Major Bleeding, Mortality, and Efficacy of Fondaparinux in Venous Thromboembolism Prevention Trials

John W. Eikelboom, MBBS, MSc; Daniel J. Quinlan, MBBS; Martin O’Donnell, MB, PhD

Background—Bleeding is a strong predictor of death in patients hospitalized for arterial thrombosis who are treated with antithrombotic therapy, but the prognostic importance of bleeding in patients receiving antithrombotic prophylaxis for venous thromboembolism is uncertain.

Methods and Results—Using Cox proportional hazards modeling, we examined the association between major bleeding and death at 30 days using pooled individual patient data from 8 large randomized controlled trials (n = 13,085) comparing fondaparinux with control (low-molecular-weight heparin or placebo) for the prophylaxis of venous thromboembolism in hospitalized surgical or medical patients. Patients who developed major bleeding were older, more likely to be male, had a lower body weight and lower creatinine clearance, and were more likely to be receiving fondaparinux. At 30 days, the risk of death was 7-fold higher among patients with a major bleeding event (8.6% versus 1.7%; adjusted hazard ratio, 6.96; 95% confidence interval, 4.60 to 10.51). There was a consistent pattern of reduced mortality in patients treated with fondaparinux irrespective of whether patients experienced major bleeding (6.8% versus 11.4%; hazard ratio, 0.58; 95% confidence interval, 0.27 to 1.23) or no major bleeding (1.5% versus 1.9%; hazard ratio, 0.77; 95% confidence interval, 0.59 to 1.02; P for heterogeneity = 0.47).

Conclusions—Major bleeding in hospitalized surgical and medical patients participating in venous thromboembolism prevention trials is a strong predictor of mortality. (Circulation. 2009;120:2006-2011.)

Key Words: bleeding ■ death ■ fondaparinux ■ venous thromboembolism

Venous thromboembolism (VTE) affects 0.5 to 2 persons per thousand in the general community and is a major potentially preventable cause of death in hospitalized patients. Anticoagulants are effective for the prevention of VTE but are associated with an increased risk of bleeding. Concern about the risk of bleeding is an important reason why anticoagulants remain underutilized for the prevention of VTE in hospitalized patients, despite guideline recommendations.

Clinical Perspective on p 2011

There is emerging evidence that bleeding is a strong predictor of mortality in patients with acute arterial thrombosis receiving antithrombotic therapy. The Organization to Assess Ischemic Syndromes (OASIS)-5 trial demonstrated that >90% of the excess deaths in patients receiving enoxaparin compared with fondaparinux occurred in patients who experienced major bleeding. It is unknown, however, whether a similar association between bleeding and mortality exists in patients with VTE.

In a recent individual patient meta-analysis of randomized controlled trials comparing fondaparinux with control (low-molecular-weight heparin or placebo) for the prevention of VTE in high-risk medical or surgical patients, a consistent pattern of reduced mortality with fondaparinux was demonstrated. Hypothesizing that major bleeding is associated with an increased risk of death in patients receiving pharmacological thromboprophylaxis for VTE prevention, we used the integrated fondaparinux VTE prevention database to explore (1) the association between major bleeding and mortality with adjustment for other patient characteristics and (2) the impact of bleeding on the efficacy of fondaparinux compared with control for the prevention of death.

Methods

GlaxoSmithKline provided access to the integrated fondaparinux database, and analyses were conducted by the company statistician. The company provided no financial support, and the authors independently developed the analysis plan, interpreted the results, wrote the article, and submitted the manuscript. Each study included in this analysis had previously been approved by relevant local research ethics boards, and all patients provided informed consent.

Study Eligibility

We analyzed an individual-patient database of all phase III randomized controlled trials that compared fondaparinux 2.5 mg once daily with low-molecular-weight heparin or placebo for the prevention of VTE. Two trials involved patients undergoing hip fracture surgery, 2 hip replacement surgery, 1 major knee surgery.
bleeding and among patients who died compared with those who did not develop major bleeding.

### Baseline Characteristics Among Patients Who Developed Major Bleeding Compared With Those Who Did Not Develop Major Bleeding

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Major Bleeding (n=314)</th>
<th>No Major Bleeding (n=12,771)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (minimum–maximum) y*</td>
<td>71 (27–99)</td>
<td>69 (17–101)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>156 (49.7)</td>
<td>5385 (43.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight, median (minimum–maximum) kg†</td>
<td>74 (37–138)</td>
<td>75 (30–226)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calculated creatinine clearance, median (minimum–maximum), mL/min‡</td>
<td>62.4 (14.5–328.3)</td>
<td>74.8 (11.8–802)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White</td>
<td>297 (94.6)</td>
<td>12179 (95.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>5 (1.6)</td>
<td>525 (4.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (3.8)</td>
<td>629 (4.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke</td>
<td>11 (3.5)</td>
<td>422 (3.3)</td>
<td>0.85</td>
</tr>
<tr>
<td>Cancer</td>
<td>110 (35)</td>
<td>3605 (28.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>59 (18.7)</td>
<td>2308 (18.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hip replacement surgery</td>
<td>117 (37.3)</td>
<td>4467 (35)</td>
<td>0.40</td>
</tr>
<tr>
<td>Major knee surgery</td>
<td>13 (4.1)</td>
<td>1036 (8.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>100 (31.8)</td>
<td>2877 (22.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any surgery</td>
<td>289 (92.0)</td>
<td>10638 (83.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medical patient</td>
<td>6 (1.9)</td>
<td>843 (6.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>191 (60.8)</td>
<td>6347 (49.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any comparator drug</td>
<td>123 (39.2)</td>
<td>6424 (50.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless indicated otherwise.
*Age data are missing for 8 patients.
†Weight data are missing for 119 patients.
‡Creatinine clearance was calculated with the use of the Cockcroft-Gault equation. Creatinine clearance data are missing for 446 patients.
any comparator drug 134 (56.1) 6413 (49.9) 0.06
Medical patient 39 (16.3) 810 (6.3)
Any surgery 186 (77.8) 10 741 (83.6) 0.02
Abdominal surgery 91 (38.1) 2836 (22.1) 0.0001
Hip fracture surgery 78 (32.6) 2289 (17.8) 0.0001
Hip replacement surgery 12 (5.0) 4572 (35.6) 0.0001
Major knee surgery 5 (2.1) 1044 (8.1) 0.001
Calculation of creatinine clearance, median (minimum–maximum), mL/minute‡
White 229 (95.8) 12 247 (95.3) 0.73
History of
VTE 8 (3.3) 522 (4.1) 0.58
Myocardial infarction 23 (9.6) 618 (4.8) 0.001
Stroke 14 (5.9) 419 (3.3) 0.03
Cancer 106 (44.4) 3609 (28.1) 0.0001
Hip fracture surgery 78 (32.6) 2289 (17.8) 0.0001
Hip replacement surgery 12 (5.0) 4572 (35.6) 0.0001
Major knee surgery 5 (2.1) 1044 (8.1) 0.001
Abdominal surgery 91 (38.1) 2836 (22.1) 0.0001
Any surgery 186 (77.8) 10 741 (83.6) 0.02
Medical patient 39 (16.3) 810 (6.3) 0.0001
Fondaparinux 105 (43.9) 6433 (50.1) 0.06
Any comparator drug 134 (56.1) 6413 (49.9) 0.06

Data are presented as n (%) unless indicated otherwise.
*Age data are missing for 8 patients.
†Weight data are missing for 119 patients.
‡Creatinine clearance was calculated with the use of the Cockcroft-Gault equation. Creatinine clearance data are missing for 446 patients.

Results

Trial Details
The main features of the 8 phase III (n=13 085 patients) trials10–17 are summarized in Table 1. Additional details of the trial design and primary results have been published elsewhere.10–17 Fondaparinux was given for 5 to 9 days in all of the orthopedic trials except the Pentasaccharide in Hip Fracture Surgery Plus Study (PENTHIFRA-PLUS), in which fondaparinux was given for 25 to 31 days (control group was given fondaparinux for 7 days and placebo for an additional 18 to 24 days).14 In 4 trials the comparator was enoxaparin (40 mg once daily in 2 trials and 30 mg twice daily in 2 trials).10–13 in 1 trial the comparator was dalteparin 5000 IU once daily,15 and in 3 trials the comparator was placebo.14,16,17

Patient Characteristics and Interventions
Baseline characteristics of patients included in the trials are summarized in Tables 2 and 3, subdivided according to whether patients developed major bleeding (n=314) or did not develop major bleeding (n=12 771) (Table 2) and subdivided according to whether they died (n=239) or survived (n=12 846) at 30 days (Table 3).

Predictors of Major Bleeding
The predictors of major bleeding are summarized in Table 4. The frequency of major bleeding by clinical population ranged from 0.7% (medical patients) to 3.5% (abdominal surgery patients). In the forward logistic regression model, the following baseline characteristics were found to be significant predictors of an increased risk of major bleeding: decreasing creatinine clearance, decreasing body weight, hip replacement surgery, fondaparinux treatment, male sex, abdominal surgery, absence of history of VTE, and any surgery.

Association Between Major Bleeding and Mortality (Primary Analysis)
The predictors of death are summarized in Table 4. The mean time between bleeding and death was 6.4 days, and the median was 3.0 days. A significantly higher proportion of
patients who experienced major bleeding had died by 30 days compared with those who did not develop major bleeding, resulting in an almost 7-fold increased hazard of death (8.6% versus 1.7%; hazard ratio, 6.83; 95% confidence interval, 4.57 to 10.22; P<0.001). Table 5 shows the results of the Cox regression model of the association between major bleeding and death. After adjustment for baseline characteristics and propensity for major bleeding, the hazard for death in patients with major bleeding remained \( \approx 7 \)-fold higher.

**Effect of Fondaparinux on Mortality in Patients With and Without Major Bleeding**

Data on the effect of fondaparinux compared with control on death in the presence and absence of bleeding are presented in Table 6. There was a consistent pattern of reduced mortality with fondaparinux compared with control in both the presence and absence of major bleeding, with no statistical evidence of heterogeneity between the 2 groups.

**Discussion**

This analysis has 3 major findings. First, male sex, lower body weight, and renal dysfunction were significant baseline predictors of major bleeding in high-risk medical or surgical patients enrolled in VTE prevention trials. Second, major bleeding in patients enrolled in these VTE prevention trials was associated with an \( \approx 7 \)-fold increased hazard of death at 30 days irrespective of whether patients had received pharmacological thromboprophylaxis. Third, the previously observed trend for a reduction in mortality with fondaparinux compared with control\(^9\) was evident irrespective of whether patients experienced major bleeding.

Preservation of the trend for a mortality benefit of fondaparinux compared with control in VTE prevention trials despite it causing an increase in major bleeding contrasts with the report from the OASIS-5 trial in patients with acute coronary syndrome in which the increase in major bleeding with enoxaparin appeared to translate into an excess in mortality.\(^7,8\) This contrast may be explained in part by differences in the severity of bleeding caused by anticoagulants in VTE prevention trials compared with acute coronary syndrome trials, as also reflected by differences in the definition of major bleeding used in the 2 types of trials. Most (>80%) major bleeding episodes in VTE prevention trials in orthopedic surgery occur within the first 48 hours of the procedure, are limited to the surgical site, and do not require transfusion,\(^12,18,19\) whereas most major bleeding episodes in patients with acute coronary syndrome occur at nonsurgical sites and require transfusion.\(^8\) Nevertheless, our findings indicate that major bleeding as defined in the VTE prevention trials is a powerful marker of increased risk of mortality.

This is first study, to our knowledge, to demonstrate that major bleeding is associated with an increase in mortality in the VTE prevention population. Our findings are consistent with the association between major bleeding and death that has been demonstrated previously in patients with acute coronary syndromes and ischemic stroke\(^4\) and confirms the importance of bleeding as a marker of adverse outcome in hospitalized patients. The reasons for the increased mortality in patients enrolled in VTE prevention trials who develop major bleeding remain uncertain. Massive bleeding can lead directly to death, but in our study only 6% of all deaths after bleeding were directly attributed to the acute bleeding event.

### Table 5. Cox Proportional Hazards Model of the Association Between Major Bleeding and Death (With Major Bleeding Included in the Model as a Time-Dependent Variable)

<table>
<thead>
<tr>
<th>Death Within 30 Days</th>
<th>Major Bleed, n/N (%)</th>
<th>No Major Bleed, n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted, n (%)</td>
<td>27/314 (8.6)</td>
<td>212/12 771 (1.7)</td>
<td>6.83 (4.57–10.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted for baseline predictors</td>
<td>6.97 (4.61–10.54)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for baseline predictors and propensity for bleeding</td>
<td>6.96 (4.60–10.51)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

### Table 6. Effect of Fondaparinux on Mortality in All Patients and in Those With and Without Major Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Fondaparinux, n/N (%)</th>
<th>Control, n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
<th>Heterogeneity for Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>105/6538 (1.6)</td>
<td>134/6547 (2.1)</td>
<td>0.79 (0.60–1.01)</td>
<td>0.06</td>
<td>...</td>
</tr>
<tr>
<td>Patients with major bleeding</td>
<td>13/191 (6.8)</td>
<td>14/123 (11.4)</td>
<td>0.58 (0.27–1.23)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Patients without major bleeding</td>
<td>92/6347 (1.5)</td>
<td>120/6424 (1.9)</td>
<td>0.77 (0.59–1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux vs LMWH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with major bleeding</td>
<td>6/164 (3.7)</td>
<td>11/115 (9.6)</td>
<td>0.37 (0.14–0.99)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Patients without major bleeding</td>
<td>71/4969 (1.4)</td>
<td>87/5023 (1.7)</td>
<td>0.82 (0.60–1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with major bleeding</td>
<td>7/27 (25.9)</td>
<td>3/8 (37.5)</td>
<td>0.51 (0.13–1.97)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Patients without major bleeding</td>
<td>21/1378 (1.5)</td>
<td>33/1401 (2.4)</td>
<td>0.64 (0.37–1.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; LMWH, low-molecular-weight heparin.
The remaining major bleeding events were less severe, and <10% of all major bleeds were considered life threatening. Clinicians are more likely to discontinue effective antithrombotic drugs in patients who develop major bleeding, which could increase the risk of cardiovascular events leading to death. Progression of undetected asymptomatic deep vein thrombosis in patients with major bleeding, who did not undergo venography, could lead to increased mortality due to fatal pulmonary embolism. Finally, patients who develop major bleeding are more likely to receive a red cell transfusion, which could lead to adverse outcomes, including increased mortality. However, the relationship between major bleeding and death is likely to be confounded by patient characteristics because male subjects, older patients with lower body weight, and those with renal impairment were at increased risk of both major bleeding and death.

The strengths of our study are that we analyzed individual patient data from a data set involving >13,000 patients, of whom >300 developed major bleeding. The same definition for major bleeding was used in all the trials. We restricted our primary analyses to the association between major bleeding and death, thereby ensuring that exposure (bleeding) preceded outcome (mortality). Although we were also interested in the association between major bleeding and risk of major venous and arterial events, information on the temporal relationship between bleeding and thrombotic events was unavailable, and thus we were unable to determine whether the bleeding preceded thrombotic events. Finally, we adjusted our analyses for baseline characteristics, treatment allocation, and propensity for major bleeding that could confound the association with mortality.

Our study has limitations. First, we are unable to clarify whether there might be a causal relationship between less severe episodes of major bleeding and mortality. Second, participants included in the integrated fondaparinux database were those eligible for clinical trials and may not represent consecutive patients in real-life clinical practice. For example, <5% of patients included in our study had a creatinine clearance of <30 mL/min, and the mean creatinine clearance was >70 mL/min. The proportion of patients with reduced creatinine clearance in real life is expected to be substantially higher, and our findings may not be applicable to patients with severe renal impairment or those with other serious comorbidities. Third, our analyses of the treatment effect of fondaparinux in patients with and without major bleeding are subgroup analyses and should be considered hypothesis generating.

In conclusion, our data indicate that major bleeding in hospitalized patients is a robust marker for increased risk of death, even when the bleeding itself is not life threatening. The trend for reduced mortality with fondaparinux despite the increase in major bleeding underscores the importance of using proven effective pharmacological thromboprophylaxis strategies according to the overall results of randomized controlled trials, even if the drugs increase the risk of bleeding. Further investigation is required to understand the determinants of major bleeding and the mechanism of increased mortality in patients who experience major bleeding while receiving VTE prophylaxis.

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Disclosures
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**CLINICAL PERSPECTIVE**

Patients receiving antithrombotic therapy for the treatment of acute coronary syndrome who develop major bleeding are at increased risk of nonfatal and fatal cardiovascular outcomes compared with those who do not develop bleeding. Whether a similar association exists between major bleeding and adverse outcomes in patients receiving anticoagulants for the prevention of venous thromboembolism is unknown. Our analyses of an individual patient database involving >13 000 surgical and medical patients receiving fondaparinux or control for the prevention of venous thromboembolism showed that patients who develop major bleeding have an almost 7-fold increased risk of death. Although fondaparinux, compared with control, was associated with a significant increase in the risk of major bleeding, it was associated with numerically fewer deaths both in patients who experienced major bleeding and in those who did not experience major bleeding. Our analyses confirm that major bleeding in hospitalized patients is a powerful predictor of death. The trend of reduced mortality with fondaparinux despite the increase in major bleeding underscores the importance of using proven effective thromboprophylaxis strategies according to the overall results of randomized controlled trials, even if drugs increase the risk of bleeding. Further investigation is required to understand the determinants of major bleeding and mechanisms that mediate the increase in mortality.
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