Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients

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BACKGROUND
The efficacy and safety of prolonging prophylaxis for venous thromboembolism in medically ill patients beyond hospital discharge remain uncertain. We hypothesized that extended prophylaxis with apixaban would be safe and more effective than short-term prophylaxis with enoxaparin.

METHODS
In this double-blind, double-dummy, placebo-controlled trial, we randomly assigned acutely ill patients who had congestive heart failure or respiratory failure or other medical disorders and at least one additional risk factor for venous thromboembolism and who were hospitalized with an expected stay of at least 3 days to receive apixaban, administered orally at a dose of 2.5 mg twice daily for 30 days, or enoxaparin, administered subcutaneously at a dose of 40 mg once daily for 6 to 14 days. The primary efficacy outcome was the 30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis, as detected with the use of systematic bilateral compression ultrasonography on day 30. The primary safety outcome was bleeding. All efficacy and safety outcomes were independently adjudicated.

RESULTS
A total of 6528 subjects underwent randomization, 4495 of whom could be evaluated for the primary efficacy outcome — 2211 in the apixaban group and 2284 in the enoxaparin group. Among the patients who could be evaluated, 2.71% in the apixaban group (60 patients) and 3.06% in the enoxaparin group (70 patients) met the criteria for the primary efficacy outcome (relative risk with apixaban, 0.87; 95% confidence interval [CI], 0.62 to 1.23; P = 0.44). By day 30, major bleeding had occurred in 0.47% of the patients in the apixaban group (15 of 3184 patients) and in 0.19% of the patients in the enoxaparin group (6 of 3217 patients) (relative risk, 2.58; 95% CI, 1.02 to 7.24; P = 0.04).

CONCLUSIONS
In medically ill patients, an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin. Apixaban was associated with significantly more major bleeding events than was enoxaparin. (Fundied by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number, NCT00457002.)
VENOUS THROMBOEMBOLISM IS A COMMON and potentially fatal complication in hospitalized surgical patients and acutely ill medical patients. The benefits of providing pharmacologic thromboprophylaxis over the entire course of the hospital stay have been validated, with efficacy and safety shown in both populations.

Among high-risk surgical patients, such as those undergoing total hip replacement, extended thromboprophylaxis in the period after hospital discharge has reduced the rate of both asymptomatic and symptomatic venous thromboembolism. On the basis of these findings, current practice guidelines recommend extended thromboprophylaxis in such patients.

One study (the Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients with Prolonged Immobilization trial [EXCLAIM; ClinicalTrials.gov number, NCT00077753]) evaluated the potential advantage of extending pharmacologic prophylaxis with enoxaparin beyond the period of hospitalization in acutely ill medical patients. Although the rates of venous thromboembolism were lower with extended thromboprophylaxis, this benefit was offset by a significant increase in major bleeding. In the MAGELLAN study (Venous Thromboembolic Event [VTE] Prophylaxis in Medically Ill Patients, NCT00077753), extended prophylaxis with rivaroxaban was compared with short-term prophylaxis with enoxaparin followed by placebo. This trial also showed lower rates of venous thromboembolism with extended thromboprophylaxis, but there were more major bleeding events with rivaroxaban than with enoxaparin.

Apixaban is an orally active direct inhibitor of activated factor X (factor Xa) with established efficacy and safety for the prevention of venous thromboembolism after elective hip or knee replacement and for the prevention of stroke in patients with atrial fibrillation. In the Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial, we evaluated the potential of apixaban to prevent venous thromboembolism in acutely ill medical patients during hospitalization and in the extended period after their discharge from the hospital.

METHODS

STUDY OVERSIGHT

The trial was designed and led by an executive committee that included academic investigators and by representatives of the sponsors (Bristol-Myers Squibb and Pfizer). The study protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The study was conducted according to the ethical principles stated in the Declaration of Helsinki. Approval was obtained from the appropriate ethics committee at each site, and all patients provided written informed consent. All the authors participated in the design of the trial and the planning of the analyses. The first author wrote the first draft of the manuscript with input from all the coauthors and revised the subsequent drafts on the basis of input from the coauthors. All the authors vouch for the accuracy and completeness of the reported data and for the fidelity of the study to the protocol.

PATIENTS

Male and female patients, 40 years of age or older, were considered for participation in the study if they were hospitalized for congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease and had an expected hospital stay of at least 3 days. Except for patients with congestive heart failure or respiratory failure, eligible patients had to have at least one of the following additional risk factors: an age of 75 years or older, previous documented venous thromboembolism or a history of venous thromboembolism for which they received anticoagulation for at least 6 weeks, cancer, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more, receipt of estrogenic hormone therapy, or chronic heart failure or respiratory failure. In addition, all patients had to be moderately or severely restricted in their mobility. Moderately restricted mobility allowed for walking within the hospital room or to the bathroom. Severely restricted mobility was defined as being confined to bed or to a chair at the bedside.

Patients were excluded if they had confirmed venous thromboembolism; a disease requiring ongoing treatment with a parenteral or oral anticoagulant agent; active liver disease, anemia or thrombocytopenia; severe renal disease (creatinine clearance of <30 ml per minute as estimated by the method of Cockcroft and Gault); a known or suspected allergy to enoxaparin; or prior heparin-induced thrombocytopenia or if they were taking two or more antiplatelet agents or aspirin at a dose higher than 165 mg per day.
Patients were also excluded if they had undergone a surgical procedure in the previous 30 days that might be associated with a risk of bleeding, had received anticoagulant prophylaxis for venous thromboembolism in the previous 14 days, were actively bleeding or were at high risk for bleeding; or had invasive procedures planned or scheduled during the treatment period. In addition, patients were excluded if they had one of the following abnormal laboratory findings: a hemoglobin level of less than 9 g per deciliter, a platelet count of less than 100,000 per cubic millimeter, an alanine or aspartate aminotransferase level more than twice the upper limit of the normal range, or direct or total bilirubin levels more than 1.5 times the upper limit of the normal range. Finally, women who might become pregnant, were pregnant, were breast-feeding, or were unwilling or unable to use an acceptable method of contraception were not eligible.

**STUDY DESIGN**

This trial was an international, multicenter, randomized, double-blind, controlled study. Patients were randomly assigned, in a 1:1 ratio, to receive apixaban, administered orally at a dose of 2.5 mg twice daily for 30 days, or enoxaparin, administered subcutaneously at a dose of 40 mg once daily during their stay in the hospital, for a minimum of 6 days. Randomization was performed through a central telephone system with the use of a computer-generated randomization list. The maximum interval allowed between admission to the hospital and randomization was 72 hours. The day of randomization was defined as day 1 of the study. In-person follow-up visits were scheduled on study days 30±2 and 90±7, with telephone contact at days 14 and 60. A systematic compression ultrasound examination was to be performed at the time of discharge (but no earlier than day 5 and no later than day 14) and at day 30. All compression ultrasound examinations were recorded and reviewed and adjudicated by the independent central adjudication committee. Bleeding was categorized as major if it was fatal or overt and was accompanied by one or more of the following: a decrease in hemoglobin of 2 g or more per deciliter over a 24-hour period; transfusion of 2 or more units of packed red cells; or intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding, bleeding that occurred in an operated joint that required reoperation or intervention, or intramuscular bleeding with the compartment syndrome. Clinically relevant nonmajor bleeding was defined as acute, clinically overt bleeding that did not meet the criteria for classification as a major bleeding event but did meet the discretion of the investigators. Patients who were randomly assigned to enoxaparin received tablets containing an apixaban placebo for 30 days. Concomitant treatment with aspirin at doses above 165 mg per day was prohibited.

**OUTCOME MEASURES**

The primary efficacy outcome was a composite during the 30-day treatment period of death related to venous thromboembolism (i.e., sudden death for which pulmonary embolism could not be excluded as a cause), fatal or nonfatal pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis as detected with the use of systematic bilateral compression ultrasonography. All components of the primary efficacy outcome were adjudicated by the independent central adjudication committee.

A key secondary efficacy outcome was the composite of total venous thromboembolism and death related to venous thromboembolism occurring from the time of randomization to the time the blinded parenteral therapy was discontinued (the parenteral-treatment period). Additional secondary efficacy outcomes included symptomatic deep-vein thrombosis or nonfatal pulmonary embolism occurring during the 60-day follow-up period, death from any cause occurring during the 30-day treatment period, and death from any cause occurring during the entire 90-day study period (i.e., the treatment period plus the follow-up period).

The main safety outcomes included major bleeding, clinically relevant nonmajor bleeding, and all bleeding reported by investigators; myocardial infarction; stroke; thrombocytopenia; and death from any cause. Each of these events was reviewed and adjudicated by the independent central adjudication committee. Bleeding was categorized as major if it was fatal or overt and was accompanied by one or more of the following: a decrease in hemoglobin of 2 g or more per deciliter over a 24-hour period; transfusion of 2 or more units of packed red cells; or intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding, bleeding that occurred in an operated joint that required reoperation or intervention, or intramuscular bleeding with the compartment syndrome. Clinically relevant nonmajor bleeding was defined as acute, clinically overt bleeding that did not meet the criteria for classification as a major bleeding event but did meet...
at least one of the following criteria: epistaxis that required medical attention or persisted for 5 minutes or more, gastrointestinal bleeding containing frank blood or coffee-ground material that tested positive for blood, endoscopically confirmed bleeding, spontaneous hematuria or hematuria persisting for 24 hours or more after urinary-tract catheterization, unusual bruising, radiographically confirmed hematoma, or hemoptysis.

**STATISTICAL ANALYSIS**

We estimated that with a sample of 6524 patients randomly assigned in a 1:1 ratio to receive apixaban or enoxaparin, the study would have 90% power to show the superiority of apixaban with respect to the primary efficacy outcome, at a one-sided alpha level of 0.025, assuming a true event rate of 2.5% in the apixaban group and 4.0% in the enoxaparin group. For the noninferiority test of the first secondary outcome (the composite of total venous thromboembolism and death related to venous thromboembolism during the parenteral-treatment period), the study would have 85% power to show the noninferiority of apixaban, at a one-sided alpha level of 0.025, assuming a true event rate of 1.6% in the apixaban group and 2.0% in the enoxaparin group, with a noninferiority margin of 1.43 for the relative risk. These estimates were based on the use of the Mantel–Haenszel test for superiority and the test for noninferiority of Yanagawa, Tango, and Hiejima, stratified according to history or no history of venous thromboembolism and status with respect to cancer.

The analysis of safety end points was performed on data from the treated population, which consisted of all patients who received at least one dose of a study drug. Adjudicated major bleeding events were summarized according to onset during the treatment period and onset during the follow-up period. An independent data and safety monitoring board reviewed the incidences of major bleeding and events of venous thromboembolism on an ongoing basis, primarily to assess safety. A formal interim efficacy analysis was performed after 50% of the planned patients had been enrolled.

**RESULTS**

**STUDY PATIENTS**

From June 2007 through February 2011, a total of 6758 acutely ill medical patients were enrolled at 302 centers in 35 countries, and 6528 subjects were randomly assigned to receive short-term prophylaxis with enoxaparin or extended prophylaxis (30 days) with apixaban. In total, 4495 patients could be evaluated for the primary efficacy outcome at day 30. Figure 1 shows the number of patients who were enrolled, who underwent randomization, and who were included in the safety and efficacy analyses. The demographic characteristics of the study population, the primary diagnoses at enrollment, and additional risk factors are shown in Table 1. Among subjects who received at least one dose of the randomly assigned study medication, the mean (±SD) duration of exposure to apixaban was 24.9±10.0 days, and the mean exposure to enoxaparin was 7.3±4.0 days.

**EFFICACY**

The primary efficacy outcome, evaluated at day 30, occurred in 2.71% of the patients who were randomly assigned to receive extended prophylaxis...
with apixaban (60 of the 2211 patients in the primary efficacy data set) as compared with 3.06% of the patients who were assigned to receive short-term prophylaxis with enoxaparin (70 of 2284 patients) (relative risk with apixaban, 0.87; 95% confidence interval [CI], 0.62 to 1.23; P=0.44). The key

Figure 1. Enrollment, Randomization, and Follow-up.
Patients who were excluded from the efficacy analysis at day 10 could be included in the analysis at day 30 if they met the criteria at day 30. Some patients who were excluded from the day 10 analysis or from the day 30 analysis had both inadequate assessment of symptomatic venous thromboembolism and ultrasound examinations that were missing or could not be evaluated.
Table 1. Baseline Characteristics of the Subjects.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Apixaban (N = 3255)</th>
<th>Enoxaparin (N = 3273)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age — yr</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.8±12.0</td>
<td>66.7±12.0</td>
</tr>
<tr>
<td>Median</td>
<td>68.0</td>
<td>67.0</td>
</tr>
<tr>
<td>Range</td>
<td>40–101</td>
<td>40–98</td>
</tr>
<tr>
<td><strong>Age distribution — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>1401 (43.0)</td>
<td>1411 (43.1)</td>
</tr>
<tr>
<td>65 to &lt;75 yr</td>
<td>890 (27.3)</td>
<td>884 (27.0)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>964 (29.6)</td>
<td>978 (29.9)</td>
</tr>
<tr>
<td><strong>Sex — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1626 (50.0)</td>
<td>1577 (48.2)</td>
</tr>
<tr>
<td>Female</td>
<td>1629 (50.0)</td>
<td>1696 (51.8)</td>
</tr>
<tr>
<td><strong>Race or ethnic group — no. (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2474 (76.0)</td>
<td>2476 (75.6)</td>
</tr>
<tr>
<td>Black</td>
<td>292 (9.0)</td>
<td>304 (9.3)</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>9 (0.3)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>320 (9.8)</td>
<td>326 (10.0)</td>
</tr>
<tr>
<td>Other</td>
<td>145 (4.5)</td>
<td>149 (4.6)</td>
</tr>
<tr>
<td><strong>Reason for hospitalization — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1270 (39.0)</td>
<td>1246 (38.1)</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1208 (37.1)</td>
<td>1213 (37.1)</td>
</tr>
<tr>
<td>Infection, without septic shock</td>
<td>701 (21.5)</td>
<td>746 (22.8)</td>
</tr>
<tr>
<td>Acute rheumatic disorder</td>
<td>39 (1.2)</td>
<td>36 (1.1)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>26 (0.8)</td>
<td>23 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (0.2)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Not reported</td>
<td>5 (0.2)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td><strong>Additional risk factors — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
<td>141 (4.3)</td>
<td>124 (3.8)</td>
</tr>
<tr>
<td>History of cancer‡</td>
<td>312 (9.6)</td>
<td>320 (9.8)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>113 (3.5)</td>
<td>98 (3.0)</td>
</tr>
<tr>
<td>Remote cancer</td>
<td>199 (6.1)</td>
<td>222 (6.8)</td>
</tr>
<tr>
<td>NYHA Class of chronic heart failure</td>
<td>1531 (47.0)</td>
<td>1537 (47.0)</td>
</tr>
<tr>
<td>I</td>
<td>60 (1.8)</td>
<td>47 (1.4)</td>
</tr>
<tr>
<td>II</td>
<td>228 (7.0)</td>
<td>240 (7.3)</td>
</tr>
<tr>
<td>III</td>
<td>854 (26.2)</td>
<td>833 (25.5)</td>
</tr>
<tr>
<td>IV</td>
<td>380 (11.7)</td>
<td>411 (12.6)</td>
</tr>
<tr>
<td>Not reported</td>
<td>9 (0.3)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>1683 (51.7)</td>
<td>1702 (52.0)</td>
</tr>
<tr>
<td>Body-mass index ≥30‡</td>
<td>1448 (44.5)</td>
<td>1451 (44.3)</td>
</tr>
<tr>
<td>Estrogenic hormone therapy</td>
<td>49 (1.5)</td>
<td>27 (0.8)</td>
</tr>
</tbody>
</table>
secondary efficacy outcome of the composite of total venous thromboembolism (i.e., asymptomatic proximal deep-vein thrombosis, proximal or distal symptomatic deep-vein thrombosis, or pulmonary embolism) or death related to venous thromboembolism evaluated at the end of the parenteral-treatment period occurred in 1.73% of patients in the apixaban group (43 of 2485 patients) and in 1.61% in the enoxaparin group (40 of 2488 patients) (relative risk, 1.06; 95% CI, 0.69 to 1.63). The rates of the primary and secondary efficacy outcomes are shown in Table 2. The results of the primary efficacy outcome were consistent across all prespecified subgroups.

The rate of symptomatic deep-vein thrombosis was lower among patients who received extended thromboprophylaxis with apixaban than among those who received enoxaparin (0.15% [5 of 3255 patients] vs. 0.49% [16 of 3273 patients]), but this difference did not reach significance. The cumulative rates of any symptomatic venous thromboembolism, including death related to venous thromboembolism, are shown in Figure 2.

SAFETY OUTCOME

Table 3 shows the results of the bleeding outcomes. Major bleeding events during the 30-day treatment period occurred in 0.47% of the patients in the apixaban group (15 of the 3184 patients who received at least one dose of apixaban) and in 0.19% in the enoxaparin group (6 of the 3217 patients who received at least one dose of enoxaparin) (relative risk with apixaban, 2.58; 95% CI, 1.02 to 7.24; P=0.04). Major plus clinically relevant non-major bleeding occurred in 2.67% of the patients who received apixaban (85 of 3184) and in 2.08% of those who received enoxaparin (67 of 3217) (relative risk, 1.28; 95% CI, 0.93 to 1.76; P=0.12). The rates of total bleeding events in the apixaban and enoxaparin groups were 7.73% (246 of 3184) and 6.81% (219 of 3217), respectively (relative risk, 1.13; 95% CI, 0.95 to 1.34; P=0.18). Figure 3 shows the Kaplan–Meier curves for major and clinically relevant nonmajor bleeding in both groups.

There was no significant difference in the rate of death between the apixaban group and the enoxaparin group (4.1% in each group [131 and 133 patients, respectively]). The rates of adverse events, including myocardial infarction, stroke, and thrombocytopenia, did not differ significantly between the two groups during the treatment period or the follow-up period. The rates of elevation of the alanine aminotransferase and total bilirubin levels to at least 3 times the upper limit of the normal range did not differ between the two groups.

DISCUSSION

The primary efficacy outcome, a composite of venous thromboembolism and death related to venous thromboembolism, occurred in 2.71% of the patients randomly assigned to apixaban and in 3.06% of those assigned to enoxaparin (P=0.44). However, there was an almost immediate increase in the risk of events when enoxaparin was stopped. After the parenteral-treatment period, the primary efficacy outcome occurred in 31 pa-
Table 2. Primary and Secondary Efficacy Outcomes.

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Apixaban (N = 2211)</th>
<th>Enoxaparin (N = 2484)</th>
<th>Relative Risk with Apixaban (95% CI)</th>
<th>Adjusted Risk Difference, Apixaban–Enoxaparin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome: total VTE or VTE-related death during treatment period</strong>*</td>
<td>Patients with Events no./total no.</td>
<td>Event Rate % (95% CI)</td>
<td>Patients with Events no./total no.</td>
<td>Event Rate % (95% CI)</td>
</tr>
<tr>
<td>60/2211</td>
<td>2.71 (2.11 to 3.49)</td>
<td>70/2284</td>
<td>3.06 (2.43 to 3.86)</td>
<td></td>
</tr>
<tr>
<td><strong>Key secondary outcome: total VTE or VTE-related death during parenteral-treatment period</strong>*</td>
<td>43/2485</td>
<td>1.73 (1.28 to 2.33)</td>
<td>40/2488</td>
<td>1.61 (1.18 to 2.19)</td>
</tr>
</tbody>
</table>

**Individual outcomes during treatment period**

- **VTE-related death**
  - Apixaban: 2/3255 (0.06)
  - Enoxaparin: 3/3273 (0.09)
- **Fat al or nonfatal pulmonary embolism**
  - Apixaban: 7/3251 (0.22)
  - Enoxaparin: 8/3266 (0.24)
- **Nonfatal pulmonary embolism**
  - Apixaban: 7/3251 (0.22)
  - Enoxaparin: 8/3266 (0.24)
- **Symptomatic deep-vein thrombosis**
  - Apixaban: 5/3255 (0.15)
  - Enoxaparin: 16/3273 (0.49)
- **Proximal deep-vein thrombosis**
  - Apixaban: 53/2207 (2.40)
  - Enoxaparin: 57/2276 (2.50)
- **Symptomatic proximal deep-vein thrombosis**
  - Apixaban: 5/3255 (0.15)
  - Enoxaparin: 12/3273 (0.37)
- **Asymptomatic proximal deep-vein thrombosis**
  - Apixaban: 52/2206 (2.36)
  - Enoxaparin: 48/2269 (2.12)
- **Symptomatic distal deep-vein thrombosis**
  - Apixaban: 0/3255 (0)
  - Enoxaparin: 5/3273 (0.15)

**Individual outcomes during parenteral-treatment period**

- **VTE-related death**
  - Apixaban: 0/3255 (0)
  - Enoxaparin: 0/3273 (0)
- **Fat al or nonfatal pulmonary embolism**
  - Apixaban: 3/3252 (0.09)
  - Enoxaparin: 3/3271 (0.09)
- **Nonfatal pulmonary embolism**
  - Apixaban: 3/3252 (0.09)
  - Enoxaparin: 3/3271 (0.09)
- **Symptomatic deep-vein thrombosis**
  - Apixaban: 1/3255 (0.03)
  - Enoxaparin: 4/3273 (0.12)
- **Proximal deep-vein thrombosis**
  - Apixaban: 40/2486 (1.61)
  - Enoxaparin: 37/2486 (1.49)
- **Symptomatic proximal deep-vein thrombosis**
  - Apixaban: 1/3255 (0.03)
  - Enoxaparin: 4/3273 (0.12)
- **Asymptomatic proximal deep-vein thrombosis**
  - Apixaban: 40/2486 (1.61)
  - Enoxaparin: 33/2483 (1.33)
- **Symptomatic distal deep-vein thrombosis**
  - Apixaban: 0/3255 (0)
  - Enoxaparin: 1/3273 (0.03)

*Total venous thromboembolism (VTE) includes fatal or nonfatal pulmonary embolism, symptomatic deep-vein thrombosis, and asymptomatic proximal-leg deep-vein thrombosis as detected with the use of systematic bilateral compression ultrasonography.
†The two-sided P value for superiority is 0.44.
tients in the enoxaparin group but in only 18 pa-
tients receiving extended treatment with apixaban
(relative risk with apixaban, 0.59%; 95% CI, 0.33
to 1.05). When only symptomatic venous thrombo-
embolism and death related to venous thrombo-
embolism were included, extended treatment with
apixaban reduced events from 18 to 8 (relative risk,
0.44; 95% CI, 0.19 to 1.00). Therefore, even though
our trial was negative, the strategy of extended
prophylaxis with apixaban may have promise.

The ADOPT trial was underpowered. The
13% reduction in the primary outcome favored
apixaban, but the between-group difference was
not significant, and thus no clinically directive
conclusion can be drawn. The results of this trial
may not be applicable to typical populations of
hospitalized medically ill patients because screen-
ing for venous thromboembolism with the use of
compression ultrasonography is not performed
routinely at the time of hospital discharge. Fur-
thermore, the curves between apixaban and enoxa-
parin began to separate well after the final dose
of enoxaparin was administered, suggesting that
the study outcome might have been positive if we
had extended the duration of apixaban therapy for
more than 30 days.

The comparator in this trial was enoxaparin
administered for 6 to 14 days. Although this is
the licensed regimen for enoxaparin prophylaxis
in medically ill patients, most patients who are
hospitalized for a medical illness remain in the
hospital for fewer than 5 days. It is standard prac-
tice to stop enoxaparin at the time of discharge,
even in patients with persistent risk factors for
venous thromboembolism. Thus, the design of
this trial favored better efficacy in the enoxapari-
lin group than would be expected with ordinary
clinical care because patients in the enoxaparin
group received prophylaxis for a longer duration
than usual.

The results of the ADOPT trial warrant com-
parison with two other contemporary trials evalu-
ating extended thromboprophylaxis in medically ill
patients. In the EXCLAIM trial, 9 5963 medically ill
patients were given open-label enoxaparin (40 mg
once daily) for an average of 10 days. As com-
pared with placebo, extended prophylaxis with
enoxaparin reduced the rate of venous thrombo-
embolism from 4.0% to 2.5% but increased the
rate of major bleeding from 0.3% to 0.8%.

The MAGELLAN trial compared extended pro-
phylaxis with oral rivaroxaban (10 mg once daily)
with a 6-to-14-day course of subcutaneous enoxa-
parin (40 mg once daily) in 8101 medically ill pa-
tients. 9 At day 35, the rate of the primary efficacy
outcome was significantly lower with extended
rivaroxaban than with enoxaparin (4.4% vs. 5.7%;
hazard ratio with rivaroxaban, 0.77; 95% CI, 0.62
to 0.96; P=0.02). However, there was an increase
in treatment-related major and clinically relevant
nonmajor bleeding with rivaroxaban as compared
with enoxaparin both during the period from 1 to
10 days (2.8% and 1.2%, respectively) and during
the period from 11 to 35 days (1.4% and 0.5%,
respectively).

In the ADOPT trial, the rate of major bleed-
ing with apixaban was less than 0.5%. This rate
is consistent with the safety of the regimen of
2.5 mg of apixaban twice daily, which is the
regimen that is licensed in Europe for thrombo-
 prophylaxis after elective hip- or knee-replace-
ment surgery.

The strengths of the current trial include the
large sample size; the randomized, double-blind,
double-dummy design; the centralized adjudica-
tion of all suspected outcomes by a committee whose
members were unaware of the treatment assign-
ments; and the enrollment of a broad population
of medically ill patients. Some limitations are the
inclusion of asymptomatic proximal deep-vein

Figure 2. Kaplan–Meier Curves for Adjudicated Symptomatic Venous
Thromboembolism or Death Related to Venous Thromboembolism
during the Treatment Period.
The inset shows the same data on an enlarged y axis.
Table 3. Bleeding Events in the Two Study Groups, According to Treatment Period.

<table>
<thead>
<tr>
<th>bleeding Events and Treatment Period</th>
<th>Apixaban</th>
<th>Enoxaparin</th>
<th>Relative Risk with Apixaban (95% CI)</th>
<th>P Value</th>
<th>Adjusted Risk Difference, Apixaban–Enoxaparin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>15/3184</td>
<td>6/3217</td>
<td>2.58 (1.02 to 7.24)</td>
<td>0.04*</td>
<td>0.29 (0.01 to 0.57)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0/3184</td>
<td>2/3217</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0/3184</td>
<td>2/3217</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other critical organ</td>
<td>1/3184</td>
<td>0/3217</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in hemoglobin†</td>
<td>14/3184</td>
<td>3/3217</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion of ≥2 units of packed red cells</td>
<td>3/3184</td>
<td>0/3217</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major plus clinically relevant nonmajor bleeding</td>
<td>85/3184</td>
<td>67/3217</td>
<td>1.28 (0.93 to 1.76)</td>
<td>0.12</td>
<td>0.59 (–0.16 to 1.33)</td>
</tr>
<tr>
<td>All bleeding</td>
<td>246/3184</td>
<td>219/3217</td>
<td>1.13 (0.95 to 1.34)</td>
<td>0.18</td>
<td>0.87 (–0.40 to 2.14)</td>
</tr>
<tr>
<td><strong>Parenteral-treatment period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>8/3181</td>
<td>4/3210</td>
<td>2.06 (0.62 to 7.85)</td>
<td>0.23</td>
<td>0.13 (–0.08 to 0.34)</td>
</tr>
<tr>
<td>Major and clinically relevant nonmajor bleeding</td>
<td>58/3181</td>
<td>44/3210</td>
<td>1.33 (0.90 to 1.97)</td>
<td>0.15</td>
<td>0.45 (–0.16 to 1.07)</td>
</tr>
<tr>
<td>All bleeding</td>
<td>170/3181</td>
<td>156/3210</td>
<td>1.09 (0.88 to 1.35)</td>
<td>0.41</td>
<td>0.45 (–0.63 to 1.53)</td>
</tr>
<tr>
<td><strong>Post–parenteral-treatment period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14/3181</td>
<td>6/3210</td>
<td>2.35 (0.92 to 6.65)</td>
<td>0.07</td>
<td>0.25 (–0.02 to 0.53)</td>
</tr>
<tr>
<td>Major and clinically relevant nonmajor bleeding</td>
<td>38/3181</td>
<td>32/3210</td>
<td>1.19 (0.75 to 1.90)</td>
<td>0.46</td>
<td>0.19 (–0.32 to 0.70)</td>
</tr>
<tr>
<td>All bleeding</td>
<td>120/3181</td>
<td>104/3210</td>
<td>1.16 (0.90 to 1.50)</td>
<td>0.25</td>
<td>0.52 (–0.38 to 1.42)</td>
</tr>
<tr>
<td><strong>Follow-up period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>11/2881</td>
<td>13/2945</td>
<td>0.44 (0.25 to 0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major and clinically relevant nonmajor bleeding</td>
<td>27/2881</td>
<td>31/2945</td>
<td>1.05 (0.74 to 1.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All bleeding</td>
<td>94/2881</td>
<td>96/2945</td>
<td>3.26 (2.68 to 3.97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Two-sided P<0.05.
† Events are included if the hemoglobin level decreased by 2 g or more per deciliter over a 24-hour period.
thrombosis as part of the primary efficacy outcome and the fact that a follow-up ultrasound examination was performed in only 64% of the patients, which reduced the statistical power of the trial. Compression ultrasonography is not performed routinely in medical patients at the time of discharge from the hospital, and is performed even more rarely at 1 month after discharge. The low rate of asymptomatic proximal deep-vein thrombosis among patients who received short-term prophylaxis validates this approach. In the ADOPT and MAGELLAN trials, the logistic complexity of performing compression ultrasonography in this frail patient population before discharge from the hospital and at 30 days after discharge probably explains the suboptimal rates of follow-up examinations.

The ADOPT trial does not provide evidence to justify a policy of extended prophylaxis in a broad population of medically ill patients after hospital discharge. However, with event rates of venous thromboembolism at 30 days that range from 3% in the ADOPT trial to 5% and 6% in the EXCLAIM and MAGELLAN trials, respectively, it is clear that the risk of venous thromboembolism increases beyond the time of hospital discharge. More precise risk-stratification methods are needed to identify a narrower spectrum of medically ill patients who may benefit from extended prophylaxis. Supported by Bristol-Myers Squibb and Pfizer.

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REFERENCES


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