The review has found this study to be an adequate and well controlled clinical trial admissible as evidence to support DVT treatment as a new indication for Lovenox Injection. However, few imperfections during the actual conduct of the trial have weakened the inferences. The final wording in the Labeling must follow real data obtained rather than the study objectives as stated.

7.5 OBJECTIVE

The following objective was prestated in the Investigation Plan: "To compare the efficacy, safety and cost benefit of enoxaparin administered subcutaneously once or twice-daily to intravenous continuous infusion heparin therapy." It has not been changed during the conduct of this study.

In case the safety and efficacy of these three regimens is equivalent, the sponsor will promote the more convenient and less expensive of two enoxaparin regimens.

7.6 THE INVESTIGATIONAL PLAN

a. Study Design

The study was designed as a multicenter (74), randomized, partially blinded, 3-parallel-group, active treatment controlled clinical trial. Its aim was to compare two enoxaparin doses (1.0 mg/kg bid, or 1.5 mg qd, for at least 5 days) with a standard heparin regimens for in hospital treatment of symptomatic DVT with or w/o PE, or symptomatic PE with objectively confirmed low extremity DVT. All three regimens included warfarin for maintenance of anticoagulation (target INR 2.0-3.0). Warfarin therapy started within 48 hours of initiation of enoxaparin or heparin anticoagulation therapy and continued up to three months.

The primary efficacy endpoint was clinically symptomatic recurrent VTE (DVT or PE) within three months of randomization. Both events had to be confirmed by objective measures. DVT was confirmed by ultrasonography and/or venography. PE was diagnosed if the lung scan was classified as "high probability," when a pulmonary angiogram was positive, or if it was discovered at autopsy.

An Outcome Adjudication Committee of ten investigators and the sponsor's representative was established to assess each case for the occurrence or non-occurrence of VTE, the classification of hemorrhage into categories of major, minor or none, the occurrence or non-occurrence of immune thrombocytopenia, the cause of death, and for the occurrence of no significant clinical event. Patient cases were reviewed using data from patient profiles, case report forms, and serious adverse experience reports. All panel members were blinded to study treatment. All discrepancies (disagreement between investigator and expert panel assessment) were resolved by the adjudication members. Ten percent of randomly selected cases were cross-validated. A Vascular Imaging Committee was involved for consultations.

Safety was assessed for events of hemorrhage, adverse events, mortality, and abnormal laboratory results during the three months of the treatment and the follow-up period. Safety was assessed by the Safety Surveillance Committee.

b. Discussion on the Design and the Choice of Control Groups

Control Group

The control group included patients assigned to heparin regimen. Heparin is a drug already approved for prophylaxis and treatment of thrombus extension in acute DVT and PE (1997 PDR, p. 2832). In this study,

as well as in the other pivotal study CPK-2091, this heparin regimen included intravenous bolus of 5,000 IU of heparin sodium, followed by intravenous infusion adjusted to keep activated partial thromboplastin time (APTT) within the targeted range between 60 and 90 seconds (2-3 times the normal range). Within 48h (study '2091') or 70h (study '529') of heparin treatment, another drug, warfarin was introduced to achieve and maintain a targeted prothrombin time (INR 2.0-3.0). Warfarin is a drug with cumulative effect. The targeted anticoagulation is usually reached within 3-5 days. Once this target is reached, there is no need for continuation of heparin, and patients can be maintained on warfarin. Three months are considered as a period of the highest probability for extension or new DVT or PE to occur. Some advise prophylaxis of thromboembolic recurrence for six months. This trial was initially designed for follow-up duration of six months, but it was amended, and shortened due to the lack of patient compliance with warfarin therapy beyond three months.

Test Groups

Two enoxaparin regimens were compared with this "heparin standard" therapy. The first was an enoxaparin twice-daily (bid) regimen, a weight-adjusted fixed dose of 1.0 mg/kg, providing more consistent blood levels. The second was an enoxaparin once-daily (qd) regimen. It was a weight-adjusted fixed dose of 1.5 mg/kg, providing less consistent, but therapeutically active blood levels for 24h. This therapeutical approach includes warfarin maintenance to begin within 48h (study '2091') or 70h (study '529'), and to continue as described for the heparin regimen. There was no laboratory monitoring of the enoxaparin effects. Duration was limited to at least five days, and until the warfarin targeted INR was reached.

Study Periods

This design provided a treatment period of 5-10 days to reach the targeted anticoagulation rate, and a follow-up period of about 80 days for anticoagulation maintenance. The assumption was that the initial anticoagulation has the major impact on the outcome of VTE, and that the rate of recurrence of VTE (treatment failure) is dependent on the initial anticoagulation (heparin vs. enoxaparin) more than on the warfarin mediated maintenance. Some of previous studies (see references for this study), tested warfarin vs. heparin in the initial anticoagulation, and have supported this view.

The implementation of this design was faced with a practical problem. Patients presenting with acute VTE who arrived in hospital during weekend days (Friday-Sunday) or holidays, could have been confirmed for diagnosis of VTE only on Monday or the next working day. Only after confirmation, investigators could have requested randomization assignment and begin the treatment period. This problem was addressed by an amendment. Due to ethical motives, those patients were given anticoagulation with standard heparin prior to randomization. About 50% (47%) of enrolled patients had entered this initial anticoagulation. Ergo, a new Pre-Treatment Period was created. A small number of patients (47, 5.2%) received this pre-randomization heparin for more than 2 days (H=10/E1=19/E2=18)(From Table 14, Vol.25, p. 90). The impact of this period to the outcomes was not analyzed by the sponsor. Randomization helped in a sense that patients who entered the pre-treatment period were assigned comparably in the three treatment groups. Therefore, the initial heparin treatment could have had a little effect to the statistical analysis of equivalence between treatment groups.

c. Study population BEST POSSIBLE
BEST POSSIBLE

The targeted population was defined as "all patients with acute symptomatic DVT and/or PE." This wide definition was substantially limited by the eligibility criteria (Table 6-1)

More than 5000 patients with symptomatic DVT or PE who reported to the hospitals were screened to allow 900 eligible patients to enroll in this study.

Sample size calculations were based on a two-sided 95% confidence interval approach of establishing equivalence of two proportions with an assumed underlying incidence rate of 10% for heparin and enoxaparin. Given this assumption, it was calculated that a sample size of 190 patients per group will have 90% power to conclude that the incidence rate for enoxaparin is not worse than heparin by more than 10%. The sponsor was able to enroll 900 patients. They were randomized in three groups (H=290/E1=298/E2=312). Therefore, the sample size in this study was sufficient to allow the power for the planned statistical analysis.

Table 6-1 ELIGIBILITY CRITERIA

Inclusion Criteria

1. Male or female
2. Eighteen years or older.
3. Symptomatic and venographically diagnosed lower extremity DVT. If ultrasonography was positive, patients were included even if venography was inconclusive.
4. Symptomatic PE diagnosed by ventilation perfusion lung scan or pulmonary angiography. Source of embolization should have been confirmed by phlebography (symptomatic or asymptomatic lower extremity DVT).
5. Life expectancy greater than six months.
6. Informed consent signed.

Exclusion Criteria

1. Treatment with therapeutic doses of heparin (unfractionated or LMWH) for more than 24 hours prior to randomization.
2. Oral anticoagulant treatment within five days.
3. Need for thrombolytic therapy.
4. Active hemorrhage, active ulcerative disease or known angiodysplasia of the intestinal tract.
5. Known disease with a hemorrhagic risk (e.g., endocarditis, stroke, hemophilia).
6. Eye, spinal cord or central nervous system surgery within one month.
7. Severe renal insufficiency (creatinine >2.0mg/dL)
8. Disorders contraindicating anticoagulant therapy including oral anticoagulant therapy.
9. Allergy to heparin, protamine sulfate (fish) or chloride, swine products, iodine or radiopaque contrast media.
10. History of heparin associated thrombocytopenia (with or w/o thrombosis), or heparin or warfarin associated skin necrosis.
11. Treatment with other investigational therapeutic agents within the previous four weeks.
12. Patient with previous or requiring vena cava interruption (filter).
13. Known pregnancy or breast feeding.

d. Patients assignment (randomization) to treatment

All patients were randomly assigned into three treatment groups. Information about randomization is provided in the Statistical Section: Randomization Scheme and Codes (Vol.30, p.2).

For their eligible patients, the investigators requested assignment number from the sponsor's Biostatistics Department. The numbers were randomly selected (in ascending order by blocks of six) by this central service. No patient stratification was performed. It was permissible to randomize patients based on ultrasonography with confirmation of diagnosis by venography within 36 hours (Amendment 1, May 15, 1995).

For patient allocation to individual investigators and centers see List . . . in Appendix 3.

e. Dose selection BEST POSSIBLE
BEST POSSIBLE

Post-randomization treatment was designed to last 7±2 days. It lasted 10 days and more in 85 (9.4%) patients (H=19/E1=34/E2=32).

ENOXAPARIN: Enoxaparin was given in individual patient weight-adjusted doses. Patients assigned to **once daily treatment** (1.5 mg/kg qd) received one ampule 200 mg/mL enoxaparin plus placebo for morning injection, and one injection placebo for evening administration. Patients assigned to **twice-daily regimen** (1.0 mg/kg bid), received one ampule enoxaparin 100 mg/mL plus one ampule placebo for morning administration and one ampule 100 mg/mL for evening administration. The highest single dose used did not exceed 200 mg.

HEPARIN: Patients assigned to the heparin regimen received an intravenous bolus of 5,000 units, followed by a continuous infusion of heparin (20,000 units in 500 mL 5% dextrose in water [D5W]) at a rate of 32 mL per hour. The dose was adjusted to maintain APTT within the target rate of 60-80 seconds.

WARFARIN: (INR adjusted therapy for three moths) was considered as a part of both enoxaparin and heparin regimens. This drug was given to all patients. Warfarin therapy began on the evening of the second day of enoxaparin therapy. The first dose of warfarin was 10mg. A prothrombin time was performed daily and the warfarin was prescribed to achieve a targeted INR of 2.0-3.0 during the entire study period of three months.

f. Blinding

The information on blinding is provided in the Study Report, section Clinical Methods: Blinding (Vol.25, p.38).

Heparin and warfarin administration were not blinded.

Only enoxaparin administration was blinded. All patients assigned to either once or twice daily enoxaparin treatment received three subcutaneous injection daily, two administered simultaneously and one 12 hours later. All study medications for these treatment groups were supplied by the sponsor and packaged individually for each patient. The individual patient boxes were identical. Boxes (containing medication for 14 day period) were labeled with study number, randomization number, an investigational drug warning, and the sponsor's name.

Although desirable, double-blind principle for drug administration could not be used in this study. A continuous intravenous infusion of heparin, peroral administration of warfarin and subcutaneous injection of enoxaparin can not be blinded. However, blinding was used for enoxaparin dose. Neither investigators, nor patients were aware of whether once- or twice daily regimen was administered.

To minimize the possibility for bias, the sponsor has used another blinding principle: an outcome adjudication committee was formed to assess venograms, duplex ultrasounds, and lung scans, and to make decision about the clinical outcome (symptomatic VTE). Members of this committee were blinded for treatment allocation. Their decision was used for the statistical analysis.

g. Efficacy and safety variables recorded and data quality insurance.

Information for both efficacy and safety assessment was recorded on Case Report Forms (CRF). Data on these forms were recorded by investigators and other research personnel if designated by the investigator. These data include information obtained during the treatment period (daily clinical monitoring, clinical personnel reporting, patient reporting) and the follow-up period (monthly visits, and patient reporting of outcome and serious adverse events). Any information for outcome event had to be confirmed by objective assessment. This design creates environment for reasonable expectation that at least outcome and serious adverse events could have not been missed.

1) *Efficacy*

a. The primary efficacy variable was defined as:

- The clinically symptomatic and objectively confirmed VTE (DVT and or PE) occurring in the intent-to-treat population within three months of randomization.

b. The secondary efficacy variables were defined as:

- The incidence of recurrent VTE for evaluable patients (P-P population).
- The absolute change in Marder score for patients with venography at baseline and at day 8±2; and the change in the ventilation perfusion lung scan or pulmonary angiography.

c. Criteria for DVT

Clinically suspected DVT was verified by a combined approach including duplex ultrasonography and/or venography. On sonography, an acute thrombus was diagnosed by noncompressibility of a vein and an increased intraluminal signal. On venography, a constant intraluminal filling defect with defined margins, or a segmental venous occlusion with an intraluminal filling defect at the proximal or distal point of occlusion, were considered as diagnostic criteria for DVT. A modified Marder's score was used for quantitative assessment of DVT. The Vascular Imaging Committee assigned a score for each venogram without knowledge of treatment group but with knowledge of whether a specific venogram represented a routine baseline, paired-sequential or suspected recurrence study.

d. Criteria for PE

Clinically suspect PE was verified by a perfusion, or ventilation-perfusion lung scanning. PE was diagnosed if the lung scan was classified as high probability for PE, and when a subsequent pulmonary angiogram was positive in a patient with a non-high probability lung scan, or if PE was discovered at autopsy. All lung scans were re-read by one member of the Vascular Imaging Committee in a blinded manner.

2) *Safety*

Safety was assessed by the incidence of hemorrhagic events, adverse events and mortality. Events were presented as absolute numbers, percent of incidence for all treatment groups, and combined.

- Hemorrhage

Hemorrhage was classified as major if it was clinically overt and associated with at least one of the following features: a fall in hemoglobin level of 2 g/dl or more, a transfusion of at least two units of blood, if it was retroperitoneal, intracranial or intraocular; if it resulted in a serious or life threatening event, if surgical or medical intervention was needed to stop or control the event, or if resulted in dead.

Hemorrhage was defined as minor if it was clinically overt, did not meet criteria for major bleeding, and was associated with at least one of the following features: epistaxis lasting more than five minutes or requiring intervention, ecchymosis or hematoma larger than five centimeters; hematuria not associated with urinary catheter trauma; gastrointestinal hemorrhage not related to intubation or nasogastric tube placement; wound hematoma and subconjunctival hemorrhage requiring cessation of medication. Hemorrhage was evaluated during the treatment period and within 48 hours after enoxaparin or heparin treatment. All occurrences were adjudicated for severity by the outcome Adjudication Committee whose classification was used in the final statistical analysis.

- Adverse Events

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Adverse events were defined as any undesirable event associated with the use of a drug, whether or not considered drug related, and included any side effect, injury, toxicity, or sensitivity reaction, including laboratory changes which did not commonly occur in the patient.

These events were observed by the investigator, reported by the patient or elicited by general questioning, between the first dose of study medication and the final evaluation (3 months).
These events were recorded by the investigator in the adverse event section of the case report form (CRF).

- Mortality

Mortality by any cause within three months was recorded as an outcome measure. The study did not show any death related to the study medications.

3) *Clinical and Laboratory Methods Used for Assessment of Efficacy and Safety*

Medical history, physical exam and laboratory analyses were conducted at baseline, whenever necessary during the treatment period, and at the end of treatment.

Laboratory analyses include: Daily coagulation: prothrombin time (PT), APTT. Hematology on day 3 and day 6: CBC, differential (not on day 3), and platelet count. Chemistry (liver and kidney profile) on day 0 and 3: alkaline phosphatase, AST, ALT, total bilirubin, creatinine and potassium. Screen for occult hemorrhage of urine and stool on day 6.

CBC, PT and APTT were assessed at each monthly follow-up visit for the three months: .

h. Concomitant medication

Concomitant medication was not forbidden. However, all medications were recorded and analyzed. Concomitant medication were defined to be medications given throughout the study treatment period, and continuing 48 hours thereafter.

7.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL

a. Statistical and Analytical Plan

Statistical Analysis Plan for Protocol RP5453-529 (final version) is presented in Vol. 30, pp. 2-10; Statistical Methodology is presented in Vol.31, pp.374-411, and the results of statistical analysis are presented on Summary Tables (Vol.30, pp.28- Vol.31, p. 374). This section of the Study Report is reviewed in detail by the Division statisticians (see Statistical Review).

The objective of the statistical analysis was to show that an anticoagulant regimen consisting of fixed dose subcutaneous enoxaparin administered once or twice-daily was as effective as a standard anticoagulant regimen consisting of heparin administered by continuous intravenous infusion.

Table 7-1
REVIEWER'S SUMMARY OF THE STATISTICAL PLAN

Parameter	Variable Analyzed	Patient population*	Statistical method
Baseline characteristics	Demographics: age, gender, race, weight, height, BMI, BSA	ITT, Evaluable	N & %
Primary efficacy	Incidence of recurrent VTE** within 3 months	Evaluable. 200 for each treatment arm.	95%CI. E1/E2 was not worse than H by 10%
Secondary Efficacy	Incidence of recurrent VTE** within 3 months	ITT	
	Change of Marder's score	Pts with venograms (or VPLS) at baseline and day 8	Signs of recurrence of worsening (OAC)#
	Incidence of symptomatic recurrent VTE	Subgroups by: age, sex, weight, predefined risk factors, country, investigator	N & %
Safety	Incidence of hemorrhage	ITT: treatment period	minor, major. N & %
	Incidence of adverse events	ITT: treatment and study period	COSTART Descending order
	Laboratory parameters of clinical concern	ITT: hemoglobin, thrombocytopenia, thrombocytosis, bilirubin, AST & ALT, Potassium	Shift tables: percent of patients outside the normal range at two contrasting time points.

*Three populations: ITT (see definition); Evaluable (excluded patients with at least one of the non-evaluability criteria); Subgroup of ITT: patients who had repeat venographies and ventilation-perfusion lung scans performed on day 8 (6-10).# OAC= Outcome Adjudication Committee.

This Statistical Plan failed to recognize warfarin as a study medication. This plan did not consider failure of warfarin maintained INR ratio (below or above the targeted range) during the follow-up period as a possible cause for occurrence of either VTE (less protection) or hemorrhage (increased anticoagulation).

The Statistical Plan recognized only two study periods: Treatment and Follow-up. The Pretreatment Period, which included almost a half of the patients, was invisible for the statistical analysis. Only exception was the part related to the use of study medications per study days (prior and after randomization).

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b. Efficacy evaluation

The primary efficacy variable was defined as the incidence rate of clinically symptomatic VTE - that is, the treatment failure rate in the all-treated patient population - within three months following randomization. Decision whether one event to be classified as VTE was left to the Clinical Outcome Adjudication Committee. Evaluability of the endpoint was not based only on objective tests, but to the assessment of clinical signs and/or objective test data by this Committee.

The secondary efficacy analyses included:

- The incidence rate of symptomatic VTE in the evaluable patient population.
- The site of the recurrences (proximal or distal, PE).
- Time to first clinically symptomatic VTE.

- Subgroup analysis of patients who had venograms both at baseline and day 8. The efficacy parameter in this analysis was the absolute change in the Marder's score between these two assessments.
- "Shift table" analysis on the same group of patients who had ventilation-perfusion lung scan both at baseline and day 8, crossing the experts classification at the two time points. .
- Incidence rate of symptomatic VTE were summarized within the following patient subsets:
  - age by decades;
  - weight in categories;
  - gender;
  - all risk factors;
  - country;
  - investigator.

[redacted] BEST POSSIBLE

c. Safety Evaluation

Safety analyses were performed on the all-treated population only on the following parameters:

- The incidence of episodes of hemorrhages (primary safety parameter). This includes the percentage of patients transfused, for the study treatment period plus 2 days, and for the whole study period. Concordance of event classification between investigator and OAC was described.
- The incidence of adverse events. AE for the treatment period plus two days, and for the entire duration of the study.;
- Laboratory parameters of clinical concern Hemoglobin, platelet counts, bilirubin, AST and ALT. Shift tables: from baseline to end of treatment period, from end of treatment period to follow-up visit month 1,2 and 3.

The observation period was three months post randomization, including day 97 (three month plus one week).

d. Sample size for statistical evaluation

The sample size calculation was based on the 95% confidence interval method for evaluating therapeutic equivalence. A true recurrent VTE incidence rate of 10% on heparin was assumed. At α=0.05 and power 90%, a total of 200 evaluable patients per arm were needed to conclude that enoxaparin is not different from heparin by more than 10% when treatments are truly equal. This number of patients per treatment group was reached.

e. Non-Evaluability criteria

Criteria for determination of non-evaluability were defined in the following order:

- DVT at entry not confirmed.
- Insufficient or wrong study therapy.
- Three months follow-up visit not completed.
- Inferior vena cava filter placement after randomization.
- Patient randomized twice.

7.8 DISPOSITION OF PATIENTS ENTERED

Patients who entered the study were evaluated for a number of clinical characteristics which, if not recognized and comparably distributed at baseline, could have created confounding variables for interpreting study outcomes. The list of these characteristics under consideration in this trial follows.

- Patient demographics
- Age (<40, 40-49, 50-59, 60-69, 70-79, ≥80)
- Gender (M/F)
- Race
- Weight in kg
- Height in cm
- BMI (body Mass Index) calculated as: weight (kg)/height(m^2)
- BSA (body surface area) calculated as: $(Weight^{0.5378})*(Height^{0.3964})*0.024265$.

- Risk Factors
- Obesity
- DVT and/or PE: Total, Only DVT, Only PE
- Prolonged immobilization
- Varicose veins
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Cancer and Chemotherapy/Radiation
- Recent surgery
- Estrogen containing medication.

During the conduct of this study, three categories of patient population were formed: all-treated, completed and evaluable. All-treated population is comparable to intent-to-treat population. It includes all patients who were randomized, and have received at least one dose of study medication. Completed population is a group of patients who completed the study but who have not necessarily received all study medication or have performed all study procedures as planned. The evaluable population included all patients who received study medication as planned, who completed all study procedures, and had endpoints evaluable for blinded assessment by adjudication committee.

These three population were formed evaluating "what happened to patients on day-by-day basis during the study." This set of characteristics analyzed includes information such as:

- Exposure to study medication
- Concomitant medication
- Dropouts before study
- Protocol violations.
- Study discontinuation by various reasons
- Deaths
- Occurrence of study endpoints.
- Serious adverse event
- Withdrawal of the consent
- Missing information

7.9 STUDY RESULTS

7.9.1 Data Sets Analyzed

a. Patient disposition

A total of 5254 patients were screened to allow 900 patients to be randomly assigned to 60 investigators (81% of planned) in 16 countries (Table 1). Seventeen investigators had ≤5 patients assigned. Seven of them had only one patient. Only six investigators had ≥30 patients.(Table 13.1 [Vol.25, p.81-2]).
At the end of this study (97 days) 740 patients were found to be evaluable. One hundred-sixty of them had one or more criteria for non-evaluability status. Non-evaluable patients are summarized (Table 7.9-1)

Table 7.9-1
SUMMARY OF PATIENTS EVALUABILITY AND STUDY COMPLETION

Patients		Heparin	E1 (enoxaparin qd)	E2 (enoxaparin bid)	Combined
All-treated		N=290	N=298	N=312	N=900
Evaluable at the end of study		235	247	258	740
Non-evaluable	Total	55	51	54	160
	No entry DVT	17	17	22	56
	Inappropriate study therapy E/H	46	35	30	111
	Inappropriate warfarin therapy	12	13	16	41
	3-month visit not completed	6	7	6	19

From Table 5: Summary of patient evaluability statis by treatment group. (Vol. 25, p.44).

Another aspect of looking to patient disposition is the study completion status (Table 9-2). A total of 136 patients discontinued the study by different reasons. The study procedures were completed as scheduled by 762 patients (H=223/E1=264/E2=275). Reasons for discontinuation during the entire study (treatment + follow-up) and number of patients discontinued are summarized (Table 7.9-2).

Table 7.9-2
SUMMARY ON STUDY COMPLETION

COMPLETION STATUS			Heparin N=290	Enoxaparin qd N=298	Enoxaparin bid N=312	Combined N=900
Treatment period 7±2 days	Patient Completed		223 (77.2)	264 (88.6)	275 (88.4)	762 (84.9)
	Early Termination		66	34	36	136
	ADE	Total	6	9	4	19
		Major hemorrhage	3	2	0	5
		Other	3	7	4	14
	Protocol Deviation		39	16	20	75
Follow-up period Month 1	Alive		284	288	307	880
	Death		6	7	5	18
	VTE recurrence		9	8	5	22
	Major hemorrhage		11	7	5	23
	Serious adverse event		35	31	31	97
Month 2	Alive		279	282	303	864
	Death		6	7	5	18
	VTE recurrence		0	0	4	4
	Major hemorrhage		3	2	0	5
	Serious adverse event		17	18	11	46
Month 3	Alive		273	277	297	847
	Death		9	11	7	27
	VTE recurrence		3	5	0	8
	Major hemorrhage		1	1	1	3
	Serious adverse event		14	16	13	43
Follow-up Cumulative	Alive		273	277	297	847
	Death		21	25	17	63
	VTE recurrence		12	13	9	34
	Major hemorrhage		15	10	6	31
	Serious adverse event		66	65	55	186
Completed study	Evaluable patients		235 (81.0) ?	247 (82.9)	258 (82.7)	740 (82.2)
	Non-evalu-able	DVT not confirmed	17	17	22	56
		Insufficient therapy	32	26	23	81
		Inappropriate warfarin	18	16	16	50
		3-month visit not done	6	7	6	19

From Table 6(Vol.25, p.64), and Table 5(Vol.24, p.62). ADE= adverse event. One patient may had more than one reason

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There was no significant difference of any of parameters studied in this section between the treatment groups.

b. Patient Demographics

This subsection includes demographic and baseline features of individual patients and comparability of treatment groups. Demographics of patients in the ITT population was comparable between treatment groups (Table 7.9-3)

Table 7.9-3
PATIENT DEMOGRAPHICS. ALL-TREATED PATIENT POPULATION

PATIENT CHARACTERISTICS		HEPARIN		ENOXAPARIN qd		ENOXAPARIN bid		COMBINED	
		N=290	%=100	N=298	%=100	N=312	%=100	N=900	%=100
SEX	Male	150	51.7	161	54.0	181	58.0	492	54.7
	Female	140	48.3	137	46.0	131	42.0	408	45.3
AGE	Mean	60.9		60.7		60.7		60.7	
	Range	18-91		19-91		18-92		18-92	
	<40	40	13.8	38	12.8	38	12.2	116	12.9
	40-49	28	9.7	31	10.4	38	12.2	97	10.8
	50-59	50	17.2	52	17.4	54	17.3	156	17.3
	60-69	70	24.1	73	24.5	74	23.7	217	24.1
	70-79	71	24.5	72	24.2	83	26.6	226	25.1
	≥80	31	10.7	32	10.7	25	8.0	88	9.8
RACE	Caucasian	270	93.1	272	91.3	288	92.3	830	92.2
Weight (kg)	mean	78.5		80.0		81.0		79.9	
	range	41-146		44-151		47-155		41-155	
Height (cm)	mean	170.0		170.5		171.0		170.5	
	range	145-206		142-198		140-198		140-206	
BMI*	mean	27.1		27.6		27.7		27.5	
	range	14.9-53.6		16.6-46.6		17.4-47.0		14.9-53.6	
BSA**	mean	1.93		1.96		1.97		1.96	
	range	1.36-2.82		1.40-2.82		1.44-2.88		1.36-2.88	

From Table 7 (Vol. 25, p.66). *Body Mass Index: Weight (kg) divided by squared height (m^2). **Body Surface Area: $(Weight^{0.6378})*(Height^{0.3694})*0.024265$.

Although numbers are not the same, the Evaluable population had a comparable distribution of demographic characteristics with ITT population. There was no significant difference of any parameters studied between the two treatment groups.

c. Risk Factors

All patients had one or more risk factors at presentation. There was no predominance of a single risk factor in treatment groups (Table 7.9-4)

Table 7.9-4
SUMMARY OF RISK FACTORS FOR DVT AND/OR PE AT BASELINE. ALL-TREATED PATIENT POPULATION

RISK FACTORS		Heparin		Enoxaparin qd		Enoxaparin bid		Combined	
		N=290	%=100	N=298	%	N=312	%	N=900	&
Obesity		122	42.1	137	46.0	146	46.8	405	45.0
DVT and/or PE*	Total	77	26.6	66	22.1	74	23.7	217	24.1
	Only DVT	72	24.8	62	20.8	73	23.4	207	23.0
	Only PE	22	7.6	16	5.4	16	6.1	54	6.0
Prolonged Immobilization		38	13.1	38	12.8	40	12.8	116	12.9
Varicose veins		41	14.1	45	15.1	52	16.7	138	15.3
Congestive Heart Failure		9	3.1	12	4.0	8	2.6	29	3.2
Chronic Obstructive Pulmonary D.		25	8.6	19	6.4	28	9.0	72	8.0
Cancer and chemotherapy/radiation		64	22.0	76	25.5	68	21.8	208	23.1
Recent Surgery		55	19.0	57	19.1	65	20.8	177	19.7
Estrogen containing medication		26	9.0	21	7.0	25	8.0	72	8.0

From Table 8(Vol.25, p.68). *= Excluding present episode

d. Diagnositic Method Presenting Symptoms and Venous Thromboembolic Disease Location

Criteria qualifying for enrollment were symptomatic DVT, PE or both. DVT had to be confirmed by venography or ultrasonography (if venography was inadequate). PE had to be confirmed by pulmonary angiography of ventilation perfusion lung scan (VQLS).

At baseline there was no difference between treatment groups with respect to these criteria (Table 7.9-5)

Table 7.9-5
ALLOCATION OF PATIENTS IN TREATMENT GROUPS ACCORDING TO PRESENTING DIAGNOSIS

PRESENTING SYMPTOMS		Heparin N=290	Enoxaparin qd N=298	Enoxaparin bid N=312	Combined N=900	%
VTE	DVT	206	224	234	664	74
	PE	12	11	7	30	3
	DVT+PE	57	51	57	165	18
Confirmation	Venography	266	280	285	831	92
	Ultrasound	9	6	13	28	8
DVT location	Proximal only	29	31	39	99	11
	Proximal & Distal	193	204	198	595	66
	Distal Only	51	46	57	154	17
	Any iliac	22	23	21	66	-
Extremity involved	Bilateral	23	32	33	88	14
	Unilateral	252	254	265	771	86
PE confirmed	Total	88	94	105	287	32
	with DVT	44	54	59	157	-

From Table 9(Vol.25, p.53)

PE was diagnosed by objective criteria in 287 patients. Only 195 of them (67.9%) had clinical symptoms. They are recorded (PE and DVT+PE). One third of patients with PE was asymptomatic.

e. Prior Medication

[redacted]
[redacted]

Many patients (763, 84.8%) came into the study premedicated with anticoagulants, anti-platelet agents, chemotherapy/radiotherapy and estrogen containing medications. They were allocated in all treatment groups. There was no difference between treatment groups at baseline (Table 10.1[Vol.25, p.55]).

The important information is that 494 (54.9%) patients were premedicated with heparin (H=159/E1=155/E2=180) and 463 (51.4%) with warfarin (H=146/E1=158/E2=159). Heparin and warfarin were considered as the first line therapy before randomization.

f. Concomitant Medication

During the treatment period many patients used concomitant medications. The most commonly used drug was heparin (465 patients or 51.7% of ITT population). The most commonly administered concomitant medication class was anticoagulants. They were used by 555 (61.7%) patients (Table 10.2 [Vol.25, p.74]). Again, there was no significant difference between treatment groups (H=62.4%/E=59.1%/E2=63.5%).

Comment: It is not clear why, and how many times heparin was given as a concomitant medication to patients receiving enoxaparin. Enoxaparin was not given as a concomitant medication to patients receiving heparin.