

ORIGINAL ARTICLE

Idraparinux versus Standard Therapy for Venous Thromboembolic Disease

The van Gogh Investigators*

ABSTRACT

BACKGROUND

The members of the writing committee (Harry R. Buller, M.D., Ander T. Cohen, M.D., Bruce Davidson, M.D., Hervé Decousus, M.D., Alex S. Gallus, M.D., Michael Gent, M.Sc., Gerard Pillion, M.D., Franco Piovella, M.D., Martin H. Prins, M.D., and Gary E. Raskob, Ph.D.) assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Buller at the Academic Medical Center, Department of Vascular Medicine, F4-211, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at h.r.buller@amc.uva.nl.

*Affiliations of the writing committee are listed in the Appendix. The investigators participating in the van Gogh studies are listed in the Supplementary Appendix, which is available with the full text of this article at www.nejm.org.

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Venous thromboembolism is treated with unfractionated heparin or low-molecular-weight heparin, followed by a vitamin K antagonist. We investigated the potential use of idraparinux, a long-acting inhibitor of activated factor X, as a substitute for standard therapy.

METHODS

We conducted two randomized, open-label noninferiority trials involving 2904 patients with deep-vein thrombosis and 2215 patients with pulmonary embolism to compare the efficacy and safety of idraparinux versus standard therapy. Patients received either subcutaneous idraparinux (2.5 mg once weekly) or a heparin followed by an adjusted-dose vitamin K antagonist for either 3 or 6 months. The primary efficacy outcome was the 3-month incidence of symptomatic recurrent venous thromboembolism (nonfatal or fatal).

RESULTS

In the study of patients with deep venous thrombosis, the incidence of recurrence at day 92 was 2.9% in the idraparinux group as compared with 3.0% in the standard-therapy group (odds ratio, 0.98; 95% confidence interval [CI], 0.63 to 1.50), a result that satisfied the prespecified noninferiority requirement. At 6 months, the hazard ratio for idraparinux was 1.01. The rates of clinically relevant bleeding at day 92 were 4.5% in the idraparinux group and 7.0% in the standard-therapy group ($P=0.004$). At 6 months, bleeding rates were similar. In the study of patients with pulmonary embolism, the incidence of recurrence at day 92 was 3.4% in the idraparinux group and 1.6% in the standard-therapy group (odds ratio, 2.14; 95% CI, 1.21 to 3.78), a finding that did not meet the noninferiority requirement.

CONCLUSIONS

In patients with deep venous thrombosis, once-weekly subcutaneous idraparinux for 3 or 6 months had an efficacy similar to that of heparin plus a vitamin K antagonist. However, in patients with pulmonary embolism, idraparinux was less efficacious than standard therapy. (ClinicalTrials.gov numbers, NCT00067093 and NCT00062803.)

THE STANDARD TREATMENT FOR BOTH deep venous thrombosis and pulmonary embolism is an initial course of unfractionated heparin or low-molecular-weight heparin, followed by a vitamin K antagonist for 3 to 12 months.^{1,2} This therapy is effective but requires laboratory monitoring and dose adjustments. Idraparinux (Sanofi-Aventis) is a novel synthetic pentasaccharide that inhibits activated factor X and differs from fondaparinux in its substantially longer half-life. Initial clinical experience suggests that a fixed dose given subcutaneously once weekly is effective and causes less bleeding than vitamin K antagonists in the treatment of venous thromboembolism.^{3,4} In two studies in patients presenting with either deep venous thrombosis or pulmonary embolism, we tested the hypothesis that idraparinux alone in a fixed dose can replace the combination of unfractionated heparin or low-molecular-weight heparin with a vitamin K antagonist.

METHODS

STUDY ORGANIZATION

We conducted two separate, randomized, open-label trials: one compared the efficacy and safety of idraparinux with those of standard therapy in patients with deep venous thrombosis (the DVT Study), and the other made a similar comparison of therapies in patients with pulmonary embolism (the PE Study). The two trials were sponsored by Sanofi-Aventis.

The steering committee (including two representatives of the sponsor) had final responsibility for the study designs, protocols, statistical analysis, study oversight, verification of the data, and data analysis. The protocols were approved by the institutional review board at each center. The data were gathered and maintained by the sponsor. All suspected outcome events were classified by a central adjudication committee, whose members were unaware of treatment assignments. An independent data and safety monitoring board periodically reviewed the studies' outcomes and advised the steering committee. The writing committee wrote the first and subsequent drafts of the manuscript and vouches for the accuracy and completeness of the reported data.

PATIENTS

Consecutive patients over 18 years of age who presented with acute symptomatic deep venous throm-

bosis or pulmonary embolism were eligible. Patients presenting with lower-extremity symptoms were considered to be candidates for participation in the DVT Study, and those presenting with chest symptoms were considered to be candidates for participation in the PE Study.

The criteria for deep venous thrombosis were a calf trifurcation or more proximal vein that was not compressible on ultrasonography or an intraluminal filling defect on venography.^{5,6} Criteria for pulmonary embolism were an intraluminal filling defect in subsegmental or more proximal pulmonary arteries on spiral computed tomography (CT) or pulmonary angiography, a high-probability finding on a ventilation-perfusion lung scan, or a nondiagnostic finding with documented deep venous thrombosis.^{5,6} Patients without chest symptoms in whom deep venous thrombosis was diagnosed were not routinely tested for pulmonary embolism.

Patients were ineligible if they met one or more of the following criteria: receipt of a therapeutic dose of low-molecular-weight heparin or unfractionated heparin administered for more than 36 hours before randomization; treatment with thrombolysis, embolectomy, or a vena cava filter required for the current episode; another indication for a vitamin K antagonist; pregnancy or breast-feeding; a creatinine clearance of less than 10 ml per minute; uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg); or a life expectancy of less than 3 months.

After giving written informed consent, patients were randomly assigned to receive either idraparinux or standard therapy with the use of a computerized voice-response system. Randomization was stratified according to center and intended treatment duration (3 or 6 months on the basis of the perceived risk of recurrence, as assessed by the treating physician).

TREATMENT REGIMENS

Patients who were assigned to the idraparinux group received a once-weekly subcutaneous dose of 2.5 mg. For patients with a creatinine clearance of less than 30 ml per minute (as calculated with the Cockcroft-Gault formula), the second and subsequent doses were 1.5 mg.

Patients who were assigned to receive standard therapy received tinzaparin, enoxaparin, or intravenous heparin adjusted for the activated partial-

thromboplastin time (ratio, 1.5 to 2.5), followed by warfarin or acenocoumarol (international normalized ratio [INR], 2.0 to 3.0), which was started within 24 hours after randomization. During initial treatment, INRs were determined frequently. Heparin was discontinued when the INR was 2.0 or more for 2 consecutive days and the patient had received at least 5 days of initial treatment. Thereafter, the INR was determined at least once per month.

SURVEILLANCE AND FOLLOW-UP

Patients were contacted weekly up to week 4 and at weeks 7 and 13 (as well as at week 26 in the 6-month stratum). For all patients, a single additional visit was scheduled 3 months after the end of the study period (regardless of whether the discontinuation was planned or premature). At each contact, a checklist was used to elicit information on symptoms and signs of recurrent venous thromboembolism and bleeding. Patients were instructed to report to the study center immediately if any of these symptoms occurred. In case of suspected recurrent pulmonary embolism or deep venous thrombosis, the protocol required objective testing.

OUTCOME ASSESSMENT

The primary efficacy outcome was symptomatic recurrent venous thromboembolism, defined as objectively documented recurrent pulmonary embolism, deep venous thrombosis, or death attributed to pulmonary embolism. The criteria for diagnosis of recurrent pulmonary embolism were one or more of the following findings: a new intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of more than 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non-high-probability perfusion defect associated with deep venous thrombosis as documented by ultrasonography or venography, or a new pulmonary embolism confirmed at autopsy. The criteria for the diagnosis of recurrent deep venous thrombosis were one or more of the following findings: a new noncompressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography.

The main safety outcomes were clinically rel-

evant bleeding (major or clinically relevant nonmajor hemorrhage) and death from all causes. Bleeding was defined as major or as clinically relevant with the use of criteria described previously (Table 1).^{3,5,6} Death was classified as due to pulmonary embolism, bleeding, cancer, or other established diagnoses. Pulmonary embolism was considered the cause of death if there was objective documentation or if the cause of death was unexplained and pulmonary embolism could not be confidently ruled out.

STATISTICAL ANALYSIS

For each study, we assumed a 4% incidence of the primary efficacy outcome in the standard-therapy group at 3 months.⁷ We hypothesized that idraparinix would be at least as effective as the standard treatment. In previous studies involving patients with venous thromboembolism who received inadequate treatment, the reported incidence of recurrence was approximately 20%.⁸ With the use of noninferiority analysis, idraparinix was to be considered at least as effective as standard therapy if the upper limit of the 95% confidence interval for the odds ratio was less than 2. This corresponded to a preservation of at least 54% of the minimal effect, as derived from a literature review.^{7,8} A sample of 1100 patients per group would provide a power of 90% to show noninferiority with a one-sided type I error of 0.025.⁹

Near the end of the planned recruitment periods, lower-than-expected overall rates of recurrent venous thromboembolism were observed in each study. According to the protocols, without unblinding of the steering committee, we considered increasing the sample to 1450 per group to maintain the power of each study at 80%. This increase was implemented for the DVT Study but not for the PE Study on the basis of a recommendation from the data and safety monitoring board.

The primary analysis of efficacy for each study was based on the incidence of recurrent venous thromboembolism at 3 months; odds ratios and 95% confidence intervals were calculated with the use of the normal approximation of the log odds ratio. For each study, the null hypothesis that we tested was that the upper limit of the 95% confidence interval for the odds ratio was greater than 2.0. Planned secondary analyses of efficacy included the calculation of the cumulative incidence of recurrent venous thromboembolism with the use of nonparametric Kaplan–Meier estimates and

a comparison of these incidences at 6 months in the 6-month treatment stratum with the use of a Cox proportional-hazards model.

If the prespecified criteria for noninferiority were met, we planned to test for a reduced incidence of clinically relevant bleeding at 3 months and 6 months with the use of the chi-square test and to compare the incidences of major bleeding at 3 months and 6 months. All analyses included all randomized patients. All reported P values are two-sided, except for those in the primary efficacy analyses.

RESULTS

PATIENTS

Between May 2003 and November 2004, a total of 6054 patients were screened for the DVT Study, of whom 2904 were randomly assigned to study groups (1452 to the idraparinux group and 1452 to the standard-therapy group). For the PE Study, 4628 patients were screened and 2215 were randomly assigned (1095 to the idraparinux group and 1120 to the standard-therapy group). A diagram of the enrollment of patients and randomization is shown in the Supplementary Appendix, which is available with the full text of this article at www.nejm.org.

The baseline characteristics of the patients are presented in Table 2. The mean age of the patients was 58 years in the DVT Study and 62 years in the PE Study. Men accounted for 54% of patients in the DVT Study and 48% of patients in the PE Study. The mean interval between the onset of symptoms and randomization was 8 days in both trials. On the basis of the clinician's judgment, a treatment duration of 3 months was planned for 22% of patients in the DVT Study and for 9% of patients in the PE Study; 6 months of treatment was planned for the remaining patients (see the Supplementary Appendix).

TREATMENT AND FOLLOW-UP

Data on treatment with idraparinux and initial and subsequent treatment in the standard-therapy group are shown in Table 3. In the standard-therapy groups of both studies, more than 80% of patients had an INR of 2.0 or more at the end of initial treatment (82.8% in the DVT Study and 84.6% in the PE Study). Reasons for premature discontinuation of treatment are listed in Table 3. Follow-up with respect to the primary efficacy out-

Table 1. Definition of Major and Clinically Relevant Bleeding.*

Major bleeding

- Bleeding associated with a fall in hemoglobin of 2 g per deciliter or more
- Bleeding that led to a transfusion of 2 or more units of packed red cells or whole blood†
- Bleeding that involved a critical organ (intracranial, intraocular, intraspinal, retroperitoneal, or pericardial)
- Bleeding that contributed to death

Clinically relevant bleeding

- Any bleeding compromising hemodynamics
- Any bleeding leading to hospitalization
- Subcutaneous hematoma larger than 25 cm², or 100 cm² if there was a traumatic cause
- Intramuscular hematoma documented by ultrasonography
- Epistaxis that lasted for more than 5 minutes, was repetitive (i.e., two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g., packing or electrocoagulation)
- Gingival bleeding occurring spontaneously (i.e., unrelated to eating or tooth brushing) or lasting for more than 5 minutes
- Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal hemorrhage, including at least one episode of melena or hematemesis, if clinically apparent with positive results on a fecal occult-blood test
- Rectal blood loss, if more than a few spots on toilet paper
- Hemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism
- Any other bleeding type considered to have clinical consequences for a patient — such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug — or associated with pain or impairment of activities of daily life

* Any one or more of the criteria met the definition of either major or clinically relevant bleeding.

† A red-cell unit was defined as the quantity of red cells obtained from or corresponding to approximately 500 ml of whole blood.

come was similar in all four groups in the two studies and was complete in 99.3% of patients in the DVT Study and 99.1% of patients in the PE Study.

RECURRENT VENOUS THROMBOEMBOLISM

In the DVT Study, 191 patients in the idraparinux group had at least one episode of suspected recurrent venous thromboembolism before day 92, of whom 42 had a confirmed recurrence. In the standard-therapy group, the corresponding numbers were 145 and 43, respectively. Thus, the incidence of recurrent venous thromboembolism at day 92 was 2.9% in the idraparinux group and 3.0% in the standard-therapy group (Table 4), for an odds ratio of 0.98 (95% confidence interval [CI], 0.63 to 1.50) in the idraparinux group. Hence, the

Characteristic	DVT Study			PE Study		
	Idraparinux (N=1452)	Standard Therapy (N=1452)	P Value	Idraparinux (N=1095)	Standard Therapy (N=1120)	P Value
Age — yr	58.0±17.3	58.9±17.0	0.17	62.2±16.4	61.6±16.2	0.38
Male sex — no. (%)	799 (55.0)	769 (53.0)	0.26	525 (47.9)	552 (49.3)	0.53
Weight — no. (%)			0.46			0.52
<50 kg	26 (1.8)	21 (1.5)		16 (1.5)	21 (1.9)	
50–100 kg	1217 (84.6)	1207 (83.6)		911 (84.1)	917 (82.5)	
>100 kg	196 (13.6)	216 (15.0)		156 (14.4)	174 (15.6)	
Missing data	13	8		12	8	
Creatinine clearance — no. (%)			0.83			0.18
<30 ml/min	19 (1.3)	22 (1.5)		30 (2.8)	25 (2.3)	
30 to <50 ml/min	154 (10.9)	164 (11.5)		153 (14.2)	142 (12.9)	
50 to <80 ml/min	394 (27.9)	407 (28.6)		363 (33.8)	342 (31.0)	
≥80 ml/min	845 (59.8)	828 (58.3)		528 (49.2)	593 (53.8)	
Missing data	40	31		21	18	
Time between onset of symptoms and randomization — days	8.1±12.5	8.3±11.5	0.69	8.3±19.9	8.3±24.4	0.97
Diagnostic method for index DVT — no. (%)						
Compression ultrasonography only	1388 (96.4)	1395 (97.1)	0.30			
Venography only	52 (3.6)	45 (3.1)	0.48			
Other diagnostic test	1 (<0.1)	0				
Missing data	12	15				
Diagnostic method for index PE — no. (%)						
High-probability lung scanning				256 (24.1)	281 (25.7)	0.38
Spiral computed tomography				676 (63.6)	691 (63.2)	0.86
Pulmonary angiography				73 (6.9)	71 (6.5)	0.73
Positive test for DVT				58 (5.5)	50 (4.6)	0.35
Missing data				32	27	
Risk factors — no. (%)						
Previous venous thromboembolism	314 (21.6)	305 (21.0)	0.68	258 (23.6)	266 (23.8)	0.92
Cancer						
Any history	220 (15.2)	201 (13.8)	0.32	155 (14.2)	165 (14.7)	0.70
Active disease	146 (10.1)	138 (9.5)	0.62	92 (8.4)	94 (8.4)	0.99
Surgery or trauma within the previous 3 mo†	136 (9.4)	145 (10.0)	0.57	48 (4.4)	47 (4.2)	0.83
Immobilization for >3 days†	93 (6.4)	99 (6.8)	0.65	30 (2.7)	37 (3.3)	0.44
Estrogen therapy†	71 (4.9)	55 (3.8)	0.15	10 (0.9)	16 (1.4)	0.26
Known thrombophilic condition	57 (3.9)	63 (4.3)	0.58	37 (3.4)	34 (3.0)	0.65
Postpartum period†	4 (0.3)	9 (0.6)	0.17	1 (<0.1)	2 (0.2)	0.58
None of the above	780 (53.7)	808 (55.6)	0.30	541 (49.4)	525 (46.9)	0.23
Intended duration of treatment — no. (%)			0.82			0.92
3 mo	321 (22.1)	316 (21.8)		102 (9.3)	103 (9.2)	
6 mo	1131 (77.9)	1136 (78.2)		993 (90.7)	1017 (90.8)	

* Plus-minus values are means ±SD. Not all percentages total 100 because of rounding. DVT denotes deep venous thrombosis, and PE pulmonary embolism.

† This category applies only to patients with transient risk factors.

Table 3. Characteristics of Treatment in Each Study.*

Variable	DVT Study			PE Study		
	Idraparinux (N=1452)	Standard Therapy (N=1452)	P Value	Idraparinux (N=1095)	Standard Therapy (N=1120)	P Value
Patients who received a dose of low-molecular-weight heparin or unfractionated heparin before randomization — no. (%)	980 (67.5)	1050 (72.3)	0.005	915 (83.6)	937 (83.7)	0.96
Duration of heparin therapy before randomization — days	0.8±0.6†	0.8±0.4	0.12	0.9±0.4†	0.9±0.4	0.09
Patients who received at least one dose of assigned treatment — no. (%)	1448 (99.7)	1450 (99.9)	0.69	1081 (98.7)	1118 (99.8)	0.002
Initial heparin treatment‡:						
Type of treatment — no. (%)						
Unfractionated heparin	NA	17 (1.2)		NA	119 (10.9)	
Low-molecular-weight heparin	NA	1408 (98.3)		NA	914 (83.7)	
Both	NA	8 (0.6)		NA	59 (5.4)	
Missing data	NA	19		NA	28	
Duration of treatment — days	NA	9.2±10.7		NA	9.2±11.8	
INR at the end of initial treatment — no. (%)						
<2.0	NA	243 (17.3)		NA	166 (15.4)	
2.0–3.0	NA	874 (62.2)		NA	691 (64.0)	
>3.0	NA	289 (20.6)		NA	222 (20.6)	
Missing data	NA	46		NA	41	
Mean time in INR range — %§						
<2.0	NA	26.2		NA	26.9	
2.0–3.0	NA	54.4		NA	54.8	
>3.0	NA	19.4		NA	18.3	
Duration of treatment with study drug — days						
3-mo stratum	90.4±18.7	88.4±14.9	0.15	87.2±24.1	85.3±21.0	0.61
6-mo stratum	171.8±45.8	170.9±38.1	0.55	170.2±49.7	167.6±44.4	0.22
Premature discontinuation of treatment — no. (%)						
Before 3 mo	132 (9.1)	93 (6.4)	0.007	126 (11.5)	87 (7.8)	0.003
Investigator-suspected lack of efficacy	32 (2.2)	14 (1.0)		22 (2.0)	3 (0.3)	
Adverse events	71 (4.9)	42 (2.9)		71 (6.5)	52 (4.6)	
Other reason	29 (2.0)	37 (2.5)		33 (3.0)	32 (2.8)¶	
Between 3 and 6 mo	45 (4.0)	61 (5.4)	0.12	35 (3.5)	59 (5.8)	0.02
Investigator-suspected lack of efficacy	2 (0.2)	1 (0.1)		2 (0.2)	2 (0.2)	
Adverse events	32 (2.8)	23 (2.0)		24 (2.4)	33 (3.2)	
Other reason	11 (1.0)	37 (3.3)	0.11	9 (0.9)§	24 (2.4)	0.48

* Plus–minus values are means ±SD. Not all percentages total 100 because of rounding. INR denotes international normalized ratio, and NA not applicable.

† One patient who had an aberrant value (at 365 days) was excluded.

‡ Some patients received a type of low-molecular-weight heparin other than that specified in the protocol.

§ Values indicate the percentage of time during initial treatment in which the INR was in the category shown.

¶ Data were missing for one patient.

|| Percentages in this category were calculated for all patients who underwent randomization in the 6-month stratum (in the DVT Study, 1131 patients in the idraparinux group and 1136 in the standard-therapy group; in the PE Study, 993 in the idraparinux group and 1017 in the standard-therapy group).

Table 4. Clinical Outcomes.*

Variable	DVT Study			PE Study		
	Idraparinux (N=1452)	Standard Therapy (N=1452)	Odds Ratio (95% CI)	Idraparinux (N=1095)	Standard Therapy (N=1120)	Odds Ratio (95% CI)
No. of patients						
3-mo stratum	321	316		102	103	
6-mo stratum	1131	1136		993	1017	
Patients with recurrent venous thromboembolism						
At day 92 — no. (%)	0.98 (0.63–1.50)			2.14 (1.21–3.78)		
Total	42 (2.9)	43 (3.0)		37 (3.4)	18 (1.6)	
Fatal PE	4	3		12	5	
Nonfatal PE	21	22		15	3	
DVT only	17	18		10	10	
3-mo stratum	4 (1.2)	5 (1.6)		2 (2.0)	2 (1.9)	
Fatal PE	0	0		2	2	
Nonfatal PE	3	3		0	0	
DVT only	1	2		0	0	
6-mo stratum	38 (3.4)	38 (3.3)		35 (3.5)	16 (1.6)	
Fatal PE	4	3		10	3	
Nonfatal PE	18	19		15	3	
DVT only	16	16		10	10	
			Hazard Ratio (95% CI)			Hazard Ratio (95% CI)
At day 183, 6-mo stratum — no. (%)	1.01 (0.66–1.55)			2.09 (1.22–3.57)		
Total†	42 (3.7)	42 (3.7)		40 (4.0)	20 (2.0)	
Fatal PE	5	6		11	4	
Nonfatal PE	19	18		16	4	
DVT only	18	18		13	12	

prespecified noninferiority criterion was met ($P < 0.001$). Between day 92 and 183, an additional four events occurred in the 6-month stratum of each treatment group. For this stratum, the hazard ratio during the 6-month study period was 1.01 (95% CI, 0.66 to 1.55), which also met the noninferiority criterion. The occurrence of events over time is shown in Figure 1. The types of events are listed in Table 4.

In the PE Study, 171 patients in the idraparinix group had at least one episode of suspected recurrent venous thromboembolism before day 92, of whom 37 had a confirmed recurrence. In the standard-therapy group, the corresponding numbers were 108 and 18, respectively. Thus, the incidence of recurrent venous thromboembolism at day 92 was 3.4% in the idraparinix group and 1.6% in the standard-therapy group (Table 4), for an odds

ratio of 2.14 (95% CI, 1.21 to 3.78) in the idraparinix group. Hence, the prespecified noninferiority criterion was not met ($P = 0.59$). Furthermore, because the lower limit of the 95% confidence interval is above 1.0, the idraparinix regimen was inferior to standard treatment. Between day 92 and 183, an additional five events occurred in the 6-month stratum of the idraparinix group versus four in the standard-therapy group. Hence, the hazard ratio during the 6-month period was 2.09 (95% CI, 1.22 to 3.57), which did not meet the noninferiority criterion. The occurrence of events over time is shown in Figure 1. The difference in incidence of recurrence between the two groups originated mainly during the first 2 weeks of treatment. The types of events are detailed in Table 4.

A comparison of the relative treatment effect for the primary efficacy outcome between the two

Table 4. (Continued.)

Variable	DVT Study			PE Study		
	Idraparinux (N=1452)	Standard Therapy (N=1452)	P Value	Idraparinux (N=1095)	Standard Therapy (N=1120)	P Value
Patients with any clinically relevant bleeding						
At day 92 — no. (%)						
Total	65 (4.5)	101 (7.0)	0.004	63 (5.8)	92 (8.2)	0.02
Major	12	17	0.35	12	24	0.05
Clinically relevant nonmajor	53	84		51	68	
3-mo stratum						
Total	13 (4.0)	28 (8.9)		7 (6.9)	10 (9.7)	
Major	2	5		2	0	
Clinically relevant nonmajor	11	23		5	10	
6-mo stratum						
Total	52 (4.6)	73 (6.4)		56 (5.6)	82 (8.1)	
Major	10	12		10	24	
Clinically relevant nonmajor	42	61		46	58	
At day 183 — no. (%)						
6-month stratum						
Total	94 (8.3)	92 (8.1)	0.85	76 (7.7)	99 (9.7)	0.10
Major	21	17	0.50	14	28	0.04
Clinically relevant nonmajor	73	75		62	71	
Death (adjudicated cause)						
At day 92, all patients — no. (%)						
Total	33 (2.3)	29 (2.0)	0.61	56 (5.1)	32 (2.9)	0.006
PE	4	3		12	5	
Bleeding	2	4		0	1	
Cancer	17	17		23	13	
Other	10	5		21	13	
At day 183, 6-mo stratum — no. (%)						
Total	55 (4.9)	44 (3.9)	0.25	64 (6.4)	45 (4.4)	0.04
PE	5	6		11	4	
Bleeding	3	4		1	1	
Cancer	34	25		30	28	
Other	13	9		22	12	

* Percentages for the 3-month stratum and the 6-month stratum were calculated on the basis of the number of patients in each stratum, rather than on the total number in the study group. PE denotes pulmonary embolism, and DVT deep-vein thrombosis.

† One patient receiving standard therapy in the DVT Study had a nonfatal pulmonary embolism before day 92, and a new pulmonary embolism developed that was fatal after that date.

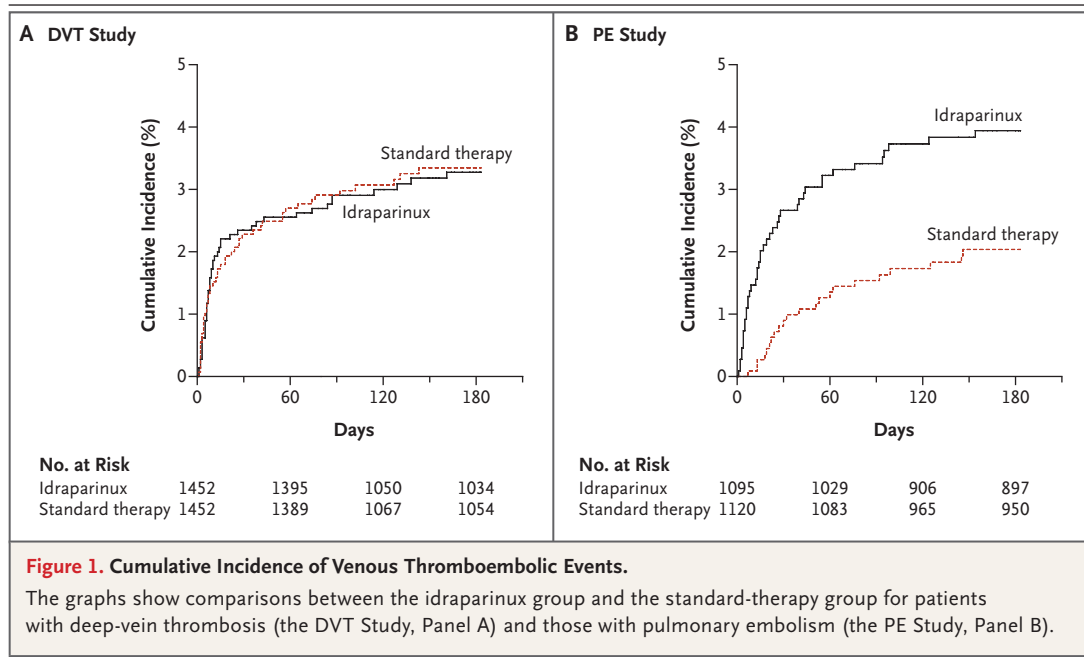
studies indicated that the different efficacies of idraparinux as compared with standard therapy were unlikely to be due to chance ($P=0.03$).

BLEEDING COMPLICATIONS

In the DVT Study, the incidence of clinically relevant bleeding at day 92 was 4.5% in the idraparinux group and 7.0% in the standard-therapy group ($P=0.004$) (Table 4). At day 183, the incidence of

clinically relevant bleeding in the 6-month stratum was 8.3% in the idraparinux group and 8.1% in the standard-therapy group ($P=0.85$). The corresponding rates of major bleeding were 0.8% and 1.2%, respectively, at day 92 ($P=0.35$) and 1.9% and 1.5% at day 183 ($P=0.50$).

In the PE Study, the incidence of clinically relevant bleeding at day 92 was 5.8% in the idraparinux group and 8.2% in the standard-therapy group



(Table 4). At day 183, these rates in the 6-month stratum were 7.7% and 9.7%, respectively. The corresponding rates of major bleeding were 1.1% and 2.1% at day 92 and 1.4% and 2.8% at day 183.

ADVERSE EVENTS

Adverse events that were reported in the two trials, including those leading to permanent discontinuation of the study drug, are listed in Table 5. In the DVT Study, cancer was reported more often as a cause of discontinuation in the idraparinux group than in the standard-therapy group, although no consistent tumor site was noted; this difference was not noted in the PE Study. Rash, dermatitis, and urticaria were reported more often in the idraparinux groups of both trials. In the PE Study, cardiac failure was reported more often in the idraparinux group than in the standard-therapy group (in 28 vs. 16 patients). In the DVT Study, cardiac failure was more frequent in the standard-therapy group than in the idraparinux group (in 6 vs. 18 patients).

RATE OF DEATH

In the DVT Study, the rate of death at day 92 was 2.3% in the idraparinux group and 2.0% in the standard-therapy group ($P=0.61$) (Table 4). At day 183, the death rate in the 6-month stratum was 4.9% in the idraparinux group and 3.9% in the standard-therapy group ($P=0.25$).

In the PE Study, the death rate at day 92 was

5.1% in the idraparinux group and 2.9% in the standard-therapy group ($P=0.006$) (Table 4). At day 183, the death rate in the 6-month stratum was 6.4% in the idraparinux group and 4.4% in the standard-therapy group ($P=0.04$). The causes of death are detailed in Table 4.

DISCUSSION

We conducted two parallel trials comparing idraparinux with standard anticoagulant therapy for the treatment of deep venous thrombosis and pulmonary embolism. The findings differed between the two trials. In patients with deep venous thrombosis, the efficacy of idraparinux in preventing subsequent thromboembolic events was similar to that of standard therapy. In contrast, in patients with pulmonary embolism, the efficacy of idraparinux was inferior to that of standard therapy. This difference in efficacy was due to an excess of early fatal and nonfatal recurrences of pulmonary embolism and was associated with an increase in total mortality. Bleeding rates in the idraparinux groups were similar to or lower than those in the standard-therapy groups.

If the apparent difference in efficacy that we observed in our trials is real, this observation challenges the concept that the same anticoagulant regimen is adequate for both deep venous thrombosis and pulmonary embolism.¹ This concept is based on a large body of clinical experience in

Table 5. Adverse Events.*

Event	DVT Study			PE Study		
	Idraparinux (N=1452)	Standard Therapy (N=1452)	P Value	Idraparinux (N=1095)	Standard Therapy (N=1120)	P Value
All events						
Cancer	97	91	0.65	76	69	0.48
Bleeding	275	311	0.07	237	288	0.02
Cardiac failure	6	18	0.01	28	16	0.06
Rash, dermatitis, or urticaria	62	46	0.11	62	45	0.08
Infection	262	295	0.09	284	287	0.94
Other event	778	754	0.17	785	781	0.19
Event leading to discontinuation of treatment						
Cancer	28	17	0.88	21	22	0.56
Bleeding	25	21	0.26	17	23	0.14
Cardiac failure	1	1	0.74	6	2	0.20
Rash, dermatitis, or urticaria	12	0	0.004	4	1	0.22
Infection	5	7	0.15	4	8	0.16
Other event	37	21	0.63	48	40	0.64

* For each category, the number of patients with at least one event is listed. The most frequent (>1% in any study) and significant events are reported as separate categories.

which the same fixed doses of subcutaneous low-molecular-weight heparin or fondaparinux had similar efficacy for deep venous thrombosis and pulmonary embolism.^{2,5-7,10} By contrast, earlier observations suggested a difference in pharmacokinetic and pharmacodynamic responses to unfractionated heparin in patients with pulmonary embolism, who required larger doses than did patients with deep venous thrombosis.^{11,12} Preliminary analyses of results of the first week of therapy in our studies did not suggest a substantial difference in pharmacokinetics between the two idraparinux groups (data not shown). Furthermore, a plausible explanation for the observed differences is lacking, especially since many patients with deep venous thrombosis probably had concurrent asymptomatic pulmonary embolism, which was not systematically ruled out by objective testing at study entry.

It should be noted that in the PE Study, the rate of recurrence of thromboembolism in the standard-therapy group was lower than anticipated. In most of the contemporary studies, the recurrence rate has been 4 to 5% in the first 3 months, with recurrent pulmonary embolism accounting for about two thirds of events.^{2,6,10} In the PE Study, the recurrence rate in the standard-therapy group was only 1.6% at 3 months, and recurrences were

pulmonary embolism in less than half of the patients (44%), whereas the observed rates in the idraparinux group were consistent with those in previous studies.^{6,10} One possible explanation for the low event rate in the standard-therapy group is selection of a low-risk population. However, the demographic profile of patients in the PE Study was similar to the profiles both in the DVT Study and in previous studies. Although the trials had an open-label design, outcome adjudication was blinded; we therefore do not believe that the event rates were influenced by observer bias.

One other observation requires comment. Although in the DVT Study, the rate of death at day 183 was higher in the idraparinux group than in the standard-therapy group, the difference was not significant and was mainly explained by an excess of deaths from cancer. It should be noted that at study entry there was no stratification for cancer and there were slightly more patients with cancer in the idraparinux group of this study. For the PE Study, the excess mortality both at 3 and 6 months is explained by an excess of deaths from pulmonary embolism as well as other deaths (Table 3). The excess of deaths from pulmonary embolism reinforces concern about the decreased efficacy of idraparinux in patients with pulmonary embolism in this setting.

Another factor that was not specifically addressed in these two trials, but which should be considered in evaluating the risks and benefits of idraparinux, is the absence of a specific antidote for this anticoagulant that could be administered during bleeding. Although this is also true of some other anticoagulants used in the treatment of venous thromboembolic disease, it is a particular liability for an agent with such a long duration of action. In some cases, patients with major bleeding were treated with recombinant activated factor VII or with activated prothrombin complex concentrates.

In conclusion, in two clinical trials, idraparinux was compared with standard therapy for the treatment of deep venous thrombosis and pulmonary

embolism. Although the efficacy of idraparinux was not inferior to that of standard therapy in the DVT Study, it was inferior in the PE Study.

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APPENDIX

The writing committee's affiliations are as follows: the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam (H.R.B.); King's College Hospital, London (A.T.C.); the Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, Seattle (B.D.); INSERM CIE3, Université Saint-Etienne, Centre Hospitalier Universitaire de Saint-Etienne, Hôpital Bellevue, Service de Médecine Interne et Thérapeutique, Saint-Etienne, France (H.D.); Flinders Medical Centre, Bedford Park, SA, Australia (A.S.G.); Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada (M.G.); Sanofi-Aventis, Antony, France (G.P.); U.O. Angiologia I, Malattie Thromboemboliche, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy (F.P.); Department of Epidemiology, Care and Public Health Research Institute, University of Maastricht, and Department of Clinical Epidemiology and Medical Technology Assessment, Academic Hospital, Maastricht, the Netherlands (M.H.P.); and College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City (G.E.R.).

REFERENCES

1. Büller HR, Agnelli GA, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:Suppl 3:401S-428S. [Erratum, *Chest* 2005;127:416.]
2. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2004;140:175-83.
3. The PERSIST Investigators. A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep-vein thrombosis: a phase II evaluation. *J Thromb Haemost* 2004;2:47-53. [Erratum, *J Thromb Haemost* 2004;2:540.]
4. Herbert JM, Hérault JP, Bernat A, et al. Biochemical and pharmacological properties of SANORG34006, a potent and long-acting pentasaccharide. *Blood* 1998;91:4197-205.
5. Büller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004;140:867-73.
6. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695-702. [Erratum, *N Engl J Med* 2004;350:423.]
7. van Dongen CJ, van den Belt AG, Prins MH, Lensing AW. Fixed dose subcutaneous low-molecular-weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2004;4:CD001100.
8. Brandjes DPM, Heijboer H, Büller HR, de Rijk M, Jagt H, ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1992;327:1485-9.
9. Tu D. On the use of the ratio or the odds ratio of cure rates in therapeutic equivalence trials with binary endpoints. *J Biopharm Stat* 1998;8:263-82.
10. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657-62.
11. Hirsh J, van Aken WG, Gallus AS, Doltery CT, Cade JF, Yung WL. Heparin kinetics in venous thrombosis and pulmonary embolism. *Circulation* 1976;53:691-5.
12. Simon TL, Hyers TM, Gaston JP, Harker LA. Heparin pharmacokinetics: increased requirements in pulmonary embolism. *Br J Haematol* 1978;39:111-20.

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