Treatment of venous thromboembolism: focus on patient characteristics and bleeding complications
Brekelmans, M. P. A.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Recurrent venous thromboembolism in patients with pulmonary embolism and right ventricular dysfunction: a post-hoc analysis of the Hokusai-VTE study

Marjolein P.A. Brekelmans
Walter Ageno
Ludo F. Beenen
Benjamin Brenner
Harry R. Büller
Cathy Z. Chen
Alexander T. Cohen
Michael A. Grosso
Guy Meyer
Gary E. Raskob
Annelise Segers
Thomas Vanassche
Peter Verhamme
Philip S. Wells
George Zhang
Jeffrey I. Weitz

Abstract

**Background** In patients with pulmonary embolism (PE), right ventricular dysfunction (RVD) is associated with early mortality. The Hokusai-VTE study used N-terminal pro-brain natriuretic peptide (NT-proBNP) and right ventricular to left ventricular (RV/LV) diameter ratio on CT as indicators of RVD and reported that recurrent venous thromboembolism (VTE) rates were lower with edoxaban than warfarin. The aim of the current study was to further explore the significance of RVD and investigate potential explanations for the superiority of edoxaban; i.e., differences in baseline clinical characteristics, duration of initial heparin treatment, bleeding rates, or quality of warfarin treatment.

**Methods** The Hokusai-VTE trial (NCT00986154) was a randomized, double-blind, event-driven non-inferiority trial in patients from centres in 37 countries that compared edoxaban with warfarin in the treatment of acute VTE. Patients received treatment for at least 3 months and up to a maximum of 12 months. Patients were followed up for 12 months. Outcome data at 12 months was collected for all patients irrespective of treatment duration. This pre-specified subgroup analysis focuses on the included patients with PE. The primary efficacy outcome was the incidence of adjudicated symptomatic recurrent VTE defined as a composite of deep vein thrombosis or non-fatal or fatal PE at 12 months. Recurrence rates with edoxaban and warfarin were compared in patients with and without RVD. In those with NT-proBNP concentrations of 500 pg/mL or higher, we compared baseline characteristics, duration of heparin treatment, and bleeding leading to study drug discontinuation in the edoxaban and warfarin groups. We also assessed quality of warfarin treatment. All analyses were done with the modified intention-to-treat population. The Hokusai-VTE trial is registered with ClinicalTrials.gov, number NCT00986154.

**Results** Between Jan 28, 2010, and Oct 5, 2012, 8292 patients were enrolled from 439 centres, of whom 8240 received at least one dose of study drug. 3319 patients had PE. NT-proBNP was 500 pg/mL or higher in 465 (30%) of 1565 patients given edoxaban and in 507 (32%) of 1599 given warfarin. Recurrent VTE occurred in 14 (3%) of 465 patients in the edoxaban group and 30 (6%) of 507 in the warfarin group (hazard ratio [HR] 0.50, 95%CI 0.26-0.94; p=0.033). The RV/LV diameter ratio was 0.9 or higher in 414 (44%) of 937 patients in the edoxaban group and 427 (45%) of 946 in the warfarin group. Recurrent VTE occurred in 11 (3%) of 414 and 20 (5%) of 427 patients in the edoxaban and warfarin groups (HR 0.57, 95%CI 0.27-1.17; p=0.13). Baseline characteristics, duration of heparin treatment, and rates of bleeding leading to study drug discontinuation were similar in the edoxaban and warfarin groups and the quality of warfarin management was adequate for patients with NT-proBNP concentrations of 500 pg/mL or higher.
Conclusion Findings from our analysis suggest that edoxaban is more effective than warfarin in the treatment and prevention of recurrent VTE in patients with PE and evidence of RVD.
Chapter 3

Introduction

Venous thromboembolism (VTE) is a common disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The direct oral anticoagulants (DOACs) are as effective as warfarin for VTE treatment and are associated with a lower risk of bleeding (1,2). Although DOACs are widely used for DVT treatment, there remains some reluctance to use them for treatment of PE, especially in patients with more severe PE (3). Right ventricular dysfunction (RVD) identifies patients with PE at higher risk for early complications (4,5). Indicators of RVD include raised concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) and right ventricular dilatation as determined by an increased right ventricular to left ventricular (RV/LV) diameter ratio on CT images or echocardiography (6,7).

After initial treatment with heparin, the Hokusai-VTE study compared edoxaban with warfarin in a wide range of patients with VTE (8). The study assessed two indicators of RVD in PE patients and therefore was the first to provide the opportunity to examine the efficacy of a direct oral anticoagulant in patients with PE and evidence of RVD. The rate of recurrent VTE was lower with edoxaban than with warfarin in these patients (8). The current study was undertaken to first confirm this finding in the complete set of patients and second to investigate in depth potential explanations for the recorded difference.

Methods

Study design and participants

As previously described, the Hokusai-VTE study was a large, international, multicentre, randomised trial comparing edoxaban with warfarin in 8292 patients aged 18 years or older with a diagnosed acute symptomatic DVT or PE (NCT00986154) (8). A coordinating committee in collaboration with the funder had responsibility for study design, protocol, and oversight. An independent committee, unaware of study group assignment, adjudicated all suspected outcomes. The institutional review board at each centre approved the protocol. All patients provided written informed consent. Patients qualifying for thrombolytic treatment were excluded. The full list of exclusion criteria is provided in the original publication (8).

In this subgroup analysis, we focused on patients with a PE. PE was defined as symptoms of PE with one of the following findings: an intraluminal filling defect in (sub)segmental or more proximal branches on spiral CT scan, an intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram, a perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy, or a non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography (8).
Randomization and masking
Patients were randomly assigned (1:1) to receive either edoxaban or warfarin using a double-blind, double-dummy method (i.e., patients receiving active warfarin also received dummy edoxaban, and patients receiving active edoxaban also received dummy warfarin). The local site study physician or study coordinator did the randomisation using an interactive web-based system, with stratification according to the qualifying diagnosis (DVT or PE), presence or absence of temporary risk factors, and the dose of edoxaban. The system then directed which treatment kit the patient was to receive. All investigators, coordinators, patient caregivers, and patients were masked to treatment.

Procedures
All patients received initial treatment with enoxaparin or unfractionated heparin for at least 5 days and were then given either edoxaban or warfarin for a minimum of 3 months and a maximum of 12 months. Edoxaban (or placebo) was started after discontinuation of initial heparin treatment. The dose of edoxaban was 60 mg once a day, which was reduced to 30 mg in patients with a creatinine clearance of 30-50 mL per min, a bodyweight of 60 kg or lower, or in those receiving concomitant P-glycoprotein inhibitors (verapamil or quinidine). Warfarin (or placebo) was started concurrently with enoxaparin or unfractionated heparin and the target international normalised ratio (INR) was between 2.0 and 3.0. INR measurement was done with a point-of-care device that provided the actual INR for patients receiving warfarin and a sham INR value for patients given edoxaban. INR measurement was done at least once a month. Patients were followed up for 12 months (8).

The protocol of the Hokusai-VTE study pre-specified a subgroup comparison of edoxaban with warfarin in patients with PE and indicators of RVD at baseline (8,9). RVD was defined as a concentration of NT-proBNP of 500 pg/mL or higher (10) or CT evidence of right ventricular dilatation based on a reformatted chamber view RV/LV diameter ratio of 0.9 or higher (11,12). We chose NT-proBNP because it reflects right ventricular volume and function in patients with PE (13). Because the most recent PE guidelines from the European Society of Cardiology suggest a cut-off for NT-proBNP at 600 pg/mL or higher, we also did an analysis using this threshold (4,7).

We measured serum NT-proBNP concentrations in samples collected at enrolment. Assays were done centrally in Quintiles Laboratories (Marietta, GA, USA) with the Elesys NT-proBNP electrochemiluminescence kit on the Roche Cobas e411 platform. The RV/LV diameter ratio was assessed on all available digital CT images by an independent expert radiologist masked to treatment allocation and patient data. To obtain reformatted chamber views (12), images were imported in an image workstation with multiplanar reformatting features using commercially available software (eFilm Workstation for Windows [version 3.4.0], Build 10, Merge Technologies, Milwaukee, Wisconsin, USA). If ventilation/perfusion
scanning or direct pulmonary angiography only was used for the diagnosis or no digital CT images could be processed in the viewer, RV/LV diameter ratio could not be assessed.

At the time of original publication (8), 175 NT-proBNP samples were not available for analysis because of delayed overseas shipment. We included these samples in the current subgroup analysis. Furthermore, RV/LV diameter measurements were calculated in 1002 of the patients in the original publication, whereas an additional 881 measurements were available for the present study. The difference is explained by the time-consuming analysis needed for the assessment of RV/LV diameter ratios. Data for clinical parameters at moment of presentation with PE were not available because of a delay between presentation and randomisation in the study. Therefore, scores on the simplified PE severity index (sPESI) could not be calculated.

Outcomes
The primary efficacy outcome was the incidence of symptomatic recurrent VTE defined as a composite of DVT or nonfatal or fatal PE at 12 months (8). The outcome was assessed by a central adjudication committee whose members were masked to study group assignments and evidence of RVD at inclusion. In the current analysis, we made a further distinction between fatal PE, non-fatal PE, and DVT alone.

When a difference was recorded in the rate of recurrent VTE between edoxaban and warfarin recipients, several factors were investigated to provide insight into potential explanations for this difference. The examined factors included baseline clinical characteristics, the duration of initial heparin therapy, the rates of bleeding that led to study drug discontinuation, and the recurrence rates on-treatment and off-treatment. Additionally, we compared the quality of warfarin treatment defined as percentage of time of INR below, in, or above the therapeutic range in PE patients with NT-proBNP concentrations of 500 pg/mL or higher with that in those with lower concentrations. For these latter three comparisons, we chose a priori an observation period of the first 120 days to better focus on early divergence in recurrence rates in the two groups.

Statistical analysis
The Hokusai-VTE study was designed as an event-driven trial to test the hypothesis that edoxaban would be non-inferior to warfarin for 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 happen for the study to have 85% power to show the non-inferiority of edoxaban. When the targeted number of events was expected to be accrued, the date for concluding the study was set (study closure), such that the last patient randomly assigned
would complete 6 months of study treatment and follow up. Assuming a 3% incidence of the primary efficacy outcome, we expected to enrol at least 7500 patients. The statistical analysis plan pre-specified subgroup analysis of the patients with PE.

All efficacy analyses were done with the modified intention-to-treat population, defined as all randomly assigned patients who received at least one dose of the study drug. The primary efficacy point was analysed using a Cox proportional hazards model with dose-adjustment (30 mg vs 60 mg) and risk factor (temporary vs other) as covariates for all patients who had taken at least one dose of study drug and with adjudication committee confirmed index PE. Patients without recurrent VTE were censored. We calculated time-to-event curves with the Kaplan-Meier method. We used SAS (version 9.3) for all analyses. This study is registered with ClinicalTrials.gov, number NCT00986154.

Role of the funding source
Daichii Sankyo provided financial support for the study. A coordinating committee in collaboration with the funder was responsible for the design and oversight of the study. The funder was responsible for the collection, maintenance, and analysis of data. The members of the writing committee, including employees of the funder, interpreted the data and prepared, reviewed, and approved the manuscript; the funder was not involved in the decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors had access to the primary clinical trial data, vouch for the accuracy of the analyses, and participated in the writing of the manuscript.

Results
Between Jan 28, 2010, and Oct 5, 2012, 8292 patients were enrolled in the Hokusai-VTE study in 439 centres in 37 countries, of whom 8240 received at least one dose of study drug. Of these 8240 patients, 3319 (40%) with symptomatic PE were included in the current pre-specified subgroup analysis (Figure 3.1). After an initial course of enoxaparin or unfractionated heparin, 1650 (50%) of 3319 patients were given edoxaban and 1669 (50%) of 3319 patients received warfarin. The median duration of treatment was 8.0 months (interquartile range [IQR] 6.0-12.0) in the edoxaban group and 7.3 months (6.0-12.0) in the warfarin group. Baseline NT-proBNP concentrations could be measured in 3164 (95%) of 3319 patients, whereas the RV/LV diameter ratio could be calculated in 1883 (57%) of 3319 patients. This represents an additional 175 patients with baseline NT-proBNP concentrations and 881 additional patients with RV/LV diameter ratio measurements than were reported in the primary publication (in which 2989 NT-proBNP and 1002 RV/LV diameter measurements...
3343 PE Patients underwent randomization

1663 Assigned to receive heparin–edoxaban
- 13 Did not receive heparin–edoxaban
  - 1650 Were included in modified intention to treat and safety analyses
    - 78 Did not complete the overall study period
      - 53 Died
      - 20 Withdrew consent
      - 0 Were lost to follow-up
      - 5 Had other reasons

1680 Assigned to receive heparin–warfarin
- 11 Did not receive heparin–warfarin
  - 1669 Were included in modified intention to treat and safety analyses
    - 73 Did not complete the overall study period
      - 53 Died
      - 17 Withdrew consent
      - 1 Were lost to follow-up
      - 1 Had other reasons

Figure 3.1. Patient flow diagram

were reported) (8). The NT-proBNP concentration was 500 pg/mL or higher in 465 (30%) of 1565 edoxaban recipients and in 507 (32%) of 1599 patients given warfarin. The RV/LV diameter ratio was 0.9 or higher in 414 (44%) of 937 and 427 (45%) of 946 patients in the edoxaban and warfarin groups, respectively. Of the 1817 patients in whom both indicators of RVD were available, 192 (21%) patients in the edoxaban group and 207 (23%) patients in the warfarin group had both an NT-proBNP concentration of 500 pg/mL or higher and a RV/LV diameter ratio of 0.9 or higher.

**NT-proBNP and recurrent venous thromboembolism**

In patients with PE with NT-proBNP concentrations of 500 pg/mL or higher, the median concentration was 1405 pg/mL (IQR 828-2776) in the edoxaban group and 1686 pg/mL (937-3152) in the warfarin group. In those patients, we recorded recurrent VTE in 14 (3%) of 465 patients in the edoxaban group and 30 (6%) of 507 in the warfarin group (HR 0.50, 95%CI 0.26-0.94; p=0.03; Table 3.1). The difference in risk between edoxaban and warfarin was -2.9% (95%CI -5.5 to -0.3). The number needed to treat (NNT) is 34. Hence, 34 patients need to be treated with edoxaban to prevent one recurrent VTE event compared to treatment with warfarin. In contrast, in patients with NT-proBNP levels below 500 pg/mL, recurrent VTE occurred in 30 (3%) of 1100 and 33 (3%) of 1092 patients given edoxaban and warfarin, respectively. Figure 3.2 shows Kaplan-Meier cumulative recurrent VTE rates for patients with NT-proBNP concentrations of 500 pg/mL or higher.

When the NT-proBNP cutoff was set at 600 pg/mL or higher, we recorded recurrent VTE
Recurrent venous thromboembolism in patients with right ventricular dysfunction

in 14 (3%) of 429 patients given edoxaban and 28 (6%) of 464 given warfarin (HR 0.54, 95%CI 0.28-1.02; p=0.056).

Investigation into potential explanations for the difference in outcomes in PE patients with NT-proBNP concentrations of 500 pg/mL or higher showed that baseline characteristics were similar in patients in both the edoxaban and warfarin treatment groups (Table 3.2). Additionally, we noted no differences in durations of initial heparin treatment and rates of bleeding leading to study drug discontinuation in the first 120 days between the groups. Furthermore, in the first 120 days of treatment, all recurrences in the edoxaban group and ten (67%) of the 15 recurrences in the warfarin group happened on-treatment. Although prevalence of thrombophilia differed between the edoxaban and warfarin groups, no recurrent VTE events were recorded in patients with a known thrombophilia. Of the five recurrences in the warfarin group that occurred off treatment, two patients discontinued treatment shortly after suffering a clinically relevant non-major bleeding event. The quality of warfarin treatment in PE patients with NT-proBNP concentrations of 500 pg/mL or higher was similar to that in patients with lower NT-proBNP concentrations. The INR was in the therapeutic range for 60% of the time in patients with NT-proBNP concentrations of 500 pg/mL or higher, and for 62% of the time in patients with NT-proBNP levels below 500 pg/mL, respectively.

Table 3.1. Rates of recurrent venous thromboembolism in patients with pulmonary embolism as a function of NT-proBNP concentrations

<table>
<thead>
<tr>
<th>NT-proBNP ≥500 pg/mL – n/N (%)</th>
<th>Edoxaban</th>
<th>Warfarin</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent venous thromboembolism – n/N (%)</td>
<td>14/465 (3.0)</td>
<td>30/507 (5.9)</td>
<td>0.50 (0.26-0.94)</td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>4</td>
<td>13</td>
<td>p=0.033</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>DVT only – n</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP &lt;500 pg/mL – n/N (%)</td>
<td>1100/1565 (70)</td>
<td>1092/1599 (68)</td>
<td></td>
</tr>
<tr>
<td>Recurrent venous thromboembolism – n/N (%)</td>
<td>30/1100 (2.7)</td>
<td>33/1092 (3.0)</td>
<td>0.89 (0.54-1.5)</td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>4</td>
<td>2</td>
<td>p=0.065</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>DVT only – n</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

NT-proBNP: N-terminal pro-brain natriuretic peptide; HR: hazard ratio; 95%CI: 95% confidence interval; DVT: deep vein thrombosis
Chapter 3

NT-proBNP and mortality
In PE patients with NT-proBNP concentrations of 500 pg/mL or higher, all-cause mortality at 30 days was recorded in nine (2%) of 465 patients in the edoxaban group and in seven (1%) of 507 warfarin recipients. All-cause mortality at 365 days was recorded in 29 (6%) of 465 patients in the edoxaban group and 32 (6%) of 507 patients in the warfarin group.

RV/LV diameter ratio and recurrent venous thromboembolism
In PE patients with a RV/LV diameter ratio of 0.9 or higher, recurrent VTE occurred in 11 (3%) of 414 patients in the edoxaban group and 20 (5%) of 427 in the warfarin group (HR 0.57, 95%CI 0.27-1.17; p=0.13; Table 3.3). The corresponding number needed to treat is 49; i.e., 49 patients need to be given edoxaban to prevent one recurrent VTE event compared with treatment with warfarin. In those with RV/LV diameter ratios lower than 0.9, recurrent VTE was recorded in 12 (2%) of 523 and 16 (3%) of 519 patients in the edoxaban and warfarin groups, respectively. Figure 3.3 shows the Kaplan-Meier cumulative rates of recurrent VTE for those with a RV/LV diameter ratio of 0.9 or higher.

Figure 3.2. Kaplan-Meier cumulative rates of recurrent venous thromboembolism with pulmonary embolism patients with NT-proBNP concentrations ≥500 pg/mL.
### Table 3.2. Comparison of baseline characteristics, duration of initial heparin therapy, rates of bleeding, study drug discontinuation, and recurrent venous thromboembolism in patients with pulmonary embolism with NT-proBNP concentration \( \geq 500 \) pg/mL

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Edoxaban N=465</th>
<th>Warfarin N=507</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean – years ± SD</td>
<td>65 ± 15</td>
<td>64 ± 15</td>
</tr>
<tr>
<td>Male – n (%)</td>
<td>209 (45)</td>
<td>233 (46)</td>
</tr>
<tr>
<td>Female – n (%)</td>
<td>256 (55)</td>
<td>274 (54)</td>
</tr>
<tr>
<td>Unprovoked – n (%)</td>
<td>309 (67)</td>
<td>337 (67)</td>
</tr>
<tr>
<td>Concomitant DVT – n (%)</td>
<td>99 (21)</td>
<td>124 (25)</td>
</tr>
<tr>
<td>Active cancer – n (%)</td>
<td>16 (3.4)</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>Previous venous thromboembolism – n (%)</td>
<td>97 (21)</td>
<td>95 (19)</td>
</tr>
<tr>
<td>Known thrombophilia – n (%)</td>
<td>4 (0.9)</td>
<td>18 (3.6)</td>
</tr>
</tbody>
</table>

#### Anatomical extent of pulmonary embolism:
- Limited or intermediate – n (%)  
  - Edoxaban: 158 (34)  
  - Warfarin: 167 (33)  
- Extensive – n (%)  
  - Edoxaban: 307 (66)  
  - Warfarin: 340 (67)  

#### Cardiovascular disease – n (%)  
- Edoxaban: 119 (26)  
- Warfarin: 143 (28)  

#### Atrial fibrillation – n (%)  
- Edoxaban: 82 (18)  
- Warfarin: 73 (14)  

#### Pulmonary disease – n (%)  
- Edoxaban: 112 (24)  
- Warfarin: 151 (30)  

#### Body weight ≤60 kg or creatinine clearance ≤50 mL/min or P-glycoprotein inhibitor use – n (%)  
- Edoxaban: 123 (27)  
- Warfarin: 123 (24)  

#### Concomitant aspirin use – n (%)  
- Edoxaban: 58 (13)  
- Warfarin: 59 (12)  

<table>
<thead>
<tr>
<th>Duration of initial heparin therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Days – median (IQR)</td>
<td>7 (6–9)</td>
<td>7 (6–9)</td>
</tr>
</tbody>
</table>

#### Bleeding and study drug discontinuation

| Major bleeding – n (%)*             | 13 (2.8) | 13 (2.6) |
| Bleeding leading to study drug discontinuation – n (%)* | 11 (2.4) | 11 (2.2) |
| All discontinuations of study drug – n (%)* | 106 (23) | 114 (22.5) |

<table>
<thead>
<tr>
<th>Recurrent venous thromboembolism in the first 120 days – n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>DVT only – n</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent venous thromboembolism on-treatment – n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>DVT only – n</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*In first 120 days. NT-proBNP: N-terminal pro-brain natriuretic peptide; SD = standard deviation; DVT: deep vein thrombosis; IQR: interquartile range
Table 3.3. Rates of recurrent venous thromboembolism in pulmonary embolism patients as a function of right ventricular to left ventricular diameter ratios

<table>
<thead>
<tr>
<th>RV/LV diameter ratio ≥0.9 – n/N (%)</th>
<th>Edoxaban</th>
<th>Warfarin</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent venous thromboembolism – n/N (%)</td>
<td>414/937 (44)</td>
<td>427/946 (45)</td>
<td>0.57 (0.27-1.17) p=0.13</td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>11/414 (2.7)</td>
<td>20/427 (4.7)</td>
<td>0.57 (0.27-1.17) p=0.13</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>7</td>
<td>7</td>
<td>0.57 (0.27-1.17) p=0.13</td>
</tr>
<tr>
<td>DVT only – n</td>
<td>3</td>
<td>7</td>
<td>0.57 (0.27-1.17) p=0.13</td>
</tr>
<tr>
<td>RV/LV diameter ratio &lt;0.9 – n/N (%)</td>
<td>523/937 (56)</td>
<td>519/946 (55)</td>
<td>0.75 (0.35-1.57) p=0.44</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism – n/N (%)</td>
<td>12/523 (2.3)</td>
<td>16/519 (3.1)</td>
<td>0.75 (0.35-1.57) p=0.44</td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>2</td>
<td>2</td>
<td>0.75 (0.35-1.57) p=0.44</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>6</td>
<td>7</td>
<td>0.75 (0.35-1.57) p=0.44</td>
</tr>
<tr>
<td>DVT only – n</td>
<td>4</td>
<td>7</td>
<td>0.75 (0.35-1.57) p=0.44</td>
</tr>
</tbody>
</table>

HR: hazard ratio; 95%CI: 95% confidence interval; RV/LV: right to left ventricular; DVT: deep vein thrombosis

Figure 3.3. Kaplan-Meier cumulative rates of recurrent venous thromboembolism in pulmonary embolism patients with right ventricular to left ventricular diameter ratio ≥0.9
RV/LV diameter ratio and mortality

In PE patients with RV/LV diameter ratios of 0.9 or higher, all-cause mortality at 30 days was recorded in three (1%) of 414 patients in the edoxaban group and in three (1%) of 427 warfarin recipients. All-cause mortality at 365 days was recorded in 11 (3%) of 414 patients in the edoxaban group and 16 (4%) of 427 in the warfarin group.

NT-proBNP and RV/LV diameter ratio and recurrent venous thromboembolism

In the 399 patients with NT-proBNP concentrations of 500 pg/mL or higher and RV/LV diameter ratio of 0.9 or higher, recurrent VTE occurred in four (2%) of 192 and in ten (5%) of 207 patients in the edoxaban and warfarin group, respectively (HR 0.44, 95%CI 0.14-1.36; p=0.17; Table 3.4 and Supplementary Figure 1).

Table 3.4. Rates of recurrent venous thromboembolism in pulmonary embolism patients as a function of NT-proBNP concentrations and right ventricular to left ventricular diameter ratios

<table>
<thead>
<tr>
<th>NT-proBNP ≥500 pg/mL and RV/LV diameter ≥0.9 – n/N (%)</th>
<th>Edoxaban</th>
<th>Warfarin</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent venous thromboembolism – n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>4/192 (2.1)</td>
<td>10/207 (4.8)</td>
<td>0.44 (0.14-1.36)</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>DVT only – n</td>
<td>1</td>
<td>2</td>
<td>p=0.15</td>
</tr>
<tr>
<td>NT-proBNP &lt;500 pg/mL and RV/LV diameter &lt;0.9 – n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent venous thromboembolism – n/N (%)</td>
<td>8/435 (1.8)</td>
<td>13/424 (3.1)</td>
<td>0.61 (0.25-1.45)</td>
</tr>
<tr>
<td>Fatal pulmonary embolism – n</td>
<td>1</td>
<td>1</td>
<td>p=0.26</td>
</tr>
<tr>
<td>Non-fatal pulmonary embolism – n</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>DVT only – n</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

NT-proBNP: N-terminal pro-brain natriuretic peptide; HR: hazard ratio; 95%CI: 95% confidence interval; RV/LV: right to left ventricular; DVT: deep vein thrombosis

Discussion

Our findings show that a regimen of heparin followed by edoxaban is more effective than heparin overlapped with and followed by warfarin in the prevention of recurrent VTE in PE patients with evidence of RVD, most notably with NT-proBNP concentrations of 500 pg/mL or higher. The time-to-event curves diverge early, which suggests that the advantage of edoxaban over warfarin is established in the first weeks and is maintained for the complete study duration. The advantage of edoxaban does not seem to be explained by an imbalance in baseline characteristics relevant to the risk of recurrent VTE, poor quality of warfarin treatment, or differences in the duration of initial heparin treatment,
or the rates of bleeding leading to study drug discontinuation. Therefore, the most likely explanation is that in these patients with evidence of RVD, edoxaban provides a more consistent antithrombotic effect than does warfarin. In other words, edoxaban has a stable pharmacokinetic and pharmacodynamic profile that allows for a predictable and constant level of anticoagulation. By contrast, the intrinsic characteristics of warfarin might result in periods of overtreatment and under treatment, leading to a less stable anticoagulant effect over time.

RVD in patients with a PE has been shown to predict mortality at hospital discharge and at 30 days (4,5,14). Additionally, persistent RVD predicts recurrent VTE (15), and raised NT-proBNP plasma concentrations are associated with long-term risk of VTE recurrence (16). To our knowledge, this is the first time a study has shown that RVD at baseline also predicts short-term and long-term risk of fatal and non-fatal recurrent VTE, especially when RVD is defined by NT-proBNP concentrations. NT-proBNP concentration cut-offs of 500 or 600 pg/mL provide directionally similar results.

In comparison to the data from the Hokusai-VTE study, the EINSTEIN and AMPLIFY studies (17,18), which assessed rivaroxaban and apixaban, respectively, had a significantly lower proportion of patients with extensive PE and did not prospectively assess markers of RVD and the relation with recurrent VTE. Confirmation of our findings in these trials would be of great interest.

Strengths of the present study include the large sample size, the double blind design, the a priori definition of RVD, the use of two indicators of RVD, the measurement of NT-proBNP in a reference laboratory, the long-term follow-up, and the masked adjudication of efficacy and safety outcomes. However, our study had several limitations. Although we used two indicators of RVD, measurements were not available for all PE patients. NT-proBNP data were available in 95% of all PE patients. In the other patients, blood was not drawn, was collected in inappropriate tubes, or no reliable measurement was obtained. It is unlikely that the missing NT-proBNP data would have affected our findings. RV/LV diameter ratios could only be determined in 57% of the patients because the calculation depended on the availability of sufficient-quality reformatted CT images. Furthermore, the protocol allowed for other modalities to establish the diagnosis of PE. Nonetheless, both indicators adequately identified high-risk patients who benefitted from edoxaban treatment. Echocardiography was not done and troponin concentrations were not measured; therefore, the utility of these tests in this setting remains unknown.

Additionally, we were unable to risk stratify patients using the sPESI score because the Hokusai-VTE study included a delay between moment of presentation and randomisation. Consequently, we do not have any information available for the moment of presentation because informed consent was not yet obtained. Furthermore, it needs to be realised that we used NT-proBNP concentration or RV/LV diameter ratio as a simple, crude marker of
RVD and did not investigate whether other (baseline) characteristics affected the predictive significance of these tests. RVD might not be the only predictor of recurrence. Finally, it is well known that NT-proBNP concentrations can be increased by other diseases such as inflammatory processes, ischaemia, heart failure, or pulmonary diseases (19). Hence, we are not able to rule out an effect of these diseases on the recorded associations.

In conclusion, the results of this study provide reassurance that a regimen of heparin followed by edoxaban can be used to treat all patients with PE eligible for anticoagulation therapy. Furthermore, the data suggest that edoxaban is a more convenient and effective anticoagulant than warfarin in the treatment and prevention of recurrence in stable PE patients with evidence of RVD.
References


Supplementary Figure 1. Kaplan-Meier cumulative rates of recurrent venous thromboembolism in pulmonary embolism patients with NT-proBNP levels ≥500 pg/mL and right ventricular to left ventricular diameter ratio ≥0.9