6.6   THE INVESTIGATIONAL PLAN

a.   Study Design

This study was designed to be a Phase III, multicenter, open-label, assessor-blinded (Central Adjudication Committee), randomized, parallel-group, active treatment controlled clinical trial.

The target population included all patients who present to the hospital with an acute symptomatic DVT without symptoms for PE. In the study, patients with DVT confirmed by phlebography (or duplex ultrasound) were randomized to receive one of the two treatment regimens:

- Outpatient Regimen: Five days subcutaneous enoxaparin plus warfarin for three months.
- Inpatient Regimen: Five days intravenous heparin plus warfarin for three months.

Efficacy was evaluated as the incidence of new, recurrent VTE (DVT confirmed by phlebography, PE confirmed by ventilation-perfusion lung scan, death from thromboembolism confirmed at autopsy) during a 3-month period following randomization and administration of the first study medication. At follow-up visits patients had mandatory bilateral plethysmography. If DVT was suspected, a confirmatory venography followed. An independent Adjudication Committee assessed all venograms. Their decisions on endpoints were used for the statistical analysis.

The study was designed to demonstrate that the two treatments have statistically equivalent efficacy. The sample size was determined to be 250 patients per treatment group (at the significance level $\alpha=0.05$, and power 80%).

In case of equivalent safety and efficacy, the more convenient (daily subcutaneous injection vs. continuous intravenous infusion) and less expensive outpatient treatment *regimen including enoxaparin would be superior for patients who may be treated at home.*

b.   Discussion on the Design and Choice of Control Group

Control Group

This study was an active treatment control, two parallel groups, clinical trial. The comparator drug was heparin. Warfarin was used for oral maintenance of anticoagulation for three months in both treatment groups.

- Heparin is approved for treatment of DVT and PE. The usual administration is inhospital, 5000 IU bolus, followed by intravenous infusion at dose adjusted to maintain anticoagulation at APTT level between 60 and 90 sec, or 2-3 times the normal laboratory level. This therapy is aimed for rapid induction of targeted anticoagulation.

- Warfarin (Coumadin tablets, DuPont-Merck Ph.) is approved for long term oral treatment of DVT. Therapy with warfarin usually starts within 48h after heparin, dose is increased daily to reach the state of anticoagulation equal to INR of 2.0 - 3.0. and is maintained at this level for 3 to 6 months, until the probability for VTE recurrence would be abolished. In this trial, the follow-up period was limited to three months due to a lack of compliance with oral therapy by majority of patients.

Protocol Implementation

A clear design of this study could not be completely implemented as desired because of
- patients arriving at any time, during weekends and holidays ; and
- need to verify acute proximal DVT by objective measures prior to randomization.

Patients who arrived during weekend and holiday hours, had to wait for the next working day for either venography or lung scan. Because of ethical principles, these patients received an emergency treatment including heparin. Therefore, a new treatment period was unwillingly inserted prior to randomization.

Outpatient Treatment

Patients who present with symptoms of VTE (DVT, PE or both) are usually hospitalized because the standard therapy requires continuous intravenous heparin administration. Those who are physically and/or mentally fully capable to care for themselves might be treated at home. Majority of patients arriving at hospitals for treatment of acute DVT belong to this category.

The sponsor believes that enoxaparin (once/twice daily subcutaneous injection without need for laboratory monitoring) may be beneficial for outpatient treatment of these patients. In this open-label study, the investigators disqualified from randomization eligible patients who were not suitable for outpatient treatment. These patients received the standard heparin regimen.

c.   Study Population

All patients who were admitted in the hospital with acute symptomatic DVT with or without symptoms of PE, were screened for eligibility criteria (Table 6.6-1). Patients of either gender, who were above age of 18 years, and had confirmed DVT by a subsequent venography or ultrasound (amended change to the protocol from October 30, 1992), were randomly assigned to either outpatient or inhospital regimen. Patients who did not meet exclusion criteria were replaced by others who did. Replaced patients were not included in the study population.

Patients with acute DVT, who had been admitted to the hospital on weekends or holidays, may have received initial heparin. They were screened and, after confirmation of DVT (venography or ultrasound), randomized to start study drug the first next working day. Only randomized patients are included in study groups. For analytical purposes patients who had this PRETREATMENT period were stratified as follows:

- Outpatients with venography diagnosis.
- Outpatients with venography diagnosis who were admitted at night or on the weekend and agreed to early discharge.
- Inpatients with venography diagnosis who were in the hospital for other reasons and had proximal DVT subsequently diagnosed.
- Outpatients with ultrasound diagnosis.
- Outpatients with ultrasound diagnosis who were admitted at night or on weekends and agreed to early discharge.
- Inpatients with ultrasound diagnosis who were in hospital for other reasons and had proximal DVT subsequently diagnosed.

Table 6.6-1:   ELIGIBILITY CRITERIA

A.	Inclusion Criteria
1.	Acute proximal DVT (thrombosis involving the popliteal or more proximal, i.e., femoral or iliac, deep veins) confirmed by either venography or duplex ultrasonography were eligible for the study.
B.	Exclusion Criteria
1.	Previous history of two or more episodes of DVT or PE.
2.	Presence of current active hemorrhage, active peptic ulcer disease, or familial hemorrhagic diathesis.
3.	Concurrent symptomatic pulmonary embolism.
4.	Had received more than 48 hours of unfractionated heparin therapy for the qualifying DVT.
5.	Inability to receive outpatient heparin therapy because of associated co-morbid conditions or potential for non-compliance.
6.	Inability to attend follow-up visits as an outpatient because of geographic inaccessibility.
7.	Known history of protein C or S deficiency.
8.	Pregnant or lactating women.
9.	Women of childbearing potential who were not covered by a medically recognized contraceptive method.
10.	Unwilling to give informed consent.

More than 1700 patients with acute DVT were screened to allow 501 patients to enter the study. The sample size calculations were based on a two-sided 95% confidence interval approach of establishing equivalence between two proportions. It was assumed that heparin will have an incidence of 6% recurrent VTE, and that enoxaparin will be better (estimated incidence 3%). It resulted in the projection of 250 patients per treatment group (intent-to-treat population). This sample size was reached.

d.   Patient Assignment (Randomization)

After confirming patient eligibility, invistigators requested treatment assignment number from a central service provided by the sponsor. Eligible patients were randomly assigned into one of two treatment groups by the Central Randomization Service at the ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮

According to the protocol, patients randomized to enoxaparin had a choice to accept this outpatient regimen, or to be treated by the standard inpatient heparin regimen. Some patients decided for the conventional treatment. They were excluded from the study, and their randomization number replaced. All other patients received at least one dose of the assigned study medication. They were included into the Intent-to-Treat population.

e.   Dose Selection

Study Medication -- Drug Administration

1)   Treatment Period

OUTPATIENT TREATMENT GROUP: Outpatients were supposed to receive enoxaparin 1 mg/kg,sc, q12h. The study drug was supplied in 1 mL ampules, each containing 100 mg of enoxaparin. Patients were trained for self-administration of subcutaneous injections. Warfarin therapy began on the evening of the second day of enoxaparin therapy. The first dose of warfarin was 10 mg. A prothrombin time was performed daily and the warfarin was prescribed to achieve a targeted INR of 2.0-3.0.

One group of patients, received enoxaparin while in hospital. These patients were admitted to the hospital according to the usual practice, but were immediately randomized. Patients who were assigned to enoxaparin were discharged as soon as clinical condition permitted and continued enoxaparin at home (Amendment to the Study Protocol, from November 12, 1992).

INPATIENT TREATMENT GROUP: Inpatients received a bolus of 5,000 units of heparin intravenously followed by a continuous infusion of 20,000 units of heparin in 500 mL 5% dextrose in water (D5W, 32 mL per hour). APTT was performed six hours after beginning the heparin therapy and the dose rate was adjusted to maintain APTT within the target rate of 60 - 90 seconds. Total number of days on continuous heparin was planned not to exceed five days. Warfarin was administered as described above.

2)   Treatment During the Follow-up Period

WARFARIN: The Follow-up period began when patients reached the targeted INR (between 2.0-3.0) under control of oral warfarin. This ratio was maintained by daily warfarin administration in an individually selected dose subject to monthly adjustment. The general principle for warfarin treatment was identical for the enoxaparin and heparin treatment groups.

3)   Pre-Randomization Treatment

The period between admission to the hospital, randomization and beginning of the assigned therapy was not identical for all patients. For some of them, who arrived on weekend or holiday days, this period was longer due to delay for completion of the objective assessment (venography or duplex ultrasound). During this period they all received a standard heparin therapy (see above). After randomization, patients were transferred to enoxaparin, or continued with heparin regimen as described above.

f.   Blinding

The study was designed as open-label. Due to different route of administration (enoxaparin subcutaneous, heparin intravenous and warfarin oral) it was impossible to blind patients and investigators for the study medication.

However, patient identification was protected. For each patient, 14 labeled ampules of enoxaparin drug were packed in three trays, wrapped in protective foam, and boxed with 14 wrapped syringes. The boxes were labeled with the study number, study dose, and investigational drug warning, and the sponsor's name and address. Patient numbers were assigned by the Center and did not appear preprinted on the labels. Heparin was provided by each participating hospital's pharmacy. Warfarin was provided to each investigator in dosage form of two, five and ten milligrams.

To minimize bias that can occur in open-label studies, the sponsor provided a blinded assessment of study outcomes (recurrent VTE and hemorrhage) by a Central Adjudication Committee. Some members of this Committee were blinded for study drug allocation. Thet were responsible for Committee decision on otcomes.

g.   Efficacy and Safety Variables

Study procedures are summarized in a Study Flow Chart inserted in this section of the submission (Vol.22, p.24). The study procedures are outlined in Table (6.6-2).

Table 6.6-2
STUDY CPK-2091 FLOW CHART

STUDY PROCEDURE	Baseline	Treatment	End of Treatment	Follow-up at 1,2,3 months
Informed Consent	x			
Demography	x			
History	x			x
Physical Examination	x			x
CBC	x		x	
Platelet count	x	x	x	
Prothrombin time (PT)	x	x	x	x
Activated Partial Thromboplastin Time (APTT)	x	x	x	
Alkaline phosphatase, AST, ALT, Bilirubin	x		x	
Blood-urea-nitrogen (BUN), creatinine	x		x	
Impedance plethysmography	x			x
Adverse events	x	x	x	x
Warfarin administration		x	x	x
Quality of Life surway (QOL)				x

From Table 3: Study Flow Chart (Vol. 22, p.24)

All outcome events were reviewed by a Central Adjudication Committee composed of three members. One of them was unaware of treatment allocation. The determination of this Committee was used to identify those patients with VTE (efficacy outcome) or hemorrhage (safety outcome) for statistical analysis.

1)   Efficacy

1a)   The primary efficacy variable was a clinically symptomatic and objectively confirmed recurrent VTE (DVT and/or PE) in the intent-to-treat population within three months of randomization.

1b)   The secondary efficacy variables were defined as:

●   Incidence of VTE recurrence in the evaluable patient population.
●   Time to the first VTE.
●   Incidence of VTE by type DVT or PE.
●   Incidence of VTE by method of diagnosis
●   Incidence of VTE by risk factor subgroups:
    -       recent trauma,
    -       recent surgery,
    -       cancer,
    -       history of prior DVT and/or PE,
    -       hospitalization prior to randomization,
    -       recent trauma and surgery combined.

Criteria for DVT

Patients symptomatic for DVT underwent objective testing using a combined approach of impedance plethysmography, duplex ultrasonography (amended), and venography. Impedance plethysmography was mandatory for each monthly visit. In addition to medical history, and physical exam, this method was considered as sufficient to confirm lack of recurrent DVT, or to raise suspicion and sent the patient to the more accurate assessment, duplex ultrasound and/or venography. A thrombus was diagnosed if there was a constant intraluminal filling defect or non compressibility on the ultrasound.

Criteria for PE

Patients symptomatic for PE underwent a ventilation-perfusion lung scanning. PE was also discovered at autopsy.

2) Safety

Safety was assessed by the incidence of hemorrhagic episodes, adverse events and mortality. Events were presented by absolute numbers and percent of incidence for both treatment groups. Period of observation for safety parameters was different:

- Three months Study Period (Treatment + Follow-up) for mortality, and for study outcomes reported as adverse events (VTE or major bleeding).
- Treatment Period (5-7 days) for: bleeding and abnormal laboratory results,.

2a) Primary Safety Variable

The primary safety variable was the incidence of major hemorrhage. Bleeding was classified as major if it was overt and associated with fall in hemoglobin level of 2 g/dL or more, or if it was clinically overt and led to a transfusion of two or more units of blood, or it was retroperitoneal or intracranial. The Outcome Adjudication Committee decided which patients had hemorrhage, severity of this event and relation to the study medication. At least one member of this Committee was not aware of study drug allocation. The sponsor provides information the blinded memeber was responsible for the final decision on the outcome. Committee protocol was not provided.

2b) Secondary safety variables

The secondary safety parameters were defined as:

- incidence of adverse events ,
- mortality, and
- abnormal clinical laboratory tests.

Laboratory Tests

All laboratory measures cited in the Flow Chart were assessed for safety reasons. Four groups of laboratory tests were performed as scheduled on the Flow Chart (table 6.6-2). General hematology included CBC and platelet count. Special coagulation tests, PT and APTT were performed to monitor anticoagulation status in patients exposed to heparin and LMWH. Liver function was monitored with serum alkaline phosphatase, and serum transaminase (AST and ALT). Renal function was monitored with BUN and serum creatinine. Only change of laboratory values indicating either abnormal increase or decrease, was recorded and plotted against time. This change was recorded as adverse event.

Three laboratory measures were considered of value for heralding the expected adverse events. Hemoglobin to measure blood loss, platelet count to indicate emerging thrombocytopenia, and serum AST and ALT levels to indicate liver injury.

Mortality

Mortality by any cause within three months of the study was recorded as an outcome measure. Deaths were related to the study medication or concomittant illnesses. None of the deaths reported in this study was related to the study medication.

h.   Concomitant Medication

Concomitant medications were defined to be medications given throughout the study treatment period and continuing 48h thereafter. This definition does not include the Follow-up period. It is important to note that warfarin has a large list of interactive drugs.   Asymptomatic interactions of this type were not recorded. Symptomatic reaction were recorded as clinical events. Concomitant medications were allowed during this study. They were recorded on CRF.

6.7   STATISTICAL METHODS

a.   Statistical and Analytical Plan

The final statistical analysis plan is presented in Vol. 23 of this submission. The entire plan for statistical analyses is summarized on table 6.7-1.

Table 6.7-1
STATISTICAL ANALYSIS PLAN

Parameter	Variable Analyzed	Patient population	Statistical Method
Baseline Characteristics	Age, Gender, Previous Hx of DVT or PE, Recent Surgery, Active Malignancy Recent Trauma	All-treated*	t-test x^2 x^2 x^2 x^2 x^2
Primary Efficacy	Incidence of Recurrent VTE (DVT and/or PE)	All -treated	Confidence Interval
Secondary Efficacy	Incidence of Recurrent VTE (DVT and/or PE)	Evaluable	Confidence Interval
	Incidence of VTE by type (DVT or PE), method of diagnosis, risk factor subgroups	All-treated	Cohran-Mantel-Haenszel $\alpha=0.15$
	Time to first VTE recurrence	Both populations	Survival analysis
Primary Safety	Incidence of all hemorrhage within treatment period and 48 hours after the last dose. All major	All-treated All-treated	Fisher's exact
	Incidence of all hemorrhage during the three months of anticoagulant therapy All major	All-treated All-treated	Fisher's exact
Secondary Safety	Mortality during the three months	All-treated	Fisher's exact
Adverse Events	Incidence of selected adverse events (>1% in at least one treatment group)	All-treated	Fisher's exact

From Appendix 1 (Summary of Planned Statistical Analysis), Vol 23, p.151.

All-treated patient population includes all randomized patients who received at least one dose of study medication. Evaluable patient population includes patient population that completed the study by the protocol. Only secondary efficacy analyses were performed on the evaluable patient population.

b. Sample Size and Power

Because of additional information published in 1992 and 1993, the sample size was amended from 800 patients in the original protocol to 500 patients. The expected recurrence rate on heparin remained 6%. A delta value of 3% was selected. Power calculations were made under the alternative hypothesis that enoxaparin would be truly better than heparin by 3%. 95% Confidence interval approach was used. For details see the Statistical Review and Evaluation.

c. Data Management

All data from CRF were entered into an Oracle® database. Data-sets for analyses were generated by Statistical Analysis System (SAS) version 6.09.

6.8 DISPOSITION OF PATIENTS ENTERED

Patients who entered the study were evaluated for a number of clinical characteristics that may generate confounding variables at baseline, or during the conduct of the study. The sponsor has tried to determine if any of these characteristics was distributed differently in the treatment groups, and if it had influenced the study outcomes. The following parameters were considered of interest for this trial.

a. Demographics
Age (by subgroups), gender (M/F), and weight.

b. Risk Factors
Including: Prior VTE, hospitalization due to DVT, recent trauma (+poisoning), cancer, and recent surgery.

c. Prior Exposure to Study Medication
Pre-randomization heparin administration.

d. Concomitant Medication
The following drugs were given a special consideration: anticoagulants, antithrombotics, antiplatelet/NSAIDs, steroids, and estrogen containing medications. Other medications were recorded, but were reported only if significant portion of patients used any of them.

e. Dropouts
Dropouts were recorded if they were due to:
1) Protocol Violations
2) Study Discontinuation because of occurrence of a study endpoint, severity of an event, death, or withdrawal of the consent.

f. Deaths
In this trial deaths by all causes were analyzed separately. Narratives for patients who died were included in the submission.

6.9 STUDY RESULTS

6.9.1 Data Sets Analyzed

a. Patient disposition

1) Center, investigator and number of patients assigned. All-treated patient population.

A list of investigators with number of patients assigned in two treatment groups is provided on table 4: Summary of patient distribution and treatment for all-treated patients (Vol.22, p.35; extracted from Table B.5.3). The List is available in Appendix 2. Five investigators had more than a half of all patients. Five investigators together had <7% of randomized patients. This imbalance was found to be of no influence to study outcomes.

Sixteen investigators screened 1731 patients who did not enter the study. Eighty-six percent of them (1495) had at least one exclusion criterion checked yes. Some of them who had been found with acceptable protocol violations (Table 6.9-2) were included in the study.

Table 6.9-2

Acceptable Protocol Deviations
- Heparin nomogram rather institutional than protocol-specified.
- Pre-randomization heparin continued for more than two days.
- Warfarin started on Day -2 to 4 rather than on Day 2.
- INR was not equal to or greater than 2.0 prior to study drug discontinuation.

Two hundred thirty-six (236) fully eligible patients were randomized, but not included into the study because of reasons summarized on Table 6.9-3

Table 6.9-3

DROPOUTS OF RANDOMIZED PATIENTS DUE TO THEIR DECISION

CAUSE	NUMBER OF PATIENTS
Does not wish to be admitted	6
Wants to be admitted	112
Wants to receive standard heparin or Refuses self injection	68
Other	50
TOTAL	236

These randomized but not treated patients were replaced. None of them was included in any study population.

Comment: The large number of patients requesting admission and standard therapy indicates to a strong public belief that hospitals are still the best providers of quality health care for patients with acute disorders. This public opinion should be considered for Labeling. Outpatient treatment of acute DVT should be suggested as a preferable choice for patients who are in clinical condition for outpatient therapy, and are apt to receive this type of treatment.

All patients found eligible were included in the study. A total of 501 (H=254/E=247) patients have been randomized and have received at least one dose of study medication. This population was considered as Intent-to-Treat or, All-treated population.

2)   Compliance

During the treatment period (five days) patients were monitored daily by study nurses. Thirty-two patients (H=13[5.1%]/ E=19[7.7%]) received less than minimum study medication, did not reach INR on time, or did not complete the 3-month follow-up visit. They were considered as unevaluable but were included in the study analysis (Table 6.9-3).

Table 6.9-3
COMPLIANCE – PATIENT EVALUABILITY BY TREATMENT GROUP

Evaluability Status		Heparin		Enoxaparin		Combined	
		N	%	N	%	N	%
All randomly assigned		254	100	247	100	501	100
All-Treated patients		254	100	247	100	501	100
Evaluable		241	94.9	228	92.3	469	93.6
Unevaluable	total	13	5.1	19	7.7	32	6.4
	enoxaparin ≤ 6 doses	0	0	4	1.6	4	0.8
	heparin < 3 days	2	0.8	0	0	2	0.4
	No INR ≥2	4	1.6	2	0.8	6	1.2
	heparin sc	2	0.8	0	0	02	0.4
	no 3-month follow-up	4	1.6	13	5.3	17	3.4
	randomized twice	1	0.4	0	0	1	0.2

From Table 6 (Vol.22, p.37)

Only 17 (3.4%) patients did not completed the follow-up period. They belonged to both the heparin (4, 1.6%), and the enoxaparin (13, 5.3%) group.

3)   Discontinuation from study

Twenty-four patients (4.8%) patients withdrew from the study before completion of the treatment period (five days). The most common cause was an adverse event (16[3.2%], H=9[3.5%]/E=7[2.8%]) There is no information how many patients discontinued warfarin treatment and left the study during the follow-up period Table 6.9-4).

4)   Patient evaluability. Evaluable patient population.

Five hundred-one patients were randomized and had received at least one dose of the study medication. Approximately five percent (4.8%) discontinued mostly due to an adverse event. Four hundred seventy-seven patients completed the study but 6.4% did not comply. They had received less than six doses of enoxaparin, heparin for less than 3 days, or by subcutaneous injection, their warfarin was not adjusted properly and had exceeded the targeted INR ratio. Finally, some of them did not complete the 3 months follow-up visit, or (one in the heparin group) were randomized twice. Their distribution is presented on the Table (6.9-4)

Table 6.9-4

PATIENT FLOW THROUGHOUT THE STUDY

Patients		Heparin		Enoxaparin		Combined	
		N=254	%	N=247	%	N=501	%
Screened		NA		NA		1,731	
Randomized: All-treated		254	100	247	100	501	100
Discontinued	Total	14	5.5	10	4.0	24	4.8
	Adverse event	9	3.5	7	2.8	16	3.2
	Other	3	1.2	1	0.4	4	0.8
	Refusal	2	0.8	2	0.8	4	0.8
Completed		240	94.5	237	96.0	477	95.2
Non-evaluable	Total	13	5.1	19	7.7	32	6.4
	Wrong therapy	8	-	6	—	14	
	No 3-Mos follow-up	5	-	13	-	18	-
Evaluable: Per protocol		241	94.9	228	92.3	496	93.6

From Table 6 (Vol.22, p.37) and Table 7 (Vol.22, p.38)

The table presents the patients flow from the randomization to the end of the study. There was no significant difference of patient flow between the treatment groups. At the end of the study two distinct population were formed: All-treated (total 501/H=254/E=247), and Evaluable (total 496/H=241/E=228). These two populations were used for statistical analyses.

b.   Patient demographics

The important baseline characteristics are summarized below (Table 6.9-5).

Table 6.9-5
Summary of Patient Demographics. All-Treated Patient Population

Parameter	Category	Heparin N=254		Enoxaparin N=247		Combined N=501	
		N	%	N	%	N	%
SEX	male	149	58.7	154	62.3	303	60.5
	female	105	41.3	93	37.7	198	39.5
AGE	N	254		247		501	
	mean	58.9		56.7		57.8	
	S.E.M.	1.0		1.1		0.7	
	median	61.0		60.0		61.0	
	range	21.0 - 96.0		19.0 - 92.0		19.0 - 96.0	
	<40 years	39	15.4	50	20.2	89	17.8
	40-49	24	9.4	31	12.6	55	11.0
	50-59	54	21.3	41	16.6	95	19.0
	60-69	65	25.6	56	22.7	121	24.2
	70-79	54	21.3	52	21.1	106	21.2
	≥ 80 years	18	7.1	17	6.9	35	7.0
WEIGHT (kg)	N	254		247		501	
	N missing	0		0		254	
	mean	-		80.7		80.7	
	S.E.M.	-		1.1		1.1	
	median	-		80.0		80.0	
	range	-		35.0 - 150.0		35.0 - 150.0	

From Table 8 (Vol. 22, p. 40). No significant difference was found between heparin and enoxaparin group in any of these categories.

Evaluable population had a comparable distribution of demographic characteristics.

c.   Disposition of risk factors

Several factors are known to contribute for recurrence of VTE, or resistance to therapy, in patients who refer for acute venothrombotic event. These risk factors have been found in majority of patients involved (Table 6.9-6)

Table 6.9-6

SUMMARY OF RISK FACTORS. ALL-TREATED PATIENT POPULATION

Risk Factor		Heparin N=254		Enoxaparin N=247		Combined N=501	
		N	%	N	%	N	%
Venous thromboembolism		37	14.6	51	20.6	88	17.6
Hospitalization prior to DVT		23	9.1	21	8.5	44	8.8
Recent Trauma (+ poisoning)		27	10.6	19	7.7	46	9.2
Presence of cancer		57	22.4	46	18.6	103	20.6
Recent Surgery	Total	45	17.7	51	20.6	96	19.2
	Musculoskeletal	27	10.6	38	15.4	65	13.0

From Table 11 (Vol.22, p.44).

Three hundred seventy-seven patients (377/501, 75.2%) had risk factors other than the acute VTE. Some of them had more than one additional risk factor (Table 6.9-6). The evaluable patient population was comparable. Overall, there was no significant difference between treatment groups with regard to baseline risk factors.

The table does not include varicose veins, obesity, age, chronic cardiac failure and other risks for DVT, the risk factors also present. They were comparably distributed between treatment groups.

d. Diagnostic method presenting symptoms

For statistical analysis, the all-treated patient population was stratified according to different diagnostic techniques (venography vs. ultrasonography), duration of hospitalization (outpatient vs. inpatient, early discharge after venography vs. ultrasonography), and difference of time of randomization vs. hospitalization. (Table 6.9-7)

Table 6.9-7

STRATIFICATION AND TREATMENT TYPE FOR ALL-TREATED POPULATION

STRATIFICATION	Heparin N=254		Enoxaparin N=247		Combined N=501	
	N	%	N	%	N	%
Outpatient, venography	61	24.0	56	22.7	117	23.4
Outpatient, ultrasonography	88	34.6	93	37.7	181	36.1
Early discharge, venography	30	11.8	25	10.1	55	11.0
Early discharge, ultrasonography	52	20.5	52	21.1	104	20.8
Hospitalized prior to DVT, venography	10	3.9	9	3.6	19	3.8
Hospitalized prior to DVT, ultrasonography	13	5.1	12	4.9	25	5.0
OUTPATIENT VS. INPATIENT						
No hospitalization after randomization	3	1.2	177	71.7	180	35.9
Hospitalization after randomization	251	98.8	70	28.3	321	64.1

From Table 9 (Vol.22, p41).

This table shows that almost 99% of patients randomized to heparin were hospitalized. Approximately 32% of them achieved early the targeted INR level and were discharged from hospital to continue outpatient treatment with warfarin. Majority of heparin patients were discharged between 4-7 days as per protocol (147/254).

Almost 30% (28.3%) of patients randomized on enoxaparin were initially hospitalized. They were discharged for outpatient enoxaparin and warfarin treatment as soon as the condition permitted. One half of hospitalized enoxaparin patients (28/70) was discharged the first day. A half of the remaining patients (24/42) were discharged during the next two days. They also continued with warfarin maintained anticoagulation in outpatient setting after completion of enoxaparin treatment. The evaluable patient population was comparable.

Except for hospitalization vs. outpatient treatment, there was no other significantly different variable between study treatment groups.

e.   Prior medication: Pre-randomization heparin

Patients who were not randomized at admission (due to waiting for objective confirmation of proximal DVT by venography), received intravenous heparin as an emergency therapy prior to randomization. Three hundred-fifteen patients (62.9% of randomized) received this type of pre-randomization treatment. The majority of them (129, or 40.9%) received intravenous heparin for two days, 24 patients received heparin for one day, and 34 patients recieved heparin for more than two days. These patients were randomly assigned to treatment groups. One hundred fifty-three (153, 61.9%) patients randomized to enoxaparin began the assigned therapy already anticoagulated with heparin.

Therefore, during the conduct of this study, a new study group was introduced: patients initially anticoagulated with heparin, then followed by enoxaparin and warfarin. This group was not recognized by the sponsor in the submission, and a request for additional information was made. The sponsor was requested (1) to identify the following groups: A. Enoxaparin heparinized patients; B. Enoxaparin non-heparinized patients; C. Heparin patients; and (2) to perform confidence interval analysis between groups at end of drug duration time, at 1 month, and 3 months endpoint after randomization. For details of this additional analysis see the Statistical Review and Evaluation.

f.   Disposition of patients who received concomitant medication

Any use of antithrombotic and antiplatelet agents was discouraged for the treatment period, and for the entire study. Medications unrelated to coagulation were not forbidden in this study. More than two thirds of patients received concomitant medication. (Table. 6.9-8)

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Table 6.9-8

SUMMARY OF PATIENTS WHO RECEIVED CONCOMITANT MEDICATIONS (≥10%) AND THERAPEUTIC CLASS OF THESE DRUGS

Concomitant Medication		Heparin		Enoxaparin		Combined	
		N=254	%	N=247	%	N=501	%
Number of patients with		211	83.1	161	65.2	372	74.3
Number of patients without		43	16.9	86	34.8	129	25.7
Therapeutic Class	Anticoagulants/ Antithrombotics	1	0.4	3	1.2	4	0.8
	Antiplatelet/NSAID	12	4.7	6	2.4	18	3.6
	Steroids	16	6.3	10	3.6	14	2.8
	Estrogen containing	5	2.0	9	3.6	14	2.8
	Chemotherapeutic/ Radiation	5	2.0	10	4.0	15	3.0
Other Drugs	Total	208	81.9	156	63.2	364	72.7
	Paracetamol (acetaminophen)	69	27.2	45	18.2	114	22.8
	Oxazepam + Lorazepam (benzodiazepine)	33+37 70	13.0+14.6 27.6	16+17 33	6.5+6.9 13.4	49+54 103	9.8+22.8 32.6
	Docusate (laxative)	39	15.4	12	4.9	51	10.2

From Table 13 (Vol.22, p.47)

Inpatients (heparin group) received significantly more pain relievers, antianxiety, laxative agents, antiplatelet/NSAID drugs and steroids, than outpatients (enoxaparin group). An opposite trend, more drugs used by outpatients, was registered for estrogen containing and chemotherapeutic agents. Is this difference due to better registration of drug use in hospitals or to insufficient reporting?

g.   Duration of hospitalization

Duration of postrandomization hospitalization was analyzed for the socioeconomic aspects of this study. Majority of enoxaparin patients (177, or 71.7%) were randomized, received the first dose of study medication and were sent home for outpatient treatment. Seventy patients were hospitalized from one to nine and more days. Fifty-two of them (74.3%) were discharged within three days.

Only five patients randomized to heparin were hospitalized ≤3 days. Others (249) spent four to nine and more days in hospital. Majority of them (194, or 76.4%) spent 5-7 days in hospital.

Comment: If the oupatient and inpatient regimen were equivalent, the less expensive outpatient treatment should be recommended. A possibility that such an advice may accompany further advertisment of Lovenox injection, must be met with distinct Labeling with regard "to whom the outpatient regimen may be recommended?"

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