Prevention of Thromboembolism with Use of Recombinant Hirudin. Results of a Double-Blind, Multicenter Trial Comparing the Efficacy of Desirudin (Revasc) with That of Unfractionated Heparin in Patients Having a Total Hip Replacement

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Results of a Double-Blind, Multicenter Trial Comparing the Efficacy of Desirudin (Revasc) with That of Unfractionated Heparin in Patients Having a Total Hip Replacement*

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ABSTRACT: Specific inhibition of thrombin is a new method for the prevention of postoperative deep-vein thrombosis. The objective of this multicenter, randomized, double-blind study was to compare the efficacy and safety of desirudin (Revasc, CGP 39393; fifteen milligrams two times a day) with that of unfractionated heparin (5000 international units three times a day) in patients having a primary elective total hip replacement. The medications were administered subcutaneously, starting preoperatively and continuing for eight to eleven days. The primary end point was a confirmed thromboembolic event during the treatment period. The presence of deep-vein thrombosis was evaluated with bilateral venograms, which were centrally assessed by two independent radiologists.

A total of 445 eligible patients were randomized: 220, to management with heparin, and 225, to management with desirudin. A per-protocol analysis of efficacy was performed for the 351 patients (79 per cent) for whom an adequate bilateral venogram had been made within eight to eleven days after the operation or who had had a proved thromboembolic event. The prevalence of confirmed deep-vein thrombosis was thirteen (7 per cent) of 174 patients who had received desirudin and forty-one (23 per cent) of 177 patients who had received heparin, a significant difference ($p < 0.0001$). The prevalence of proximal deep-vein thrombosis was also significantly reduced ($p < 0.0001$), by 79 per cent, in the group that had received desirudin (six [3 per cent] of 174 patients) compared with in the group that had received heparin (twenty-nine [16 per cent] of 177). There were no confirmed pulmonary embolisms or deaths during the period of prophylaxis. During a six-week follow-up period, pulmonary embolism was confirmed in four patients, all of whom had received heparin. There was no significant difference between the treatment groups with respect to bleeding variables or bleeding complications.

These data demonstrate that a fixed dose of fifteen milligrams of desirudin, started preoperatively and administered subcutaneously twice daily for at least eight days, provided effective, safe prevention of thromboembolic complications, with no specific requirements for laboratory monitoring, in patients who had a total hip replacement.

Thromboembolism is a major complication of total hip replacement. The rationale for the prevention of deep-vein thrombosis after high-risk operations is based on the clinically silent onset of the thrombotic process and the potential risk of subsequent fatal embolization[5]. The risk of a post-thrombotic syndrome with chronic edema and ulcers of the lower extremity may also be decreased with use of effective prophylaxis[24]. However, the prevalence of deep-vein thrombosis after total hip or knee replacement operations was shown, in a large multicenter study of more than 1200 patients, to be 21 to 55 per cent despite prophylaxis with low-molecular-weight heparin or adjusted-dose warfarin[13].

The limitations of heparin result partly from the dependence on cofactors and partly from the inability of the heparin-antithrombin-III complex to inhibit clot-bound thrombin. Low-molecular-weight heparin shares the biophysical limitations of unfractionated heparin. In contrast, hirudin and the other direct thrombin inhibitors inactivate both free and fibrin-bound thrombin and therefore can be expected to have an increased ca-

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pacity to inhibit the development of thrombi.

Specific inhibition of thrombin is a promising new method for the prevention of postoperative deep-vein thrombosis. Hirudin is a highly potent, specific, and almost irreversible inhibitor of human thrombin[18]. The recombinant hirudin desirudin, expressed by recombinant deoxyribonucleic acid (DNA) technology, has been found[25] to differ from the natural product because of the absence of a sulphate group on tyrosine 63. Natural hirudin and desirudin have been shown to be effective anticoagulants in various experimental models of thrombosis[10,14]. Their pharmacokinetic and pharmacodynamic behaviors have been well characterized in a large population of healthy subjects[2,19,26]. Furthermore, results from two clinical trials indicate that desirudin, administered subcutaneously in doses of ten, fifteen, or twenty milligrams twice daily, is safe in patients having an elective total hip replacement[8,9].

The primary objective of the present study was to assess the efficacy and safety of fifteen milligrams of desirudin as compared with heparin, administered subcutaneously as fixed doses to patients having an elective total hip replacement.

Materials and Methods

Patients

Consecutive patients who were at least eighteen years old, weighed at least fifty kilograms, and were scheduled to have an elective primary total hip replacement were eligible to participate in the study. The most important criteria for exclusion were previous inclusion in the trial; childbearing potential; a hemostatic or bleeding disorder; a hip fracture or operation within the last three months; a major operation within the last month; a cerebral ischemic attack within the last six months; uncontrolled hypertension; renal impairment; and a known allergy to hirudin, heparin, or contrast media. A computer-generated randomization scheme was used to provide balanced blocks of patient numbers for each of the two treatment groups within each center. A block size of six was used, and only complete blocks were distributed to the centers.

Design of the Study

A total of eleven centers from two Scandinavian countries participated in this multicenter, randomized, double-blind, controlled trial. The Guidelines for Good Clinical Practice[23] and the Revised Declaration of Helsinki were followed. The study was approved by the local ethics committee at each center. Written, informed consent was obtained from each patient before participation in the trial. An independent safety committee monitored the trial continuously.

Treatment Regimens and Trial Drugs

Desirudin (Revasc, CGP 39393; molecular weight, 6964 daltons; approximately 12,000 thrombin-inhibiting units per milligram of protein) was produced by recombinant DNA technology in yeast (*Saccharomyces cerevisiae*); the drug was manufactured and purified by Ciba-Geigy (Basel, Switzerland) in collaboration with GEN Therapeutica Vertriebs GmbH (Bad Zwischenahn, Germany). The effect of desirudin can be monitored by measurement of activated partial thrombin time, with a peak value of 1.37 relative to baseline; for example, an increase from thirty-five to forty-eight seconds can be expected when fifteen milligrams is administered subcutaneously twice daily to patients having a total hip replacement[8,9]. Both the desirudin and the unfractionated porcine sodium heparin (Diosynth, Oss, The Netherlands) were administered subcutaneously during a planned treatment interval of eight to eleven days; the desirudin was given in doses of fifteen milligrams twice a day and the heparin, in doses of 5000 international units three times a day. The first injection of desirudin was given after induction of anesthesia, within thirty minutes before the operation, and the first injection of heparin was given two hours before the operation. Injections of placebo were given to complete the double-blind design; all patients were given the same number of injections with identical labels and at identical time-intervals.

The use of drugs known to have an effect on fibrinolysis, coagulation, or platelet function (with the exception of the drugs used in the trial or in connection with the perioperative erythrocyte saver) was prohibited for seven days before the hip operation and during the entire trial period. The use of long-acting nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine, and dextran also was prohibited. In the event of bleeding, fresh-frozen plasma, erythrocyte concentrates, whole blood, and plasma expanders were recommended. Anticoagulants were not used routinely after venography unless a thromboembolism had been diagnosed.

Assessment of Thromboembolic Events

The primary variable of efficacy was the number of confirmed thromboembolic events (deep-vein thrombosis, pulmonary embolism, or death related to thromboembolism) during the treatment period. The presence of deep-vein thrombosis was evaluated with the use of mandatory bilateral ascending venography at the end of the prophylactic treatment period or earlier if clinical symptoms occurred. Pulmonary embolism had to be confirmed with pulmonary angiography or with a high-probability ventilation-and-perfusion scan[3,12]. In the event of death, an autopsy specifically aimed at the detection of thromboembolic manifestations was to be performed.

In the end-point evaluation, much emphasis was placed on the attainment of high-quality standardized venograms and the reduction of observer variation. Bilateral venography was performed according to the

TABLE I
DEMOGRAPHIC VARIABLES*

	Heparin Group (N = 220)	Desirudin Group (N = 225)
Age *(yrs.)*	68.2 ± 9.8	68.6 ± 9.3
Weight *(kg)*	73.7 ± 13.2	74.8 ± 12.3
Female gender	58	58
Smoking	18	19
Obesity†	32	37
Varicose veins	16	20
Medical history		
Previous hip or knee operation	15	16
Previous deep-vein thrombosis or pulmonary embolism	2	4
Malignant lesion	3	3
Cardiac failure	3	3
Myocardial infarction	5	<1
Primary diagnosis		
Osteoarthrosis	97	98
Rheumatoid arthritis	<1	<1
Osteonecrosis	<1	<1
Other	<1	1

*All values are given as percentages, except for age and weight, which are given as the mean and the standard deviation.

†A body-mass index of more than 27.2 for men and more than 26.9 for women (corresponds to 20 per cent overweight or more).

technique of Rabinov and Paulin, with minor modifications[15,28]. The use of tourniquets was avoided to facilitate filling of all of the deep veins and to improve the differentiation between intraluminal clots and insufficient filling or variable-flow defects. A radiographic table with a tilting device was used, and the patient was examined in a 60-degree semi-upright position with the involved extremity totally relaxed and non-compressed. A standard dose of 100 milliliters of non-ionic low-osmolar contrast medium (240 milligrams of iodine per milliliter) was injected into each lower extremity. Each of the three vein segments in the proximal region was examined on two projections, and the calf was examined on three projections. The minimum mandatory examination therefore comprised nine images of each extremity. All images were documented on long conventional films.

All deep stem veins, excluding the deep femoral vein and the internal iliac vein and including the muscular veins of the calf, up to the confluence with the inferior vena cava, had to be adequately opacified. Visualization of the deep femoral and internal iliac veins was not mandatory because of anatomical reasons and because of well known limitations in the venographic technique.

The venographic technique was standardized with use of consensus meetings and an educational program for all participating radiologists. There was a pre-trial central assessment and acceptance of the venographic technique from each center. In order to maintain the standardized technique, the quality of the venograms was monitored throughout the trial.

All venograms were centrally assessed by two independent expert radiologists who were unaware of the results recorded at the local centers. The only criterion for deep-vein thrombosis was a constant intraluminal filling defect of unvaried shape on at least two images. The venograms were classified as normal, as positive, or as inadequate with no confirmed deep-vein thrombosis. The third designation was given if only one extremity had been examined or if any of the deep stem veins were inadequately visualized and no thrombus could be detected. The findings on examination of the deep femoral vein and the internal iliac vein were classified as either normal or positive.

Statistical Methodology

All statistical analyses were performed with the Statistical Analysis System, Release 6.06 (SAS Institute, Cary, North Carolina). All comparisons between desirudin and heparin were based on a two-sided null hypothesis with a level of significance of 5 per cent. It was planned to have a sample size of 168 evaluable patients in each treatment group. The rationale for the sample size was based on an expected 25 per cent prevalence of confirmed thromboembolic events during the treatment period in the group that had received heparin; the goal was the detection of an absolute difference of at least 13 per cent (with a power of 80 per cent) in the group that had received desirudin. A confirmed thromboembolic event was defined as deep-vein thrombosis, pulmonary embolism, or death related to a thromboembolic event. The prevalence of thromboembolism was calculated with 95 per cent confidence intervals.

The primary outcome, the presence of a thromboembolism, was analyzed with logistic regression when the treatment group and the country were included as fixed factors. The primary-efficacy analysis of desirudin and heparin was based on confirmed thromboembolism in the per-protocol population. Patients were included in the efficacy analysis (per-protocol and intent-to-treat) if a confirmed thromboembolism had occurred during the treatment period or if an adequate venogram had been made by the end of the treatment period, between the eighth and eleventh postoperative days. Patients who

TABLE II
DATA ON THE PATIENTS WHO DID NOT HAVE VENOGRAPHY*

	Heparin Group (N = 220)	Desirudin Group (N = 225)
Discontinued study		
Adverse experience	13	9
Protocol not followed	8	10
Consent withdrawn	5	3
Administrative reason	1	1
Other reasons		
No operation	0	2
Technical problem	5	3
Total	32	28

*The values are given as the number of patients.

TABLE III
OPERATIVE DATA*

	Heparin Group (N = 220)	Desirudin Group (N = 223)
Anesthesia		
Spinal only	63	68
Epidural and spinal	23	20
General and spinal	9	6
General only	6	5
Prosthesis		
Inserted with cement	75	81
Inserted without cement	11	10
Hybrid	15	9
Duration of operation *(mins.)*	104 ± 30	101 ± 30

*The values are given as percentages, except for the duration of the operation, which is given as the mean and the standard deviation. There were no significant differences between the groups, with the numbers available.

had an inadequate venogram and no confirmed deep-vein thrombosis were excluded from the efficacy analysis both in the per-protocol and the intent-to treat data set because this outcome could not be considered as a confirmed absence of deep-vein thrombosis.

All patients who had an adequate venogram or a confirmed thromboembolism were included in the intent-to-treat analysis. Patients were not included in the per-protocol analysis if, during the period of prophylaxis, they had used dextran, thrombolytics, orally administered anticoagulants, heparin, or hirudin that was not part of the protocol; if venography had been performed more than one day after the end of the treatment period; or if venography had been performed before the eighth postoperative day with no deep-vein thrombosis having been confirmed on the central assessment.

The association between the treatment group and the severity of the deep-vein thrombosis was analyzed as a secondary variable of efficacy. Deep-vein thrombosis in the proximal region — that is, in the popliteal vein or more proximally — was considered the most severe outcome. Clinical episodes of thromboembolism during the six-week follow-up period were recorded, provided that they were confirmed by an objective method. The association between a confirmed thromboembolism and the demographic variables of age, gender, and obesity was analyzed with use of logistic regression. All 445 patients who received a trial medication were included in the evaluation of safety and tolerability.

Results

Nine hundred and ninety-four consecutive patients were screened for eligibility for the study at eleven Scandinavian centers between November 1993 and August 1994. The main reasons for exclusion before randomization were a lack of consent and an intake of acetylsalicylic acid or orally administered anticoagulants. A total of 445 patients were included in the trial and were randomized to receive double-blind treatment. Of the 445 patients, 220 were assigned to management with heparin and 225, to management with desirudin.

There were no differences between the treatment groups with respect to demographic parameters, risk factors, or primary diagnosis. Osteoarthrosis was the most common reason for the operation (434 [98 per cent] of the 445 patients; Table I). The median duration of treatment was nine days; of the 385 patients who had venography, 379 (98 per cent) received prophylaxis for at least nine days. Of the 445 patients, two (in the group that received desirudin) did not have the operation; fifty discontinued the study prematurely without having had venography; and, for an additional eight, a venogram could not be obtained because of technical problems (Table II). Venography was performed after a mean (and standard deviation) of 9.5 ± 0.9 days of treatment with heparin and after a mean of 9.4 ± 0.7 days of treatment with desirudin. Of the 385 patients, 360 (94 per cent) had an adequate bilateral venogram or a confirmed deep-vein thrombosis during the period of prophylaxis. There were no pulmonary embolisms or deaths during the period of prophylaxis. Clinical signs of deep-vein thrombosis were noted in ten patients and were confirmed in two patients from each treatment group.

Spinal anesthesia, with or without epidural anesthesia, was used for 419 (95 per cent) of the 443 patients who had an operation (Table III). General anesthesia was used in addition in thirty-three (7 per cent) of the 443 procedures because of an insufficient effect or duration of the regional block, and it was used alone in twenty-four (5 per cent). The mean duration of the operation was 102 ± 30 minutes. In 345 (78 per cent) of the 443 patients, the prosthesis was inserted with cement; in forty-nine (11 per cent), it was inserted without cement; and in forty-nine (11 per cent), a so-called hybrid prosthesis was used (Table III).

Nine of the 360 patients who had an evaluable venogram were excluded from the primary per-protocol

TABLE IV
THROMBOEMBOLIC EVENTS IN THE PER-PROTOCOL POPULATION

	Heparin Group (N = 177)	Desirudin Group (N = 174)
Deep-vein thrombosis *(no. of patients)*	41	13
Confirmed pulmonary embolism *(no. of patients)*	0	0
Fatal pulmonary embolism *(no. of patients)*	0	0
Thromboembolic event* *(per cent)*	23† (17.2-30.1)	7† (4.0-12.4)

*Confirmed deep-vein thrombosis or pulmonary embolism in patients having a total hip replacement. The 95 per cent confidence interval is in parentheses.
†$p < 0.0001$.

TABLE V
DISTRIBUTION OF DEEP-VEIN THROMBOSES IN THE PER-PROTOCOL POPULATION*

	Heparin Group (N = 177)	Desirudin Group (N = 174)	Relative Risk Reduction
Over-all	23	7†	68
Proximal	16	3†	79
Side of operation	16	5	
Contralateral side	4	<1	
Bilateral	3	2	

*The values are given as percentages.
†$p < 0.0001$, compared with the value for the group that had received heparin.

analysis because of predefined major violations of the protocol: seven were excluded because of treatment with dextran or low-molecular-weight heparin and two, because the venograms had been made before the eighth postoperative day and had revealed negative findings. The per-protocol analysis of efficacy was thus performed for 351 patients. The total prevalence of confirmed deep-vein thrombosis was thirteen (7 per cent) of 174 patients in the group that had received desirudin and forty-one (23 per cent) of 177 patients in the group that had received heparin ($p < 0.0001$; Table IV). The 95 per cent confidence interval was 4.0 to 12.4 per cent and 17.2 to 30.1 per cent for the groups that had received desirudin and heparin, respectively. The relative reduction of the risk for over-all deep-vein thrombosis was 68 per cent (Table V).

There was a highly significant reduction ($p < 0.0001$) in the prevalence of proximal deep-vein thrombosis in the group that had received desirudin (six [3 per cent] of 174 patients), compared with that in the group that had received heparin (twenty-nine [16 per cent] of 177 patients). The 95 per cent confidence interval was 1.3 to 7.4 per cent and 11.3 to 22.7 per cent for the groups that had received desirudin and heparin, respectively, and the relative reduction in risk was 79 per cent (Table V).

The intent-to-treat analysis of the 360 patients who had an adequate venogram revealed no difference in the results, compared with those of the per-protocol analysis, with respect to the prevalence of either over-all or proximal deep-vein thrombosis. The total prevalence of confirmed deep-vein thrombosis was thirteen (7 per cent) of the 180 patients who had received desirudin and forty-two (23 per cent) of the 180 who had received heparin.

Analysis of the sites of the deep-vein thromboses showed that the thrombi occurred predominantly in the extremity on the side of the arthroplasty; however, a substantial proportion were located on the contralateral side. Many patients had multifocal thrombi. There was a proportional reduction in proximal and distal thrombi in the group that had received desirudin (Table VI).

Potentially confounding factors were assessed by including the recorded demographic variables in a logistic regression analysis. None of these factors had any significant influence on the primary outcome, and the effect of treatment was not changed by including them in the model.

Follow-up consisted of a clinical examination, performed at a mean of 44 ± 6 days after the operation in the group that had received desirudin and at a mean of 44 ± 7 days in the group that had received heparin. During the interval between the termination of treatment and the follow-up evaluation, a confirmed deep-vein thrombosis developed in three patients who had received heparin and in two who had received desirudin. Pulmonary embolism was confirmed in four patients who had received heparin and in none who had received desirudin. Two patients (both of whom had received heparin) died during the follow-up period; one died of a cerebral infarction and the other, of septicemic shock in combination with thrombocytopenia.

The 445 patients who received a trial medication were included in the over-all evaluation of safety and tolerability. The two patients who did not have the operation could not be included in the analysis of blood loss and transfusion requirements. There were no significant differences between the treatment groups with respect to blood loss, transfusion requirements, or bleeding complications (Table VII). The mean total blood loss was 1435 ± 745 and 1379 ± 594 milliliters in the groups that had received heparin and desirudin, respectively. Transfusions of red blood-cell concentrates were required in 110 (50 per cent) of 220 patients and in 126 (57 per cent) of 223 patients in the groups that had received heparin and desirudin, respectively, and the mean total volume of red blood cells that was transfused was 750 ± 490 and 798 ± 507 milliliters, respectively. No patient was given whole blood. Hemoglobin values did not suggest any occult or late bleeding in the two groups.

TABLE VI
MULTIFOCAL LOCATIONS OF DEEP-VEIN THROMBOSES IN THE PER-PROTOCOL POPULATION*

	Heparin Group (N = 177)		Desirudin Group (N = 174)	
Veins	Side of Op.	Contralat. Side	Side of Op.	Contralat. Side
Muscular in calf	9	4	2	2
Anterior tibial	<1	0	0	0
Posterior tibial	5	3	2	<1
Fibular	4	3	1	1
Popliteal	3	2	<1	0
Superficial femoral	10	0	2	0
Common femoral	5	0	1	0
Deep femoral	1	<1	0	0
Internal iliac	0	0	0	0

*The values are given as percentages. The rates of deep-vein thrombosis are counted separately for each segment — that is, the figures are not mutually exclusive.

TABLE VII
DATA ON BLEEDING-RELATED VARIABLES FOR THE PATIENTS WHO HAD AN OPERATION*

	Heparin Group (N = 220)	Desirudin Group (N = 223)
Blood loss† *(ml)*		
Periop.	1171 ± 630	1136 ± 526
Postop.	275 ± 238	249 ± 183
Red blood-cell transfusion		
Amount *(ml)*	750 ± 490	798 ± 507
Percentage of patients	50	57
Plasma expanders		
Amount *(ml)*	641 ± 373	672 ± 441
Percentage of patients	20	22
Hemoglobin *(g/L)*		
Baseline	138.3 ± 11.7	138.5 ± 11.6
1 day postop.	109.6 ± 12.9	109.1 ± 13.1
6 days postop.	110.6 ± 12.0	109.5 ± 11.0

*The values are given as the mean and the standard deviation, except when designated as a percentage. There were no significant differences between the treatment groups, with the numbers available.

†Perioperative was defined as the start of the operation to twelve hours after it and postoperative, as twelve hours to six days after the operation.

A hematoma at the site of injection occurred in four patients (2 per cent) in each treatment group. Swelling of the thigh, wound hematoma, or superficial wound infection or dehiscence was reported in eleven (5 per cent) of the 220 patients who had received heparin and in fourteen (6 per cent) of the 225 patients who had received desirudin. No patient had a wound rupture or a deep infection, and no patient needed a reoperation because of bleeding. There were no differences between the treatment groups with respect to bleeding complications, and no patient had serious bleeding (hemorrhage in the central nervous system or in other vital organs). There were two instances of severe thrombocytopenia, one of which was fatal; both patients had received heparin, and the thrombocytopenia was probably related to the medication. Four patients in each of the treatment groups had an allergic reaction. None of these reactions was attributed to use of the trial medication.

Discussion

The data in the current study show desirudin to be more effective than heparin in the prevention of deep-vein thrombosis, without any increase in the requirements for transfusion or the risk of hemorrhage. The prevalences of over-all and proximal deep-vein thrombosis in the 174 patients who had been managed with desirudin and were included in the per-protocol analysis were 7 and 3 per cent (thirteen and six patients), respectively. The corresponding prevalences in the 177 patients who had been managed with heparin and were included in the per-protocol analysis were 23 and 16 per cent (forty-one and twenty-nine patients). The relative reduction of risk was 68 per cent for over-all deep-vein thrombosis and 79 per cent for proximal thrombosis in the per-protocol population; the results of the intent-to-treat analysis were almost identical.

The evaluation of new antithrombotic agents may be markedly influenced by the venographic technique and the method of assessment used in a trial. Variations in the diagnostic methodology in different clinical studies may explain a substantial part of the surprisingly high intertrial variation in efficacy that has been reported for heparin in comparable populations of patients[5,16,21]. The limited sample size in many trials, as well as demographic factors, may also contribute to intertrial variability. This suggests that the antithrombotic efficacy of new regimens should not be evaluated on the basis of the absolute rate of deep-vein thrombosis but rather on the difference in efficacy between the new agent and the control drug (the relative risk reduction). The reduction in the risk of deep-vein thrombosis in the patients who received desirudin in the present study compares favorably with that in patients who received low-molecular-weight rather than unfractionated heparin in two recent meta-analyses of orthopaedic trials[16,21].

No significant association between potentially confounding factors and thromboembolism was found in the present study. High emphasis was placed on the end-point evaluation, and the findings suggest that the precision of the standardized venographic technique used in this trial was good. The rate of evaluable venograms was 94 per cent (360 of 385), which is comparable with that in a multicenter study reported by Hull et al. in which the setting was similar to the present one with respect to venographic technique and assessment[13].

With respect to the choice of medication, unfractionated heparin is the best documented antithrombotic drug worldwide. Collins et al., in a meta-analysis, clearly demonstrated that unfractionated heparin reduced the risk of both deep-vein thrombosis and pulmonary embolism in patients who had major orthopaedic operations, and the efficacy seemed to be proportional to the risk. In a recent meta-analysis by Clagett et al., the efficacy of unfractionated heparin was shown to be comparable with that of low-molecular-weight heparin in patients who had an elective hip operation, while the effect of low-dose warfarin was inferior when used in association with either total hip or total knee-replacement procedures. The efficacy of low-molecular-weight heparin seems to be somewhat better than that of unfractionated heparin, as shown by Nurmohamed et al.

In the present study, no patient had a pulmonary embolism during the period of prophylaxis, although four patients who had received heparin had a confirmed pulmonary embolism during the follow-up period. Any conclusion with regard to pulmonary embolism as an end point in itself would be arbitrary. On the basis of the rates of events in this study, no conclusion can be

drawn, with respect to the reduction of the rate of pulmonary embolism, from a single trial unless several thousands of patients are included. This is one reason why a combined end point is often chosen in clinical trials of prophylaxis against thromboembolism. Data on symptomatic pulmonary embolism in clinical trials and large meta-analyses are difficult to interpret, as the patients are screened venographically and effective treatment with anticoagulants is started before there is clinical evidence of thromboembolism. Despite these limitations, it is interesting to evaluate the differences between drugs with respect to the prevention of pulmonary embolism after elective hip procedures. Clinical and autopsy data have shown a relationship between postoperative deep-vein thrombosis and pulmonary embolism[1,11], and these data have been corroborated in the few clinical trials that have included mandatory screening of all patients with bilateral venography and pulmonary scans[7,20]. The venography and scans have shown a considerable risk of asymptomatic pulmonary embolism in association with proximal deep-vein thrombosis and a lower risk in association with thrombi in the calf. Very few patients had a positive scintiscan and a negative venogram, which also indicates a relationship between deep-vein thrombosis and pulmonary embolism in this clinical situation[7,20]. Thus, the very low prevalence of proximal deep-vein thrombosis in patients managed with desirudin might have great clinical importance.

There has been recent debate in the literature concerning the safety of regional block anesthesia in conjunction with anticoagulants[27]. As a precaution, the first injection of desirudin in the current study was given after the induction of anesthesia and immediately before the start of the operation. As 90 per cent of the maximum concentration of desirudin is obtained within thirty minutes, the antithrombotic protection can be expected to be optimum during and immediately after the operation[25]. The preoperative administration of desirudin did not result in increased perioperative bleeding as compared with that associated with heparin. No safety problems were reported in connection with the regional anesthesia.

In the present study, almost all of the complications related to bleeding were of minor importance and there were no instances of wound rupture, reoperation due to bleeding, or deep infection. Swelling of the thigh and subcutaneous hematoma at the operative site were recorded as a wound hematoma, and the designation infection/dehiscence also included redness of the skin at the operative site or dehiscence with serous discharge. The safety of heparin and desirudin in patients having an elective hip operation is well documented. In previous studies of orthopaedic patients, a daily dose of twenty to forty milligrams of desirudin administered subcutaneously did not result in bleeding complications, and no association was found between activated partial thromboplastin time and complications related to bleeding[8,9]. Consequently, monitoring of coagulation was not considered necessary in the present study. Two of our patients (both of whom had received heparin) had thrombocytopenia, and this complication was fatal in one of them. Thrombocytopenia is an inherent threat when heparin is used, and the risk is not eliminated by use of low-molecular-weight heparin, as was shown by Colwell et al. The advantage of an efficient antithrombotic drug that is not associated with the risk of potentially fatal thrombocytopenia is obvious.

In summary, these results demonstrate that specific inhibition of thrombin by desirudin significantly reduces the rate of thromboembolic complications in patients having a total hip replacement ($p < 0.0001$). A fixed dose of fifteen milligrams of desirudin, started preoperatively and administered subcutaneously twice daily for at least eight days, provides effective, safe prevention of thromboembolism without necessitating specific laboratory monitoring.

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References

1. **Bergqvist, D.:** Incidence of pulmonary embolism. In *Postoperative Thromboembolism. Frequency, Etiology, Prophylaxis,* pp. 24-30. New York, Springer, 1983.
2. **Bichler, J.; Fichtl, B.; Siebeck, M.;** and **Fritz, H.:** Pharmacokinetics and pharmacodynamics of hirudin in man after single subcutaneous and intravenous bolus administration. *Arzneimittel-Forschung,* 38: 704-710, 1988.
3. **Biello, D. R.; Mattar, A. G.; McKnight, R. C.;** and **Siegel, B. A.:** Ventilation-perfusion studies in suspected pulmonary embolism. *AJR: Am. J. Roentgenol.,* 133: 1033-1037, 1979.
4. **Clagett, G. P.; Anderson, F. A., Jr.; Heit, J.; Levine, M. N.;** and **Wheeler, H. B.:** Prevention of venous thromboembolism. *Chest,* 108 (4 Supplement): 312S-334S, 1995.
5. **Collins, R.; Scrimgeour, A.; Yusuf, S.;** and **Peto, R.:** Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *New England J. Med.,* 318: 1162-1173, 1988.

6. **Colwell, C. W., Jr.; Spiro, T. E.; Trowbridge, A. A.; Morris, B. A.; Kwaan, H. C.; Blaha, J. D.; Comerota, A. J.;** and **Skoutakis, V. A.:** Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. *J. Bone and Joint Surg.,* 76-A: 3-14, Jan. 1994.
7. **Eriksson, B. I.; Kälebo, P.; Anthmyr, B. A.; Wadenvik, H.; Tengborn, L.;** and **Risberg, B.:** Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. *J. Bone and Joint Surg.,* 73-A: 484-493, April 1991.
8. **Eriksson, B. I.; Kälebo, P.; Ekman, S.; Lindbratt, S.; Kerry, R.;** and **Close, P.:** Direct thrombin inhibition with rec-hirudin CGP 39393 as prophylaxis of thromboembolic complications after total hip replacement. *Thromb. and Haemost.,* 72: 227-231, 1994.
9. **Eriksson, B. I.; Kälebo, P.; Ekman, S.; Baur, M.; Bach, D.; Kerry, R.;** and **Close, P.:** A dose-finding trial evaluating the efficacy and safety of three different doses of recombinant hirudin, CGP 39393 (Revasc-Ciba), in patients undergoing total hip replacement [abstract]. *Thromb. and Haemost.,* 73: 1108, 1995.
10. **Hauptmann, J.; Bruggener, E.;** and **Markwardt, F.:** Effect of heparin, hirudin, and a synthetic thrombin inhibitor on antithrombin III in thrombin-induced disseminated intravascular coagulation in rats. *Haemostasis,* 17: 321-328, 1987.
11. **Havig, Ö.:** Deep vein thrombosis and pulmonary embolism. An autopsy study with multiple regression analysis of possible risk factors. *Acta Chir. Scandinavica,* Supplementum 478, 1977.
12. **Hull, R. D.; Hirsh, J.; Carter, C. J.; Jay, R. M.; Dodd, P. E.; Ockelford, P. A.; Coates, G.; Gill, G. J.; Turpie, A. G.; Doyle, D. J.; Buller, H. R.;** and **Raskob, G. E.:** Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann. Intern. Med.,* 98: 891-899, 1983.
13. **Hull, R.; Raskob, G.; Pineo, G.; Rosenbloom, D.; Evans, W.; Mallory, T.; Anquist, K.; Smith, F.; Hughes, G.; Green, D.; Elliott, C. G.; Panju, A.;** and **Brant, R.:** A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *New England J. Med.,* 329: 1370-1376, 1993.
14. **Kaiser, B.,** and **Markwardt, F.:** Antithrombotic and haemorrhagic effects of synthetic and naturally occurring thrombin inhibitors. *Thromb. Res.,* 43: 613-620, 1986.
15. **Kälebo, P.; Anthmyr, B. A.; Eriksson, B. I.;** and **Zachrisson, B. E.:** Phlebographic findings in venous thrombosis following total hip replacement. *Acta Radiol.,* 31: 259-263, 1990.
16. **Leizorovicz, A.; Haugh, M. C.; Chapuis, F. R.; Samama, M. M.;** and **Boissel, J. P.:** Low molecular weight heparin in prevention of perioperative thrombosis. *British Med. J.,* 305: 913-920, 1992.
17. **Marbet, G. A.; Verstraete, M.; Kienast, J.; Graf, P.; Hoet, B.; Tsakiris, D. A.; Silling-Engelhardt, G.;** and **Close, P.:** Clinical pharmacology of intravenously administered recombinant desulfatohirudin (CGP 39393) in healthy volunteers. *J. Cardiovasc. Pharmacol.,* 22: 364-372, 1993.
18. **Markwardt, F.; Hauptmann, J.; Nowak, G.; Klessen, C.;** and **Walsmann, P.:** Pharmacological studies on the antithrombotic action of hirudin in experimental animals. *Thromb. and Haemost.,* 47: 226-229, 1982.
19. **Markwardt, F.; Nowak, G.; Stürzebecher, J.; Griessbach, U.; Walsmann, P.;** and **Vogel, G.:** Pharmacokinetics and anticoagulant effect of hirudin in man. *Thromb. and Haemost.,* 52: 160-163, 1984.
20. **Moser, K. M.,** and **LeMoine, J. R.:** Is embolic risk conditioned by location of deep venous thrombosis? *Ann. Intern. Med.,* 94: 439-444, 1981.
21. **Nurmohamed, M. T.; Rosendaal, F. R.; Büller, H. R.; Dekker, E.; Hommes, D. W.; Vandenbroucke, J. P.;** and **Briët, E.:** Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet,* 340: 152-156, 1992.
22. **Rabinov, K.,** and **Paulin, S.:** Roentgen diagnosis of venous thrombosis in the leg. *Arch. Surg.,* 104: 134-144, 1972.
23. Rules Governing Medicinal Products in the European Community: Vol. III (Addendum), July 1990. Guidelines for good clinical practice and directive 91/507/EEC. European GCP guidelines. *Good Clin. Pract. J.,* 1 (Supplement 1), 1994.
24. **Skinner, J. A.; Gerrard, D. J.; Zahn, H.; Cohen, A. T.; Porteous, M. J. L.;** and **Thomas, E. M.:** An assessment of deep venous function following total hip arthroplasty complicated by venographically proven deep vein thrombosis [abstract]. *Thromb. and Haemost.,* 73: 1110, 1995.
25. **Talbot, M. D.; Ambler, J.;** and **Butler, K. D.:** Recombinant desulphatohirudin (CGP 39393): comparative studies with standard and low molecular weight heparin. *Internat. Soc. Appl. Cardiovasc. Biol.,* 1: 131-146, 1990.
26. **Verstraete, M.; Nurmohamed, M.; Kienast, J.; Siebeck, M.; Silling-Engelhardt, G.; Buller, H.; Hoet, B.; Bichler, J.;** and **Close, P.:** Biologic effects of recombinant hirudin (CGP 39393) in human volunteers. European Hirudin in Thrombosis Group. *J. Am. Coll. Cardiol.,* 22: 1080-1088, 1993.
27. **Wildsmith, J. A.,** and **McClure, J. H.:** Anticoagulant drugs and central nerve blockade. *Anaesthesia,* 46: 613-614, 1991.
28. **Zachrisson, B. E.,** and **Jansen, H.:** Phlebographic signs in fresh postoperative venous thrombosis of the lower extremity. *Acta Radiol. Diag.,* 14: 82-96, 1973.