

ORIGINAL ARTICLE

Extended Prophylaxis of Venous Thromboembolism with Idraparinux

The van Gogh Investigators*

ABSTRACT

BACKGROUND

The extended use of vitamin K antagonists for prophylaxis against venous thromboembolism is often constrained by risk–benefit limitations and inconvenience. We evaluated the efficacy and safety of a 6-month extension of prophylaxis against recurrent venous thromboembolism with idraparinux in patients who had initially received 6 months of prophylaxis with an anticoagulant.

METHODS

We randomly assigned patients who had completed 6 months of prophylaxis with idraparinux or a vitamin K antagonist and in whom extended anticoagulation was warranted to receive once-weekly injections of 2.5 mg of idraparinux or placebo for 6 months without monitoring. The primary efficacy and safety outcomes were recurrent venous thromboembolism and major bleeding.

RESULTS

Of 1215 patients, 6 of 594 (1.0%) in the idraparinux group and 23 of 621 (3.7%) in the placebo group had recurrent venous thromboembolism ($P=0.002$). Major bleeding occurred in 11 patients (1.9%) in the idraparinux group and in none in the placebo group ($P<0.001$). Of these 11 episodes, 3 were fatal intracranial hemorrhages. As compared with patients whose initial treatment was a vitamin K antagonist, patients whose initial treatment was idraparinux who were assigned to 6 months in the placebo group had a lower incidence of recurrent thromboembolism (0.7% vs. 5.9%); patients who received 6 additional months of idraparinux therapy had a higher incidence of major bleeding (3.1% vs. 0.9%).

CONCLUSIONS

During a 6-month extension of thromboprophylaxis, idraparinux was effective in preventing recurrent thromboembolism but was associated with an increased risk of a major hemorrhage. (ClinicalTrials.gov number, NCT00071279.)

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PATIENTS WHO HAVE HAD VENOUS THROMBOEMBOLISM have a risk of recurrence of approximately 30% during the first 8 years after the initial episode.¹⁻³ Most of these events occur during the first 6 to 12 months after the first event.

Vitamin K antagonists are highly effective in reducing the risk of recurrence,⁴⁻⁶ but their use requires close laboratory monitoring and dose adjustments to reduce the risk of bleeding. For these reasons, vitamin K antagonists are often discontinued before the recommended period of prophylaxis for idiopathic venous thromboembolism (6 to 12 months).⁷ However, the risks and benefits of extending prophylaxis for 6 to 12 months remain uncertain.

Idraparinix (Sanofi-Aventis) is a long-acting synthetic pentasaccharide that is an antithrombin-dependent inhibitor of activated factor X. Initial clinical experience with idraparinix suggested that a fixed dose, given subcutaneously once weekly and without laboratory monitoring, is effective prophylaxis against recurrent venous thromboembolism and may be associated with a lower risk of bleeding than vitamin K antagonists.^{8,9} Our double-blind, placebo-controlled study evaluated patients who had completed 6 months of initial treatment for deep venous thrombosis or pulmonary embolism and who were then randomly assigned to receive an additional 6 months of prophylaxis with idraparinix. We evaluated the efficacy and safety of this method of thromboprophylaxis in these patients.

METHODS

STUDY DESIGN

The steering committee (including two representatives of the sponsor, Sanofi-Aventis) was responsible for the design of the study, clinical protocols, statistical analyses, study oversight, verification and analysis of the data, and writing of the manuscript. The data were collected and maintained by the sponsor and were available to all members of the steering committee. The writing committee vouches for the accuracy and completeness of this article. All suspected outcome events were reviewed and classified by a central adjudication committee, whose members were unaware of study-group assignment. An independent data and safety monitoring board periodically reviewed the study and advised the steering committee.

PATIENTS

Consecutive patients (age, ≥ 18 years) with confirmed, symptomatic deep venous thrombosis or pulmonary embolism who had been treated for 6 months with acenocoumarol or warfarin (either in previous van Gogh studies or outside these studies)¹⁰ or idraparinix (in van Gogh studies) were eligible. The diagnostic criteria for deep venous thrombosis were a calf trifurcation or a noncompressible proximal vein on ultrasonography or an intraluminal filling defect on venography. For pulmonary embolism, the criteria were an intraluminal filling defect in subsegmental or more proximal pulmonary arteries on spiral computed tomography (CT) or conventional pulmonary angiography, a high-probability finding on a ventilation-perfusion lung scan, or a nondiagnostic finding on a lung scan with objectively documented deep venous thrombosis.^{11,12}

Patients were ineligible if they met one or more of the following criteria: an indication to continue anticoagulant therapy for the index deep venous thrombosis or pulmonary embolism beyond 6 months, other indications for prophylaxis with a vitamin K antagonist, pregnancy or breastfeeding, a creatinine clearance of less than 10 ml per minute, severe hepatic disease, bacterial endocarditis, active bleeding or a high risk of bleeding, 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 patients gave written informed consent, randomization was performed centrally with the use of a computerized voice-response system. Randomization was stratified according to study center and the anticoagulant treatment received in the 6 months before randomization (idraparinix within the van Gogh studies or vitamin K antagonists within or outside the van Gogh studies).¹⁰ Randomization was to be performed not more than 1 hour before the administration of the first dose of the study drug. The institutional review board at each clinical center approved the study protocol.

TREATMENT

Patients received a once-weekly subcutaneous dose of 2.5 mg of idraparinix or placebo with an identical appearance for 6 months (26 injections). In patients who had received idraparinix before randomization, the first dose of idraparinix or pla-

cebo was given 6 to 8 days after the last injection of the drug. In patients who had received a vitamin K antagonist before randomization, the first dose was given when the international normalized ratio (INR) was 3.0 or less. For patients with a creatinine clearance of less than 30 ml per minute, the idraparinux dose was 1.5 mg, with a first dose of 2.5 mg in patients who had received a vitamin K antagonist before randomization.

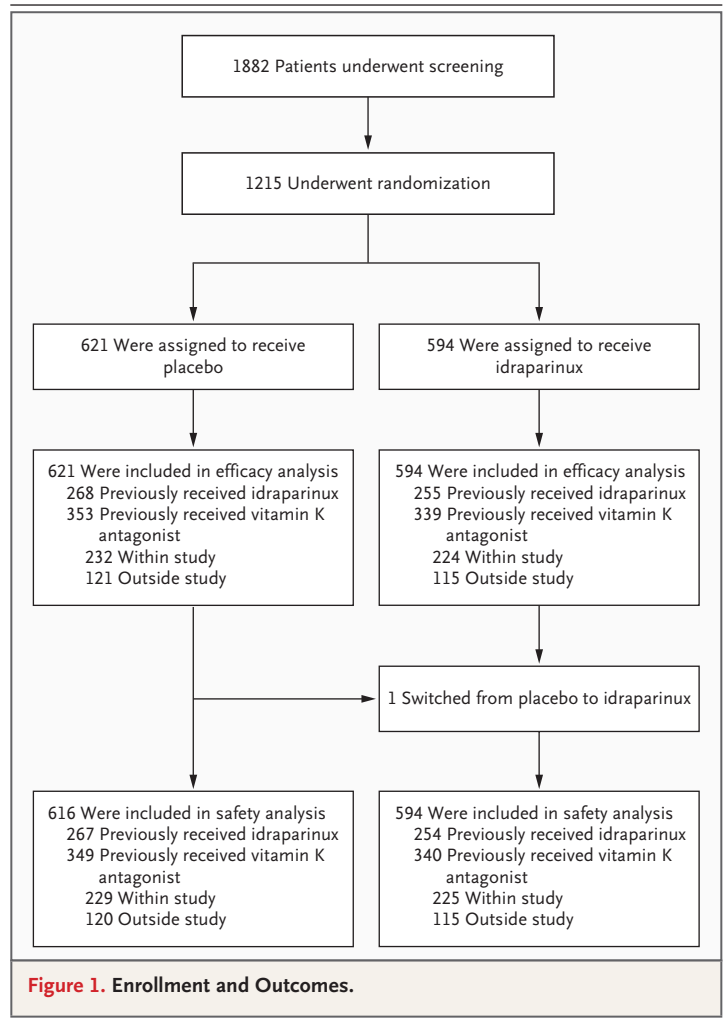
SURVEILLANCE AND FOLLOW-UP

All patients were contacted after 1 week and at 3 and 6 months. All had an observation period of at least 3 months and up to 6 months after the study drug was stopped (regardless of whether the discontinuation was planned or premature). At each contact, patients were systematically questioned concerning symptoms and signs of recurrent venous thromboembolism and bleeding. All patients were informed of the symptoms and signs of recurrent pulmonary embolism and deep venous thrombosis and the potential for bleeding. They were instructed to report to the study center immediately if any of these conditions occurred. In cases of suspected recurrent pulmonary embolism or deep venous thrombosis, objective testing was required.^{11,12}

OUTCOME ASSESSMENT

The primary efficacy outcome was the incidence of symptomatic recurrence of venous thromboembolism, defined as objectively documented recurrent pulmonary embolism, deep venous thrombosis, or death attributed to pulmonary embolism. A diagnosis of recurrent venous thromboembolism was accepted in the absence of an adequate objective test result if the investigator had treated the patient with therapeutic doses of heparin for more than 2 days or with a vena cava filter, thrombectomy, or thrombolysis, or if recurrent venous thromboembolism could not be ruled out.

The criteria for the objective diagnosis of recurrent pulmonary embolism were 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 documented on ultrasonography or venography, or a new pulmonary embolism confirmed at autopsy.



The criteria for the objective diagnosis of a new deep venous thrombosis were 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 principal safety outcome was major bleeding. Bleeding was defined as major if it was clinically overt and associated with a fall in the hemoglobin level of 2 g per deciliter or more, if it led to the transfusion of two or more units of red cells, or if it was retroperitoneal or intracranial, occurred in a critical organ, or contributed to death. All bleeding episodes that were clinically relevant but did not qualify as major bleeding (e.g., epistaxis that required an intervention or spontaneous macroscopic hematuria) constituted an additional safety outcome.^{9,11,12}

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Idraparinux (N=594)	Placebo (N=621)
Age — yr	60.2±15.2	59.9±15.4
Male sex — no. (%)	317 (53.4)	326 (52.5)
Weight — no. (%)		
<50 kg	4 (0.7)	7 (1.1)
50–100 kg	508 (86.1)	507 (82.0)
>100 kg	78 (13.2)	104 (16.8)
Missing data	4	3
Creatinine clearance — no. (%)		
<30 ml/min	7 (1.2)	3 (0.5)
30 to <50 ml/min	60 (10.4)	62 (10.4)
≥50 ml/min	511 (88.4)	534 (89.1)
Missing data	16	22
Time from diagnosis to randomization — days	193.4±12.7	193.7±19.7
Type of qualifying event — no. (%)†		
Pulmonary embolism	283 (47.6)	304 (49.0)
Deep venous thrombosis	332 (55.9)	337 (54.3)
Risk factor — no. (%)‡		
Previous venous thrombo- embolism	109 (18.4)	112 (18.0)
Cancer	53 (8.9)	67 (10.8)
Known thrombophilic condition	43 (7.2)	51 (8.2)
Idiopathic condition	364 (61.3)	371 (59.7)
Other condition	80 (13.5)	89 (14.3)

* Plus-minus values are means ±SD. Not all percentages total 100 because of rounding.

† Some patients had both pulmonary embolism and deep venous thrombosis.

‡ Some patients had more than one risk factor.

Deaths from all causes were also recorded. Death was classified as due to pulmonary embolism, bleeding, cancer, or another established diagnosis. Pulmonary embolism was considered to be the cause of death if the condition was objectively documented or if the cause of death was unexplained and pulmonary embolism could not be confidently ruled out.

STATISTICAL ANALYSIS

On the basis of an assumed 4% incidence of the primary efficacy outcome in the placebo group at 6 months, we calculated that a sample of 600 patients per group would provide a power of 90% to detect a hypothesized 75% reduction in risk in the

idraparinux group (with a two-sided type I error of 0.05).

Analysis of the primary efficacy outcome, the incidence of symptomatic recurrent venous thromboembolism at 6 months, was performed with the use of the Mantel–Haenszel test, stratified according to the previous treatment (idraparinux within or outside the van Gogh studies or a vitamin K antagonist within or outside the van Gogh studies). In addition, reductions in the adjusted risk and two-sided 95% confidence intervals were calculated with the use of the normal approximation of the log relative risk. Secondary planned efficacy analyses included a calculation of the cumulative incidence of recurrent venous thromboembolism with the use of nonparametric Kaplan–Meier estimates.

Analysis of the principal safety outcome, the incidence of major bleeding at 6 months, was performed with the use of the Mantel–Haenszel test, stratified according to the previous treatment. The effect of initial, prerandomization treatment on efficacy and safety was also analyzed. All efficacy analyses were based on the total randomized population, whereas the safety analyses were based on the total randomized population that received at least one dose of a study drug.

RESULTS

PATIENTS

Between November 2003 and February 2005, 1882 patients were screened in 145 centers; of these patients, 1215 underwent randomization (Fig. 1). There were no significant differences in the baseline characteristics of the patients between the two study groups (Table 1).

Table 2 shows data on the administration of idraparinux or placebo and the reasons for premature discontinuation of treatment. Information on efficacy 6 months after randomization was complete in 99.8% of patients in the idraparinux group and in 99.7% of patients in the placebo group.

RECURRENT VENOUS THROMBOEMBOLISM

During the 6 months of randomly assigned treatment, 6 of 594 patients in the idraparinux group (1.0%) and 23 of 621 patients in the placebo group (3.7%) had symptomatic, objectively confirmed venous thromboembolism. The reduction in the relative risk with idraparinux was 72.7% (95% con-

fidence interval [CI], 33.5 to 88.8; $P=0.002$). Figure 2 shows the occurrence of events over time, and Table 3 lists the types of recurrent episodes.

In patients who had an initial pulmonary embolism, a recurrent event occurred in 3 of 283 (1.1%) in the idraparinux group and in 13 of 304 in the placebo group (4.3%, $P=0.02$). Among patients who had deep venous thrombosis only, 3 of 311 patients (1.0%) in the idraparinux group had a recurrent event, as compared with 10 of 317 patients (3.2%) in the placebo group ($P=0.09$) (data not shown). The incidence of recurrent venous thromboembolism in the placebo group appeared to be related to the anticoagulant treatment (vitamin K antagonist or idraparinux) that was received in the 6 months before randomization ($P=0.004$) (Table 3), whereas the incidence seemed to be unrelated to previous treatment in the idraparinux group.

HEMORRHAGIC COMPLICATIONS

Major bleeding occurred in 11 of 594 patients in the idraparinux group (1.9%) and in none of the 621 patients in the placebo group ($P<0.001$). A higher incidence of major bleeding was observed in patients who had received idraparinux before randomization than in those who had received a vitamin K antagonist (3.1% vs. 0.9%, $P=0.06$) (Table 3). Three bleeding episodes in the idraparinux group were fatal intracranial hemorrhages and occurred in patients who had received idraparinux before entry into the trial. Table 3 also lists clinically relevant episodes of nonmajor bleeding.

ADDITIONAL OBSERVATIONS

During the observation period after the end of the additional 6 months of thromboprophylaxis, 7 patients in the idraparinux group (1.2%) and 13 patients in the placebo group (2.1%) had recurrent venous thromboembolism ($P=0.21$). The cumulative incidence of recurrent venous thromboembolism 1 year after randomization, as estimated with the Kaplan–Meier method, was 1.7% in the idraparinux group and 5.9% in the placebo group ($P=0.002$). In the placebo group, the cumulative incidence of recurrent thromboembolism during the entire year after randomization was lowest in the group of 268 patients who had received idraparinux in the 6 months before randomization (Fig. 3).

Table 2. Details of the Study Groups.

Variable	Idraparinux (N = 594)	Placebo (N = 621)
	no. (%)	
No receipt of study drug	1 (0.2)	4 (0.6)
Completion of study treatment	528 (88.9)	549 (88.4)
Premature discontinuation of treatment		
Discontinuation for any reason	65 (10.9)	68 (11.0)
Reason for discontinuation		
Investigator-suspected lack of efficacy	5 (0.8)	22 (3.5)
Adverse event	29 (4.9)	25 (4.0)
Request by patient	17 (2.9)	12 (1.9)
Other reason	14 (2.4)	9 (1.4)

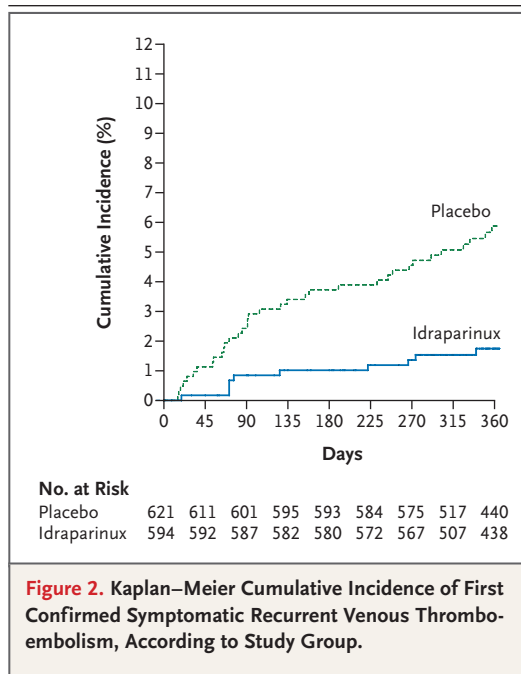


Figure 2. Kaplan–Meier Cumulative Incidence of First Confirmed Symptomatic Recurrent Venous Thromboembolism, According to Study Group.

Major bleeding after discontinuation of the study drug occurred in five patients in the idraparinux group (0.8%) and in none in the placebo group ($P=0.02$). The episodes of bleeding, none of which were fatal, occurred from 1 to 20 weeks after the discontinuation of a study drug. During the entire period of observation, a major hemorrhagic episode occurred in 16 patients in the idraparinux group and in none of the patients in the placebo group ($P<0.001$).

Table 3. Clinical Outcomes.				
Outcome	Idraparinux	Placebo	Odds Ratio (95% CI)*	P Value
	<i>no./total no. (%)</i>			
Recurrent venous thromboembolism	6/594 (1.0)	23/621 (3.7)	0.27 (0.11–0.66)	0.002
Type of recurrent event†				
Pulmonary embolism				
Fatal	2	1		
Nonfatal	1	11		
Deep venous thrombosis only				
	3	11		
Treatment received before randomization				
Idraparinux	3/255 (1.2)	2/268 (0.7)	1.58 (0.26–9.55)	0.68
Vitamin K antagonist	3/339 (0.9)	21/353 (5.9)	0.14 (0.04–0.48)	<0.001
Within study	2/224 (0.9)	10/232 (4.3)	0.20 (0.04–0.92)	0.02
Outside study	1/115 (0.9)	11/121 (9.1)	0.09 (0.01–0.69)	0.004
Bleeding				
Major bleeding	11/594 (1.9)	0/616		<0.001
Idraparinux received before randomization	8/254 (3.1)	0/267		
Vitamin K antagonist received before randomization	3/340 (0.9)	0/349		
Within study	2/225 (0.9)	0/229		
Outside study	1/115 (0.9)	0/120		
Clinically relevant (major and nonmajor) bleeding	27/594 (4.5)	9/616 (1.5)		
Idraparinux received before randomization	17/254 (6.7)	6/267 (2.2)		
Vitamin K antagonist received before randomization	10/340 (2.9)	3/349 (0.9)		
Within study	7/225 (3.1)	2/229 (0.9)		
Outside study	3/115 (2.6)	1/120 (0.8)		
Death (adjudicated)				
Death from any cause	9/594 (1.5)	4/616 (0.6)		
Cause of death				
Pulmonary embolism	2	1		
Bleeding	3	0		
Cancer	2	2		
Other cause	2	1		

* Odds ratios were adjusted according to treatment history.

† When patients had several recurrent events, they were counted in the category with the most severe outcome.

DISCUSSION

We found that in patients with venous thromboembolism who had completed 6 months of anticoagulant therapy, a further 6 months of thromboprophylaxis with idraparinux reduced the frequency of recurrent thromboembolism to 1.0%, as compared with 3.7% in the placebo group. However, there was an excess of major bleeding episodes, including fatal bleeding, in the idraparinux group (in 1.9% of patients, vs. none in the pla-

cebo group). During the entire duration of observation, including the period after discontinuation of thromboprophylaxis, 2.7% of patients in the idraparinux group had a major hemorrhagic episode, whereas there were no such episodes in the placebo group. A risk of major bleeding during an 18-month period of 1.2 to 2.5% has been reported with extended thromboprophylaxis with vitamin K antagonists.^{3-7,13}

The overall frequency of recurrences in the placebo group was lower than expected (3.7%), but

among patients in the placebo group who had received vitamin K antagonists for 6 months before randomization, the frequency of recurrence was 5.9%, which is consistent with other studies.^{13,14} By contrast, in patients who first received idraparinux, the 6-month recurrence rate in the placebo group was less than 1%. The reason for this difference is unknown, but the observation suggests a prolonged antithrombotic effect of idraparinux.

With regard to safety, no major bleeding was observed in the placebo group, including patients who initially had received idraparinux, whereas in the idraparinux group, the incidence was 1.9%. Of the 11 patients in the idraparinux group who had a major hemorrhage, 8 had previously received idraparinux, and 3 had received a vitamin K antagonist. After completion of the extended idraparinux treatment, there were another five episodes of major bleeding in the idraparinux group. These observations suggest a prolonged risk of hemorrhage in patients treated with idraparinux for more than 6 months.

The strengths of our study were its double-blind, randomized design, which minimized the risk of bias in the reporting and assessment of recurrences and bleeding complications. Moreover, all initial thrombotic events and suspected outcomes were adjudicated by a blinded and independent adjudication committee.

In summary, our placebo-controlled trial showed the efficacy of idraparinux during a 6-month extended treatment period, at the expense of an increased risk of bleeding. We conclude that the net clinical benefit of such treatment is marginal.

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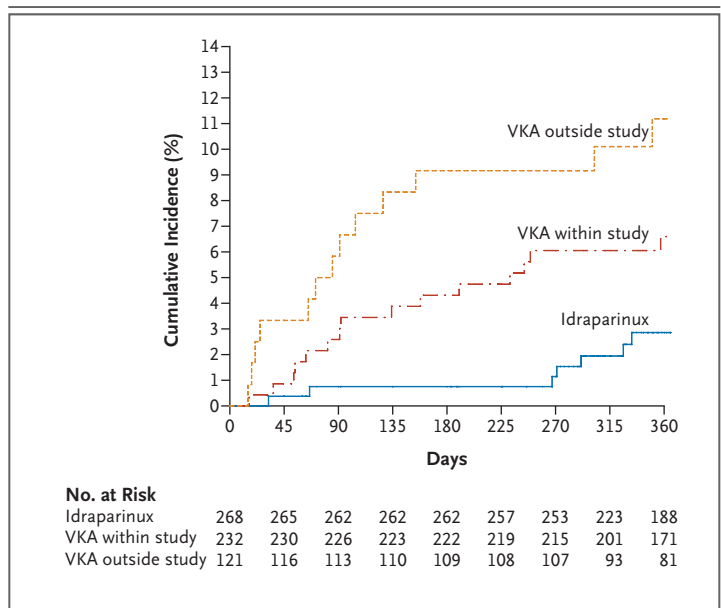


Figure 3. Kaplan–Meier Cumulative Incidence of First Confirmed Symptomatic Recurrent Venous Thromboembolism in the Placebo Group, According to Treatment Received before Randomization.

VKA denotes vitamin K antagonist.

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APPENDIX

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