EDOXABAN VERSUS WARFARIN FOR THE TREATMENT
OF SYMPTOMATIC VENOUS THROMBOEMBOLISM

The Hokusai-VTE Investigators*

ABSTRACT

BACKGROUND
Whether the oral factor Xa inhibitor edoxaban can be an alternative to warfarin in patients with venous thromboembolism is unclear.

METHODS
In a randomized, double-blind, noninferiority study, we randomly assigned patients with acute venous thromboembolism, who had initially received heparin, to receive edoxaban at a dose of 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg), or to receive warfarin. Patients received the study drug for 3 to 12 months. The primary efficacy outcome was recurrent symptomatic venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

RESULTS
A total of 4921 patients presented with deep-vein thrombosis, and 3319 with a pulmonary embolism. Among patients receiving warfarin, the time in the therapeutic range was 63.5%. Edoxaban was noninferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.70 to 1.13; P < 0.001 for noninferiority). The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group (hazard ratio, 0.81; 95% CI, 0.71 to 0.94; P = 0.004 for superiority). The rates of other adverse events were similar in the two groups. A total of 938 patients with pulmonary embolism had right ventricular dysfunction, as assessed by measurement of N-terminal pro–brain natriuretic peptide levels; the rate of recurrent venous thromboembolism in this subgroup was 3.3% in the edoxaban group and 6.2% in the warfarin group (hazard ratio, 0.52; 95% CI, 0.28 to 0.98).

CONCLUSIONS
Edoxaban administered once daily after initial treatment with heparin was noninferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism. (Funded by Daiichi-Sankyo; Hokusai-VTE ClinicalTrials.gov number, NCT00986154.)
V E N O U S  T H R O M B O E M B O L I S M  I S  T H E  T H I R D  m o s t  c o m m o n  c a r d i o v a s c u l a r  d i s e a s e  a f t e r  m y o c a r d i a l  i n f a r c t i o n  a n d  s t r o k e ,  a f f e c t i n g  a t l e a s t  7 0 0 , 0 0 0  p e r s o n s  a n n u a l l y  i n  N o r t h  A m e r i c a . 1 - 3  
T h e  s t a n d a r d  t r e a t m e n t  c o n s i s t s  o f  l o w - m o l e c u l a r - w e i g h t  h e p a r i n  f o l l o w e d  b y  v i t a m i n  K  a n t a g o n i s t s . 4  
A  n u m b e r  o f  s t u d i e s  h a v e  e s t a b l i s h e d  t h a t  n e w  o r a l  a n t i c o a g u l a n t s  w i t h  o r  w i t h o u t  i n i t i a l  h e p a r i n  t h e r a p y  a r e  e f f e c t i v e  a l t e r n a t i v e s . 5 - 8  
Edoxaban  i s  a  d i r e c t  i n h i b i t o r  o f  a c t i v a t e d  f a c t o r  X  w i t h  r a p i d  o n s e t  o f  a c t i o n . 9 - 1 1  
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M E T H O D S  
S T U D Y  O V E R S I G H T  
I n  t h i s  r a n d o m i z e d ,  d o u b l e - b l i n d  t r i a l ,  w e  c o m - 
pared  h e p a r i n  ( e n o x a p a r i n  o r  u n f r a c t i o n a t e d  h e p a r i n )  f o l l o w e d  b y  e d o x a b a n  w i t h  h e p a r i n  f o l - 

R A N D O M I Z A T I O N  A N D  S T U D Y  T R E A T M E N T  
R a n d o m i z a t i o n  w a s  p e r f o r m e d  w i t h  t h e  u s e  o f  a n  i n t e r a c t i v e  W e b - b a s e d  s y s t e m ,  w i t h  s t r a t i f i c a - 

P A T I E N T S  
P a t i e n t s  1 8  y e a r s  o f  a g e  o r  o l d e r  w e r e  e l i g i b l e  i f  t h e y  h a d  o b j e c t i v e l y  d i a g n o s e d ,  a c u t e ,  s y m p t o m a t i c  d e e p - v e i n  t h r o m b o s i s  

T h e  s t u d y  w a s  d e s i g n e d  w i t h  t h e  a i m  o f  b r o a d e n i n g  a p p l i c a b i l i t y  t o  r e a l - w o r l d  p r a c t i c e  a n d  e n c o u r a g i n g  t h e  e n - 

T h e  s t u d y  w a s  c o n d u c t e d  t o  e v a l u a t e  e d o x a b a n  f o r  t h e  t r e a t - 

P a t i e n t s  w e r e  e x c l u d e d  i f  t h e y  h a d  c o n t r a i n d i c a t i o n s  t o  h e p a r i n  o r  w a r f a r i n ,  h a d  r e c e i v e d  t r e a t m e n t  f o r  m o r e  t h a n  4 8  

P a t i e n t s  r e c e i v e d  t h e  i n i t i a l  t h e r a p y  w i t h  o p e n - l a b e l  e n o x a p a r i n  o r  u n f r a c t i o n a t e d  h e p a r i n  f o r  a t  l e a s t  5  d a y s . 1 2  

P a t i e n t s  r e c e i v e d  t h e  i n i t i a l  t h e r a p y  w i t h  o p e n - l a b e l  e n o x a p a r i n  o r  u n f r a c t i o n a t e d  h e p a r i n  f o r  a t  l e a s t  5  d a y s . 1 2  

T h e  s t u d y  w a s  c o n s i d e r e d  t o  b e  c o m p l e t e  f o r  a l l  p a t i e n t s  t h a t  d i d  n o t  h a v e  o b j e c t i v e l y  d i a g n o s e d  c a n c e r .  

T h e  c o n t r i b u t i o n s  o f  a l l  c o n t r i b u t o r s  a r e  l i s t e d  i n  t h e  a u t h o r s ’  a c c e s s i b i l i t y  c o m m i t t e e .  T h e  w r i t i n g  c o m - 

T h e  c o n t r i b u t i o n s  o f  a l l  c o n t r i b u t o r s  a r e  l i s t e d  i n  t h e  a u t h o r s ’  a c c e s s i b i l i t y  c o m m i t t e e .  T h e  w r i t i n g  c o m - 

T h e  c o n t r i b u t i o n s  o f  a l l  c o n t r i b u t o r s  a r e  l i s t e d  i n  t h e  a u t h o r s ’  a c c e s s i b i l i t y  c o m m i t t e e .  T h e  w r i t i n g  c o m - 

T h e  c o n t r i b u t i o n s  o f  a l l  c o n t r i b u t o r s  a r e  l i s t e d  i n  t h e  a u t h o r s ’  a c c e s s i b i l i t y  c o m m i t t e e .  T h e  w r i t i n g  c o m -
with the study regimen of heparin, with adjustment of the dose to maintain the international normalized ratio (INR) between 2.0 and 3.0. All measurements were performed by means of a point-of-care device that provided an actual INR value for patients receiving warfarin and a sham INR value for patients receiving edoxaban.\textsuperscript{12} INR measurements were required to be performed at least monthly.

Treatment with edoxaban or warfarin was to be continued for at least 3 months in all patients and for a maximum of 12 months. The duration was determined by the treating physician on the basis of the patient’s clinical features and patient preference.

**OUTCOME MEASURES**

The primary efficacy outcome was the incidence of adjudicated symptomatic recurrent venous thromboembolism, which was defined as a composite of deep-vein thrombosis or nonfatal or fatal pulmonary embolism. Death was adjudicated as related to venous thromboembolism, other cardiovascular disease, bleeding, or other causes. Pulmonary embolism was considered to be the cause of death if there was objective documentation that a pulmonary embolism caused the death or if the death could not be attributed to a documented cause and pulmonary embolism could not be ruled out. Prespecified secondary efficacy outcomes included the primary efficacy outcome combined with either death from cardiovascular causes or death from any cause.

The principal safety outcome was the incidence of adjudicated clinically relevant bleeding, which was defined as a composite of major or clinically relevant nonmajor bleeding. Bleeding was defined as major if it was overt and was associated with a decrease in hemoglobin of 2 g per deciliter or more or required a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death.\textsuperscript{13} Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life.\textsuperscript{14} Net clinical benefit was determined on the basis of the composite of symptomatic recurrent venous thromboembolism or major bleeding. The criteria for adjudication of outcomes are provided in the Supplementary Appendix, available at NEJM.org.

**SURVEILLANCE AND FOLLOW-UP**

Patients underwent assessment, in the clinic or by telephone, on days 5 through 12, 30, and 60 after randomization and monthly thereafter while they were taking the study drug or every 3 months after discontinuing the study drug. All patients were to be contacted at month 12. Patients were instructed to report symptoms suggestive of recurrent venous thromboembolism or bleeding. Appropriate diagnostic testing, laboratory testing, or both were required in patients with suspected events.

**STATISTICAL ANALYSIS**

The study was designed as an event-driven trial to test the hypothesis that edoxaban would be noninferior to warfarin with respect to the primary efficacy outcome, with an upper limit of the confidence interval for the hazard ratio of 1.5 and a two-sided alpha level of 0.05. This margin corresponds to retention of at least 70% of the treatment effect of warfarin.

Assuming equal efficacy of edoxaban and warfarin, we estimated that 220 events would need to occur for the study to have 85% power to show the noninferiority of edoxaban. When we determined that the targeted number of events was expected to be accrued, we set the date for concluding the study (study closure) such that the last patient who underwent randomization would complete 6 months of study treatment and follow-up. Assuming a 3% incidence of the primary efficacy outcome, we estimated that we would have to enroll at least 7500 patients.

All efficacy analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization and received at least one dose of the study drug. The primary analysis included all efficacy outcomes from randomization through the end of 12 months or study closure (overall study period), regardless of the duration of the patient’s study treatment. The time to the first primary efficacy outcome was analyzed with the use of a Cox proportional-hazards model with stratification factors as covariates. In addition, the primary efficacy outcome was evaluated for the on-treatment period — the time during which the patients were receiving the study drug or within 3 days after the study drug was stopped or interrupted.

Analyses of bleeding outcomes included patients who received at least one dose of the study drug.
(safety population). The time to clinically relevant bleeding during the on-treatment period was compared with the use of the same Cox proportional-hazards model that was used for the primary efficacy outcome. Time-to-event curves were calculated with the use of the Kaplan–Meier method.

Prespecified subgroup analyses were performed in subgroups defined according to the qualifying diagnosis and according to status with respect to right ventricular dysfunction (evidence or no evidence) in patients with pulmonary embolism. The time in the therapeutic INR range was calculated with the use of standard methods, with the initial heparin lead-in period not included and with correction for planned interruptions. In all patients with pulmonary embolism, N-terminal pro–brain natriuretic peptide (NT-proBNP) levels were measured at baseline (morning sample) in a core laboratory. Right ventricular dysfunction was defined as an NT-proBNP level of 500 pg per milliliter or higher. In addition, an independent reviewer who was unaware of the treatment assignments evaluated right ventricular dimensions on the qualifying computed tomographic scan in a random sample of 1002 patients. Right ventricular dysfunction was defined as the ratio of right ventricular diameter to left ventricular diameter of 0.9 or more.

**RESULTS**

**PATIENTS AND TREATMENT**

From January 2010 through October 2012, a total of 8292 patients were enrolled at 439 centers in 37 countries (Fig. 1). The baseline characteristics of the patients were similar in the two study groups (Table 1). The median duration of heparin treatment after randomization was 7 days. Details of the actual duration of treatment with the study drug are provided in Table S2 in the Supplementary Appendix: 40% of patients were treated for 12 months. Adherence to edoxaban treatment was 80% or more in 99% of the patients in that group. Among patients receiving warfarin, the INR was in the therapeutic range for 63.5% of the time, above 3.0 for 17.6% of the time, and below 2.0 for 18.9% of the time.

**RECURRENT VENOUS THROMBOEMBOLISM**

A recurrence of venous thromboembolism during the overall study period occurred in 130 of 4118 patients (3.2%) in the edoxaban group and in 146 of 4122 patients (3.5%) in the warfarin group (hazard ratio with edoxaban, 0.89; 95% confidence interval [CI], 0.70 to 1.13; P<0.001 for noninferiority). The difference in risk (edoxaban minus warfarin) was −0.39 percentage points (95% CI, −1.16 to 0.39). The types and time
The upper limits of the 95% confidence intervals of the hazard ratios for recurrent venous thromboembolism in patients with deep-vein thrombosis or pulmonary embolism did not exceed the prespecified margin of 1.5 (Table 2). Among patients with pulmonary embolism and evidence of right ventricular dysfunction (NT-proBNP level of ≥500 pg per milliliter),
Table 2. Clinical Outcomes during Overall Study Period and On-Treatment Period.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Edoxaban (N = 4118)</th>
<th>Warfarin (N = 4122)</th>
<th>Hazard Ratio with Edoxaban (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy outcome: first recurrent VTE or VTE-related death — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event during overall study period</td>
<td>130/4118 (3.2)</td>
<td>146/4122 (3.5)</td>
<td>0.89 (0.70–1.13)</td>
<td>&lt;0.001 (for noninferiority)</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>4/4118 (0.1)</td>
<td>3/4122 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, with PE not ruled out</td>
<td>20/4118 (0.5)</td>
<td>21/4122 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal PE with or without DVT</td>
<td>49/4118 (1.2)</td>
<td>59/4122 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT alone</td>
<td>57/4118 (1.4)</td>
<td>63/4122 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event during on-treatment period</td>
<td>66/4118 (1.6)</td>
<td>80/4122 (1.9)</td>
<td>0.82 (0.60–1.14)</td>
<td>&lt;0.001 (for noninferiority)</td>
</tr>
<tr>
<td>Patients with index DVT</td>
<td>2468/4188 (59.9)</td>
<td>2453/4122 (59.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event during overall study period</td>
<td>83/2468 (3.4)</td>
<td>81/2453 (3.3)</td>
<td>1.02 (0.75–1.38)</td>
<td></td>
</tr>
<tr>
<td>Event during on-treatment period</td>
<td>48/2468 (1.9)</td>
<td>50/2453 (2.0)</td>
<td>0.96 (0.64–1.42)</td>
<td></td>
</tr>
<tr>
<td>Patients with index PE</td>
<td>1650/4118 (40.1)</td>
<td>1669/4122 (40.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event during overall study period</td>
<td>47/1650 (2.8)</td>
<td>65/1669 (3.9)</td>
<td>0.73 (0.50–1.06)</td>
<td></td>
</tr>
<tr>
<td>Event during on-treatment period</td>
<td>18/1650 (1.1)</td>
<td>30/1669 (1.8)</td>
<td>0.60 (0.34–1.08)</td>
<td></td>
</tr>
<tr>
<td>Safety outcome during on-treatment period — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary safety outcome: first major or clinically relevant nonmajor bleeding</td>
<td>349 (8.5)</td>
<td>423 (10.3)</td>
<td>0.81 (0.71–0.94)</td>
<td>0.004 (for superiority)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>56 (1.4)</td>
<td>66 (1.6)</td>
<td>0.84 (0.59–1.21)</td>
<td>0.35 (for superiority)</td>
</tr>
<tr>
<td>Fatal</td>
<td>2 (&lt;0.1)</td>
<td>10 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>0</td>
<td>6 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (&lt;0.1)</td>
<td>2 (&lt;0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal in critical site</td>
<td>13 (0.3)</td>
<td>25 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>5 (0.1)</td>
<td>12 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>0</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (0.2)</td>
<td>10 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal in noncritical site</td>
<td>41 (1.0)</td>
<td>33 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>298 (7.2)</td>
<td>368 (8.9)</td>
<td>0.80 (0.68–0.93)</td>
<td>0.004 (for superiority)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>895 (21.7)</td>
<td>1056 (25.6)</td>
<td>0.82 (0.75–0.90)</td>
<td>&lt;0.001 (for superiority)</td>
</tr>
</tbody>
</table>

Other adverse event — no. (%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Any adverse event occurring during on-treatment period</th>
<th>Any serious adverse event</th>
<th>Any serious adverse event leading to permanent discontinuation of the study drug</th>
<th>Any drug-related adverse event leading to permanent discontinuation of the study drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2821 (68.5)</td>
<td>503 (12.2)</td>
<td>121 (2.9)</td>
<td>41 (1.0)</td>
</tr>
<tr>
<td></td>
<td>2928 (71.0)</td>
<td>544 (13.2)</td>
<td>105 (2.5)</td>
<td>51 (1.2)</td>
</tr>
</tbody>
</table>

* The primary efficacy and safety outcomes were assessed by means of time-to-first-event analyses. Patients could have more than one event. The overall study period was 12 months; the on-treatment period included the time during which the patients were receiving the study drug or within 3 days after the study drug was stopped or interrupted.
recurrent venous thromboembolism occurred in 15 of 454 patients (3.3%) in the edoxaban group and in 30 of 484 patients (6.2%) in the warfarin group (hazard ratio, 0.52; 95% CI, 0.28 to 0.98). Similar results were observed among patients with right ventricular dysfunction as assessed by means of computed tomography (hazard ratio, 0.42; 95% CI, 0.15 to 1.20).

Among patients who qualified for the 30-mg dose of edoxaban, recurrent venous thromboembolism occurred in 22 of 733 patients (3.0%) receiving edoxaban, as compared with 30 of the 719 patients (4.2%) receiving warfarin (hazard ratio, 0.73; 95% CI, 0.42 to 1.26). The hazard ratios for recurrent venous thromboembolism in the other prespecified subgroups are shown in Figure S1 in the Supplementary Appendix.

**Bleeding Outcomes**
Clinically relevant bleeding (major or nonmajor) occurred in 349 of 4118 patients (8.5%) in the edoxaban group and in 423 of 4122 patients (10.3%) in the warfarin group (hazard ratio, 0.81; 95% CI, 0.71 to 0.94; P=0.004 for superiority). The difference in risk (edoxaban minus warfarin) was −1.8 percentage points (95% CI, −3.04 to −0.53). Major bleeding occurred in 56 patients (1.4%) in the edoxaban group and in 66 patients (1.6%) in the warfarin group (hazard ratio, 0.84; 95% CI, 0.59 to 1.21). The clinical presentation and time course of bleeding events are provided in Table 2 and Figure 3.

Among patients who qualified for the 30-mg dose of edoxaban, clinically relevant bleeding occurred in 58 of 733 patients (7.9%) who received edoxaban, and in 92 of the 719 patients (12.8%) who received warfarin (hazard ratio, 0.62; 95% CI, 0.44 to 0.86). Major bleeding occurred in 11 patients (1.5%) in the edoxaban group and in 22 patients (3.1%) in the warfarin group (hazard ratio, 0.50; 95% CI, 0.24 to 1.03). The hazard ratios for bleeding in the other prespecified subgroups are provided in Figure S2 in the Supplementary Appendix.

**Deaths and Other Adverse Events**
The number and causes of death, as well as results with respect to the net clinical benefit, are shown in Table S3 in the Supplementary Appendix. There were 21 acute coronary events in the edoxaban group (0.5%) and 16 in the warfarin group (0.4%). The rates of other adverse outcomes were also similar in the two groups. (Table 2, and Table S3 in the Supplementary Appendix).
In this large, double-blind study involving patients with venous thromboembolism, treatment with heparin followed by oral edoxaban once daily, as compared with standard therapy, was noninferior with respect to efficacy and superior with respect to bleeding. We succeeded in enrolling patients across a broad spectrum of venous thromboembolic manifestations, ranging from limited proximal deep-vein thrombosis to severe pulmonary embolism, and the relative efficacy was observed throughout. In analyses of safety, the results were consistent with respect to both major bleeding and clinically relevant nonmajor bleeding, with fewer fatal and intracranial bleeds in the edoxaban group (Table 2), although the between-group difference with respect to major bleeding did not reach statistical significance.

Efficacy was evaluated at 12 months of follow-up, regardless of the duration of treatment — a study design that was different from that of earlier studies. The design of the Hokusai-VTE study, as compared with a design calling for on-treatment analyses only, allowed for a better understanding of the outcomes that may be expected in clinical practice. In the on-treatment analysis, we observed low rates of recurrence that were similar to those seen in contemporary studies. In our study, the relative efficacy of edoxaban was not limited to patients receiving medication, but it was evident even among those who stopped treatment before 12 months (Fig. 2).

Some aspects of our trial warrant comment. Three recent studies focused on a single-drug approach for all treatment phases. Thus, the use of the traditional sequence of a heparin lead-in followed by an oral agent may be considered a limitation of the Hokusai-VTE study. However, given the global acceptance of, and confidence in, initial parenteral treatment, the heparin lead-in encouraged investigators to enroll a high proportion of patients with severe grades of venous thromboembolism. When designing the study, we anticipated that a considerable proportion of patients with right ventricular dysfunction due to pulmonary embolism would be included. We measured NT-proBNP levels in all patients with pulmonary embolism and assessed right ventricular dimensions by means of computed tomography in a random subgroup of 1002 of these patients. Approximately one third had right ventricular dysfunction. There was a reduction in recurrences among patients with elevated NT-proBNP levels in the edoxaban group, and this finding was supported by the analysis of
patients with right ventricular dysfunction as assessed by means of computed tomography.

The study design aimed to address concerns that new oral anticoagulants may confer a higher risk of bleeding among patients with renal impairment and low body weight. We identified approximately one fifth of patients with these risk factors. Halving of the daily dose of edoxaban to 30 mg maintained efficacy with significantly less bleeding than that observed in the warfarin group.

To ensure best practice with the comparator, the quality of warfarin therapy was proactively monitored throughout the study. This resulted in an overall time in the therapeutic range of 63.5%, which is a higher percentage of time in the therapeutic range than the 40 to 50% seen in registries of clinical practice. Our findings are likely to be generalizable. In this global study, we included patients with both provoked and unprovoked venous thromboembolism, and treatment durations varied from 3 to 12 months at the discretion of the treating physician. Loss to follow-up was very low (<0.2%), as was the rate of withdrawal of consent (<0.9%).

In conclusion, the Hokusai-VTE study showed that in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism, edoxaban administered once daily after initial heparin was noninferior to standard therapy with warfarin after initial heparin, with significantly less bleeding.

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**APPENDIX**

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