficacy endpoints

1. The composite event rate of non-CABG major bleeding [up to 48 hours (H48) following the index PCI], all-cause mortality, non-fatal myocardial infarction (MI), and urgent target vessel revascularization (UTVR) (by either PCI or CABG) at Day 30 following the index PCI.
2. The composite of all-cause mortality, non-fatal MI at day 30.
3. The time to event, defined as the time between index PCI and date of all-cause mortality, non-fatal MI, or UTVR at Day 30, whichever occurred first.

Safety data
Adverse events reported by the subject and noted by the investigator; laboratory tests including hematology (hemoglobin, hematocrit, platelet count), and blood chemistry (creatine kinase-myocardial band isoenzyme (CK-MB), creatine kinase (CK), troponin I and T); 12-lead electrocardiogram (ECG).

Statistical procedures
Primary safety endpoint
The incidence of non-CABG major and minor bleeding up to H48 was compared between each enoxaparin group (0.50 mg/kg and 0.75 mg/kg) and the UFH group in the intent-to-treat (ITT) population using logistic regression model, with treatment group as explanatory variable, and GpIIb/IIIa inhibitor use and the time of randomization (before or after 22 November 2004, date when randomization in the enoxaparin 0.50 mg/kg arm was stopped) as adjusting covariates.

If superiority of enoxaparin over UFH was not observed, the non-inferiority of enoxaparin to UFH would be tested using 2-sided confidence intervals of the differences in event rates, adjusted on GpIIb/IIIa inhibitor use and time of randomization. The non-inferiority margin Δl was to be taken as 30% of UFH rate; non-inferiority of each dose of enoxaparin versus UFH would be concluded if the upper limit of the confidence interval was =Δl.

The same analysis was conducted in the per-protocol (PP) population.

Main secondary efficacy endpoint:
Target anti-Xa and target ACT: the percentage of subjects that were treated with enoxaparin who reached the target anti-Xa levels and the percentage of subjects that were treated with UFH who reached the target ACT levels were compared in the ITT population using logistic regression model, with treatment group as explanatory variable, and GpIIb/IIIa inhibitor use and the time of randomization as adjusting covariates.

Other secondary efficacy endpoints:
Composite of all-cause mortality, non-fatal MI, UTVR up to Day 30 and non-CABG major bleeding up to H48 was to be compared between each enoxaparin group and UFH with the objective to show non-inferiority. Logistic regression model was to be used, with treatment group as explanatory variable, and the time of randomization as adjusting covariate. The 95% adjusted confidence interval of the difference in percentage between the two treatment groups was calculated; the non-inferiority margin Δl was to be taken as 39% of UFH rate. Non-inferiority of each dose of enoxaparin versus UFH would be concluded if the upper limit of the confidence interval was =Δl.

Time to event of the composite of all-cause mortality, non-fatal MI at day 30, and time to event of all-cause mortality, non-fatal MI and UTVR until Day 30: the hazard ratios and its 95% CI (adjusted for time of randomization) with the associated p-value were to be calculated for each enoxaparin dose versus UFH.

Simes adjustment for multiplicity was used.

Interim analysis
The Data Monitoring Committee (DMC) reviewed the data on an ongoing basis. At the fourth interim analysis on 3089 patients, the DMC noted that the all-cause mortality in enoxaparin 0.50 mg/kg group tended to be higher than in either the UFH group (p=0.1477) or the enoxaparin 0.75 mg/kg group (p=0.0265). Even though the numbers were small, the DMC recommended that randomization in the enoxaparin 0.50 mg/kg arm be stopped as the Pocock boundary of 0.02664 was crossed.

Results - Study subjects and conduct

Distribution of the study subjects:

	Enox 0.5	Enox 0.75	UFH	All
ITT population	1070	1228	1230	3528
Per-protocol population	955 (89.3%)	1123 (91.4%)	1131 (92.0%)	3209 (91.0%)
Safety population *	1041	1202	1223	3466

Enox = enoxaparin; UFH = unfractionated heparin

* 2 subjects were treated without any randomization (1 patient with enoxaparin 0.50 mg/kg, the other with UFH); they were included in the safety analysis only

Subject characteristics at baseline:

	Enox 0.5 N=1070	Enox 0.75 N=1228	UFH N=1230	All N=3528
Age (years) Mean (SD)	63.4 (10.5)	63.6 (10.2)	63.5 (10.2)	63.5 (10.3)
≥75	16.7%	14.7%	15.0%	15.4%
Male	74.7%	76.1%	74.0%	74.9%
Ethnic group				
White	93.0%	94.0%	93.2%	93.4%
Black	2.8%	2.3%	3.2%	2.8%
Asian/Oriental	2.3%	2.1%	1.6%	2.0%
Other	1.9%	1.6%	2.0%	1.8%
Weight (kg) Mean (SD)	84.0 (16.9)	84.2 (16.7)	83.3 (16.0)	83.8 (16.5)
BMI ≥30 kg/m^2	37.2%	33.9%	34.6%	35.1%
Renal insufficiency	18.7%	19.0%	19.6%	19.1%
Diabetes	30.3%	29.2%	30.9%	30.1%
Prior MI				
MI ≤7 days	1.9%	2.7%	2.2%	2.4%
MI ≤48 hours	0.4%	0.7%	0.2%	0.5%
Prior UA				
UA ≤7 days	11.8%	12.9%	11.6%	12.1%
UA ≤48 hours	5.1%	5.9%	4.9%	5.3%
UA or MI within the previous 7 days	13.1%	14.7%	13.0%	13.6%
Prior PCI	34.7%	36.5%	38.9%	36.8%
Prior CABG	14.4%	12.7%	15.1%	14.1%
Platelet count <80 000/mm^3	0.1%	0.1%	0.0%	0.1%
Hemoglobin <10 g/dL for women or 11g/dL for men	1.7%	3.2%	3.2%	2.8%

Enox = enoxaparin; UFH = unfractionated heparin; SD = standard deviation; BMI = body mass index; MI = myocardial infarction; UA = unstable angina; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

Results – Study endpoint

1. Analysis of non-CABG major and minor bleeding up to H48 in the ITT population, the primary study endpoint:

	Enox 0.5 N=1070	Enox 0.75 N=1228	UFH N=1230
Evaluable for non-CABG bleeding up to H48	1046	1206	1212
Subjects with major and minor bleeding	63 (6.0%)	80 (6.6%)	105 (8.7%)
p-value for comparison versus UFH	0.014*	0.052	
95% CI of the adjusted difference (Enoxaparin – UFH)	[-4.8%; -0.5%]	[-4.1%; 0.0%]	
Minor bleeding	51 (4.9%)	65 (5.4%)	72 (5.9%)
Major bleeding	13 (1.2%)	15 (1.2%)	34 (2.8%)

Enox = enoxaparin; UFH = unfractionated heparin; CI = confidence interval
Simes adjustment was used: * indicates significant difference

There was a significantly lower bleeding rate with enoxaparin 0.50 mg/kg than with UFH: 31% reduction rate but no significant difference between enoxaparin 0.75 mg/kg and UFH, although there was a 24% reduction rate with enoxaparin 0.75 mg/kg versus UFH.

Enoxaparin 0.75 mg/kg was found non-inferior to UFH: the non-inferiority margin of 2.6% defined in the protocol as 30% of observed rate in UFH group was greater than the upper bound of the 95% CI equal to 0.0%.

Both enoxaparin 0.50 mg/kg and enoxaparin 0.75 mg/kg provided a 57% reduction rate versus UFH in non-CABG major bleeding up to H48 (p-values of 0.005 and 0.007, respectively).

2. Analysis of target anti-Xa values and ACT in the ITT population, the main secondary endpoint:

	Enox 0.5 N=1070	Enox 0.75 N=1228	UFH N=1230
Evaluable for anti-Xa/ACT	978	1139	1134
Target reached at beginning and end of procedure	771 (78.8%)	1045 (91.7%)	223 (19.7%)
p-value from comparison versus UFH	<0.001*	<0.001*	

anti-Xa = anti-factor X activated; ACT = activated clotting time; Enox = enoxaparin; UFH = unfractionated heparin
Simes adjustment was used: * indicates significant difference

Significantly more patients were in the target range in the enoxaparin groups compared to UFH group.

3. Analysis of the combined event rate of non-CABG major bleeding up to H48, all-cause mortality, non-fatal MI, UTVR up to Day 30 in the ITT population:

	Enox 0.5 (N=1070)	Enox 0.75 (N=1228)	UFH (N=1230)
Evaluable for composite endpoint	1032	1191	1198
Number of subjects with:			
Major bleeding	13	15	34
Death	10	3	5
Non-fatal MI	50	76	65
UTVR	8	14	8
Composite of non-CABG major bleeding up to H48, death, non-fatal MI, UTVR up to Day 30	74 (7.2%)	94 (7.9%)	101 (8.4%)
p-value for comparison versus UFH	0.477	0.636	
95% CI of the adjusted difference (Enoxaparin – UFH)	[-3.2; 1.5]	[-2.7; 1.6]	

Enox = enoxaparin; UFH = unfractionated heparin; MI = myocardial infarction; UTVR = urgent target vessel revascularization
Simes adjustment was used: * indicates significant difference
Non-inferiority margin, 39% of UFH = 3.3 %

Both enoxaparin 0.50 mg/kg and enoxaparin 0.75 mg/kg were non-inferior to UFH: the 95% CI upper bounds exclude the 3.3% non-inferiority margin.

4. Analysis of hazard rates for death, non-fatal MI, UTVR up to Day 30 and for composites thereof - Adjusted analysis - ITT population

	Enox 0.5 (N=1070)	Enox 0.75 (N=1228)	UFH (N=1230)
Evaluable for time to event analysis	1070	1228	1230
Death: n (%)	10 (1.0%)	3 (0.2%)	5 (0.4%)
Hazard ratio, 95% CI, p-value versus UFH	3.35 [0.92;12.19] 0.066	0.61 [0.15;2.54] 0.495	
Non-fatal MI: n (%)	50 (4.7%)	76 (6.1%)	65 (5.2%)
Hazard ratio, 95% CI, p-value versus UFH	0.91 [0.62;1.34] 0.636	1.18 [0.85;1.65] 0.322	
UTVR: n (%)	8 (0.8%)	14 (1.1%)	8 (0.7%)
Hazard ratio, 95% CI, p-value versus UFH	1.35 [0.47;3.88] 0.582	1.77 [0.74;4.21] 0.199	
Death or non-fatal MI: n (%)	59 (5.6%)	79 (6.4%)	70 (5.6%)
Hazard ratio, 95% CI, p-value versus UFH	1.02 [0.71;1.47] 0.914	1.14 [0.83;1.58] 0.419	
Death, non-fatal MI or UTVR: n (%)	66 (6.2%)	84 (6.8%)	72 (5.8%)
Hazard ratio, 95% CI, p-value versus UFH	1.12 [0.79;1.60] 0.513	1.18 [0.86;1.62] 0.298	

% are hazard rates
Enox = enoxaparin; UFH = unfractionated heparin; MI = myocardial infarction; UTVR = urgent target vessel revascularization
Simes adjustment was used: * indicates significant difference.

Results - Safety

Incidence of treatment-emergent adverse events (TEAE), serious adverse events (SAEs) leading to death and other SAE:

	Enox 0.5 (N=1041)	Enox 0.75 (N=1202)	UFH (N=1223)
	n (%)	n (%)	n (%)
Subjects with TEAEs	431 (41.4)	539 (44.8)	516 (42.2)
Subjects with possibly-related TEAEs	183 (17.6)	261 (21.7)	258 (21.1)
Subjects with SAE up to H48 leading to death	5 (0.5)	0 (0.0)	2 (0.2)
Subjects with SAE up to Day 30 leading to death*	10 (1.0)	3 (0.2)	6 (0.5)
Subjects with SAE possibly-related up to Day 30 leading to death	4 (0.4)	0 (0.0)	0 (0.0)
Subjects with SAEs up to Day 30	127 (12.2)	136 (11.3)	145 (11.9)
Subjects with possibly-related SAEs up to Day 30	23 (2.2)	32 (2.7)	25 (2.0)

Enox = enoxaparin; UFH = unfractionated heparin; TEAE = treatment-emergent adverse event;
SAE = serious adverse event
*one subject in UFH group had an SAE up to Day 30 (on Day 23) leading to death, but the death occurred at Day 45, therefore he was not taken into account in the efficacy analysis

The incidence of SAEs was similar in the 3 treatment groups. Overall, Cardiac disorders, Vascular disorders, General disorders and administration site conditions, and Nervous system disorders were the most frequently reported classes of SAEs. These SAEs were considered as possibly related only in small percentages of subjects (=3%).

The slight increase in mortality noticed by the DMC in enoxaparin 0.50 mg/kg group (n=10 or 1.0%) was still not significantly different than enoxaparin 0.75 mg/kg (n=3 or 0.2%, p=0.06) nor than UFH (n=5 or 0.4%, p=0.07) at the end of the trial.

Date of the report : 27 February 2006