Fondaparinux was not inferior to unfractionated heparin for symptomatic pulmonary embolism


**Question**
In patients with symptomatic pulmonary embolism (PE), is fondaparinux noninferior to unfractionated heparin (UFH)?

**Design**
Randomized (allocation concealed*), blinded (monitoring committee),* controlled non-inferiority trial with 3-month follow-up (Matisse).

**Setting**
235 centers worldwide.

**Patients**
2213 patients (mean age 63 y, 56% women) who had acute symptomatic PE and required antithrombotic therapy. Exclusion criteria were receipt of low-molecular-weight heparin or oral anticoagulants > 24 hours; need for thrombolysis, embolectomy, or a vena cava filter; contraindication to anticoagulant therapy; serum creatinine level > 177 µmol/L; uncontrolled hypertension; pregnancy; or life expectancy < 3 months. Follow-up was 99.4%.

**Intervention**
Patients were allocated to fondaparinux (n = 1103) or UFH (n = 1110). Fondaparinux was given as a single daily subcutaneous injection of 5.0 mg if body weight < 50 kg, 7.5 mg for body weight 50 to 100 kg, and 10.0 mg for body weight > 100 kg. UFH was given as an initial intravenous bolus ≥ 5000 IU and ≥ 1250 IU/h as a continuous intravenous infusion. Fondaparinux and UFH were given for ≥ 5 days until the international normalized ratio was > 2.0. All patients received a vitamin K antagonist within 72 hours of study treatment for 3 months.

**Main Outcome Measures**
Composite endpoint of symptomatic recurrent venous thromboembolism (VTE) (recurrent PE and new or recurrent deep venous thrombosis), with 95% power to reject an absolute recurrence rate of 3.5% higher with fondaparinux than UFH. Safety outcomes were major bleeding during initial treatment and mortality at 3 months.

**Main Results**
Analysis was by intention to treat for the composite endpoint. For the composite endpoint of VTE, fondaparinux was noninferior to UFH (Table). The rates for major bleeding or mortality were not higher in the fondaparinux group than in the UFH group (Table).

**Conclusion**
In patients with acute symptomatic pulmonary embolism, initial treatment with fondaparinux was noninferior to unfractionated heparin and had similar rates of major bleeding and mortality.

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*See Glossary.

Fondaparinux vs unfractionated heparin (UFH) for symptomatic pulmonary embolism (PE) at 3 months†

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Fondaparinux</th>
<th>UFH</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism‡</td>
<td>3.8%</td>
<td>5.0%</td>
<td>1.2% (−0.5 to 3.0)</td>
</tr>
<tr>
<td>Major bleeding§§</td>
<td>2.0%</td>
<td>2.4%</td>
<td>0.4% (−0.9 to 1.7)</td>
</tr>
<tr>
<td>Major bleeding during initial treatment§§</td>
<td>1.3%</td>
<td>1.1%</td>
<td>0.2% (−0.7 to 1.1)</td>
</tr>
<tr>
<td>Mortality¶¶</td>
<td>5.2%</td>
<td>4.4%</td>
<td>0.8% (−1.0 to 2.6)</td>
</tr>
</tbody>
</table>

1 CI defined in Glossary.
2 Composite endpoint of recurrent PE and new or recurrent deep venous thrombosis.
3 Lower limit of the CI indicates a true difference > 0.5% in favor of UFH was unlikely, thus fondaparinux was clearly noninferior.
4 Based on 1072 patients in each group who received treatment.
5 Calculated from data in article.

**Commentary**
Fondaparinux is a synthetic pentasaccharide that exerts its anticoagulant effect by direct and specific inhibition of factor Xa (1). Unlike UFH, it has a more predictable dose-response relation, does not require laboratory monitoring in most circumstances, and can be given as treatment for VTE once daily by subcutaneous injection. Another important advantage of fondaparinux is that there is little or no risk for immunemediated thrombocytopenia. A disadvantage is its higher cost.

Strengths of the study by the Matisse investigators include large size, central randomization, very low dropout rate, and clear demonstration of noninferiority in preventing recurrent VTE events over 3 months. The open-label design raises the possibility that physicians may have been more likely to suspect recurrences in patients who received UFH or to ignore recurrences in patients assigned to fondaparinux. However, the rate of confirmed VTE among all clinically suspected VTE was 30% (42 of 140) in the fondaparinux group and 46% (56 of 122) in the UFH group, and all outcomes were assessed by blinded adjudicators.

Low-molecular-weight heparins (LMWHs) have also been shown to be at least as effective and safe as UFH for acute PE (2). Because they share many of the same advantages, a study that directly compares LMWHs with fondaparinux in acute PE is probably warranted. As is true with LMWHs, fondaparinux can be given in the outpatient setting, and in this study almost 15% of patients in the fondaparinux group were discharged from hospital early. Unfortunately, the characteristics of patients who received outpatient treatment were not described. Future studies should define specific criteria for outpatient treatment and determine if the potential benefits of fondaparinux justify its higher cost.

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**References**