Idraparinux was noninferior to standard therapy for deep venous thrombosis but inferior for pulmonary embolism

The van Gogh Investigators. **Idraparinux versus standard therapy for venous thromboembolic disease.** N Engl J Med. 2007;357:1094-104.

Clinical impact ratings: Emergency Med ★★★★★★☆ Hematol/Thrombo ★★★★★★☆ Pulmonology ★★★★★★☆

QUESTION

In patients with deep venous thrombosis (DVT) or pulmonary embolism (PE), is idraparinux as effective as standard therapy (heparin followed by a vitamin K antagonist) in preventing recurrence of venous thromboembolism (VTE)?

METHODS

Design: 2 randomized, controlled, noninferiority trials.
Allocation: Concealed.*
Blinding: Blinded (central outcome adjudication committee).*
Follow-up period: 3 and 6 months.
Setting: 318 centers in 25 countries in North and South America, Europe, Africa, and Australia/New Zealand.
Patients: Patients ≥ 18 years of age with acute symptomatic DVT (n = 2904, mean age 58 y, 54% men) or PE (n = 2215, mean age 62 y, 52% women). Exclusion criteria included receipt of heparin for > 36 hours; need for thrombolysis, embolectomy, or a vena cava filter; another indication for a vitamin K antagonist; pregnancy; creatinine clearance < 10 mL/min; and uncontrolled hypertension.
Intervention: Idraparinux, 2.5 mg subcutaneously once weekly (in patients with creatinine clearance < 30 mL/min, dose was 1.5 mg after the first injection) (n = 1452 in the DVT study and 1095 in the PE study), or standard therapy (tinzaparin, enoxaparin, or intravenous heparin followed by warfarin or acenocoumarol, with monitoring and dose adjustment as required) (n = 1452 in the DVT study and 1120 in the PE study). Treatment duration was either 3 mo (22% of patients in the DVT study and 9% in the PE study) or 6 months, based on the physician's assessment of recurrence risk.
Outcomes: Objectively confirmed symptomatic recurrent VTE, clinically relevant bleeding, and death from all causes.
Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

Risk for recurrent VTE at 3 months was higher with idraparinux than with standard therapy in the PE study, but groups did not differ in the DVT study (Table). Similar results were seen at 6 months in patients treated for the longer period (Table). In both studies, idraparinux had less risk for bleeding than standard therapy at 3 months (Table), but groups did not differ at 6 months. Idraparinux increased risk for death from all causes in the PE study (including 12 vs 5 cases of fatal PE) but not in the DVT study (4 vs 3 cases of fatal PE) (Table).

CONCLUSION

For prevention of recurrent venous thromboembolism, idraparinux was noninferior to standard therapy in patients with deep venous thrombosis but was inferior to standard therapy in patients with pulmonary embolism.

Source of funding: Sanofi-Aventis.

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*See Glossary.

Idraparinux vs standard therapy (heparin followed by a vitamin K antagonist) to prevent recurrence of venous thromboembolism (VTE) in patients with deep venous thrombosis (DVT) or pulmonary embolism (PE)†

Outcomes	Follow-up	Study	Idraparinux	Standard therapy	Odds ratio (95% CI)	NNH (CI)
Recurrent VTE	3 mo	DVT	2.9%	3.0%	1.0 (0.6 to 1.5)‡	Not significant
		PE	3.4%	1.6%	2.1 (1.2 to 3.8)	57 (24 to 304)
					RRI (CI)	
	6 mo§	DVT	3.7%	3.7%	1% (–34 to 53)	Not significant
		PE	4.0%	2.0%	107% (22 to 248)	47 (21 to 231)
Death	3 mo	DVT	2.3%	2.0%	14% (–30 to 86)	Not significant
		PE	5.1%	2.9%	79% (17 to 173)	45 (26 to 157)
					RRR (CI)	**NNT (CI)**
Clinically relevant bleeding	3 mo	DVT	4.5%	7.0%	36% (13 to 52)	41 (24 to 126)
		PE	5.8%	8.2%	30% (5 to 49)	41 (22 to 295)

†Abbreviations defined in Glossary. RRR, RRI, NNH, NNT, and CI calculated from data in article.
‡Criterion for noninferiority was met because the upper limit of the CI was < 2.
§Analysis includes only the 78% of patients in the DVT study and the 91% of patients in the PE study who received treatment for 6 mo.

COMMENTARY

The inferiority of the long-acting pentasaccharide factor Xa inhibitor idraparinux to standard therapy among patients with PE is intriguing, especially in contrast to its noninferiority among patients with DVT. Although recent clinical data support the efficacy of standard dosing for both DVT and PE, earlier studies suggested that a more rapid clearance of heparin necessitates a higher initial dose among patients with PE (1-3). Therefore, a pharmacokinetic difference in Xa inhibition may exist (possibly as it pertains to long-acting Xa inhibitors). Although the van Gogh Investigators reported no substantial difference in pharmacokinetics between the idraparinux and conventional therapy groups, the difference in incidence of recurrent VTE between the 2 groups originated mainly during the first 2 weeks of therapy. This finding raises the possibility of variable Xa inhibition in the acute period among patients with PE. It is worth noting that the recurrence rate in the conventional therapy group of the PE study (1.6%) was considerably lower than expected and lower than that seen in the DVT study (3.0%). Further study of idraparinux in patients with DVT and PE may explain the divergent outcomes noted in this trial.

Certain populations (e.g., patients with cancer or those for whom monitoring of international normalized ratio is difficult) would benefit from the easily administered treatment regimen that idraparinux affords. Trials have yet to show the superiority of pentasaccharides over vitamin K antagonists, as has been shown with low-molecular-weight heparins in patients with cancer. Further study is needed to better characterize the efficacy of idraparinux in the treatment of PE before it can be recommended in this population.

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Extended prophylaxis with idraparinux prevented recurrence of venous thromboembolism but increased risk for bleeding

The van Gogh Investigators. **Extended prophylaxis of venous thromboembolism with idraparinux.** N Engl J Med. 2007;357:1105-12.

Clinical impact ratings: Hematol/Thrombo ★★★★★★☆ Pulmonology ★★★★★★☆

QUESTION

In patients with venous thromboembolism (VTE) who have completed 6 months of anticoagulant therapy, is idraparinux more effective than placebo in preventing recurrence in the following 6 months?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded (patients, clinicians, and central outcome adjudication committee).*

Follow-up period: 6 months.

Setting: 157 centers in 23 countries in North and South America, Europe, Africa, and Australia/New Zealand.

Patients: 1215 patients ≥ 18 years of age (mean age 60 y, 53% men) with symptomatic deep venous thrombosis (55% of patients) and/or pulmonary embolism (48%) who had been treated for 6 months with a vitamin K antagonist (warfarin or acenocoumarol) or idraparinux. Exclusion criteria included an indication to continue anticoagulation for the index VTE or another reason, pregnancy, creatinine clearance < 10 mL/min, severe hepatic disease, high risk for or active bleeding, and uncontrolled hypertension.

Intervention: Idraparinux, 2.5 mg subcutaneously once weekly (in patients with creatinine clearance < 30 mL/min, dose was 1.5 mg after the first injection) (n = 594), or placebo (n = 621), for 6 months.

Outcomes: Objectively confirmed symptomatic recurrent VTE, major bleeding, clinically relevant bleeding, and death from all causes.

Patient follow-up: 99.8% (intention-to-treat analysis).

MAIN RESULTS

Idraparinux reduced risk for recurrent VTE more than placebo (Table). Episodes of major bleeding occurred only in the idraparinux group (Table); 3 of these episodes were fatal intracranial hemorrhage. Idraparinux increased risk for clinically relevant bleeding (Table). Groups did not differ for death (Table).

CONCLUSION

In patients with venous thromboembolism who had completed 6 months of anticoagulant therapy, idraparinux prevented recurrence in the following 6 months but increased risk for bleeding.

Source of funding: Sanofi-Aventis.

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*See Glossary.

Idraparinux vs placebo for extended prophylaxis against recurrence of venous thromboembolism (VTE)†

Outcomes at 6 mo	Idraparinux	Placebo	RRR (95% CI)	NNT (CI)
Recurrent VTE	1.0%	3.7%	72% (33 to 89)	38 (31 to 82)
			RRI (CI)	NNH (CI)
Major bleeding	1.9%	0%	–	54
Clinically relevant bleeding‡	4.5%	1.5%	211% (50 to 546)	33 (20 to 82)
Death	1.5%	0.6%	133% (–23 to 611)	Not significant

†Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.
‡Includes major bleeding.

COMMENTARY *(continued from page 19)*

The potent Xa inhibition and long half-life of idraparinux, which are among the desirable characteristics of this anticoagulant, are also possible explanations for the increased bleeding observed among patients randomized to idraparinux in the extended anticoagulation trial. Bleeding during idraparinux therapy poses challenges, because no known drug antidote exists (although investigational studies are ongoing). In the meantime, treatment should include transfusion of packed red blood cells or fresh frozen plasma when clinically indicated, and use of prothrombin concentrate or recombinant factor VIIa can be considered.

An effective anticoagulant is needed that does not require dose adjustment and offers a favorable safety profile and predictable pharmacokinetics. The trials by the van Gogh Investigators provide valuable insight into the potential benefits and limitations of idraparinux. However, the coagulation cascade presents multiple opportunities to intervene. Newer anticoagulants, including rNAPc2 (which inhibits the tissue factor/activated factor VII complex), oral factor Xa inhibitors, and oral direct thrombin inhibitors, show promise.

A compelling role for idraparinux would involve use in the emergency department on diagnosis of DVT, because once-weekly dosing would facilitate discharge and follow-up in the outpatient setting. A trial of idraparinux specifically in outpatients would be welcome.

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