Fondaparinux was as effective as (noninferior to) enoxaparin in acute symptomatic deep venous thrombosis

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.

QUESTION

In patients with acute symptomatic deep venous thrombosis (DVT), is fondaparinux as effective as (noninferior to) enoxaparin for reducing symptomatic recurrent venous thromboembolic complications, major bleeding, or all-cause mortality?

METHODS

Design: Randomized controlled trial.

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, and outcome assessors).*

Follow-up period: Patients were contacted daily during initial treatment and at 1 and 3 months.

Setting: 154 centers worldwide.

Patients: 2205 patients > 18 years of age (61 y, 53% men) who had acute symptomatic DVT (defined as a noncompressible vein found on ultrasonography or an intraluminal filling defect found on venography) involving the popliteal, femoral, or iliac veins or the trifurcation of the calf veins and required antithrombotic therapy. Exclusion criteria included therapeutic anticoagulation for > 24 hours, thrombolytic therapy, or vena cava filter; contraindication to anticoagulant therapy; symptomatic pulmonary embolism; and life expectancy < 3 months.

Intervention: Patients were stratified by center and allocated to fondaparinux, 7.5 mg (5.0 mg in patients weighing < 50 kg and 10.0 mg in patients weighing > 100 kg) subcutaneously once daily (n = 1098) or enoxaparin, 1 mg/kg of body weight, subcutaneously twice daily for ≥ 5 days and until vitamin antagonists induced an international normalized ratio > 2.0 (n = 1107).

Outcomes: Symptomatic recurrent venous thromboembolic complications, major bleeding during the initial treatment and during the entire study, and all-cause mortality. The study had 95% power for rejecting the hypothesis that the rate of recurrence with fondaparinux would be 3.5% higher than with enoxaparin.

Patient follow-up: 99%.

MAIN RESULTS

The groups did not differ for number of patients with ≥ 1 episode of symptomatic recurrent venous thromboembolism, major bleeding, or all-cause mortality (Table).

CONCLUSION

In patients with acute symptomatic deep venous thrombosis, fondaparinux was as effective as (noninferior to) enoxaparin for reducing symptomatic recurrent venous thromboembolic complications, major bleeding, and all-cause mortality.

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*See Glossary.

Fondaparinux vs enoxaparin for acute symptomatic deep venous thrombosis†

Outcomes at 3 mo	Fondaparinux	Enoxaparin	Difference (95% CI)‡
Recurrent venous thromboembolism	3.9%	4.1%	–0.15% (–1.8 to 1.5)§
Major bleeding during initial treatment	1.1%	1.2%	–0.10% (–1.0 to 0.8)
Major bleeding during the entire study	2.6%	2.4%	0.2% (–1.1 to 1.5)
All-cause mortality	3.8%	3.0%	0.8% (–0.8 to 2.3)

†CI defined in Glossary.

‡All differences are not statistically different.

§Criteria for noninferiority were met because the upper limit of this CI is < 3.5% (the clinically important difference).

COMMENTARY

In this large and methodologically rigorous trial, Büller and colleagues compared fondaparinux with enoxaparin in patients with acute DVT and concluded that the rates of recurrent DVT and bleeding were virtually identical. Based on these results and on those from another study (1), fondaparinux was licensed for use in the United States.

Does fondaparinux offer any advantages? It is given in a weight-adjusted dose; however, unlike LMWH, the dose is based on broad weight categories. This marginally increases its ease of use. Although heparin-induced thrombocytopenia (HIT) is rare in patients treated with LMWH, the risk for HIT should be further reduced in patients treated with fondaparinux. Finally, fondaparinux is synthetic, unlike other heparins, which are derived from animal tissues.

How is fondaparinux similar to current "standard treatment" with LMWH? Both drugs require antithrombin, are given parenterally using a once-daily unmonitored dose, seem to be equivalently efficacious for treatment of acute DVT with similar bleeding risks, are unlikely to be routinely used for long-term therapy (with the exception of long-term LMWH therapy in patients with DVT and cancer) because they require daily injections, do not have a completely efficacious antidote, and are not known to interact with other medications. How is fondaparinux inferior to LMWH? Fondaparinux is likely to be more expensive, which will probably hinder its application in many jurisdictions.

Overall, these observations suggest that fondaparinux is an effective treatment for DVT. As shown in this study, it should be considered equivalent to current treatments. The choice of which medication to use in patients with DVT should be based on such issues as convenience, cost, familiarity, and local availability. Because both LMWH and fondaparinux are used in combination with warfarin, clinicians must remain familiar with oral anticoagulants, irrespective of the drug they choose for acute treatment.

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Reference

1. **Büller HR, Davidson BL, Decousus H, et al.** Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med. 2003;349:1695-702.