Treatment of venous thromboembolism: focus on patient characteristics and bleeding complications
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Clinical impact and course of major bleeding with edoxaban versus vitamin K antagonists

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Abstract

Background Edoxaban is a once-daily direct oral anticoagulant (DOAC). The Hokusai-VTE study revealed that, after initial treatment with heparin, edoxaban was non-inferior to and safer than vitamin K antagonists (VKA) in the prevention of recurrent deep vein thrombosis and pulmonary embolism. This is the first report on the clinical relevance and management of bleeding events with edoxaban.

Method All major bleeding events were classified blindly by three study-independent adjudicators. Pre-defined criteria were used to classify severity of clinical presentation and, separately, the clinical course and outcome into 4 categories.

Results Major bleeding occurred in 56 patients treated with edoxaban and 65 patients treated with VKA. The severest categories (3 or 4) of the clinical presentation were assigned to 46% of the major bleeding episodes in edoxaban recipients versus 58% of the major bleeds in VKA recipients (odds ratio [OR] 0.62, 95% confidence interval [95%CI] 0.30-1.27; p=0.19). Clinical course was classified as severe (category 3 or 4) in 23% of the edoxaban and 29% of the VKA-associated bleeds (OR 0.73, 95%CI 0.32-1.66; p=0.46).

Conclusion Edoxaban-associated major bleeding events have a comparable clinical presentation and course to major bleeds with VKA in patients treated for venous thromboembolism in the Hokusai-VTE study. These results may assure physicians that it is safe to prescribe this medication. If a major bleeding during edoxaban treatment occurs, its clinical presentation and clinical course are not worse than in VKA treated patients.
Clinical impact of bleeding with edoxaban

Introduction

Oral anticoagulants (OAC) are indicated for the treatment and prevention of venous thromboembolism (VTE). For six decades vitamin K antagonists (VKA) were the only available OAC and although VKA are highly effective in prevention of thromboembolism, there are several limitations to their use, such as a narrow therapeutic index, inter- and intra-individual variability, interactions with food and other drugs and a variable dose response which all necessitate frequent monitoring and dose adjustments (1-3). The most important side effect of VKA is an increased risk of bleeding. As such, VKA have been prominent at the top of the list of medications that lead to hospital admission (4).

The direct oral anticoagulants (DOACs) were developed as an alternative for VKA treatment. Advantages of DOACs are a short half-life, few interactions with food and other drugs and a stable pharmacokinetic and pharmacodynamic profile allowing a fixed dose regimen (5). For treatment of VTE, DOACs have been evaluated in large phase III clinical trials with a total of 26872 patients (6-9). A meta-analysis of these studies showed that DOACs are as effective as VKA in the treatment of VTE and reduce the risk of major bleeding. In addition, the risk of intracranial haemorrhage (ICH) was reduced by 30-70% in patients using DOACs compared to VKA (10,11).

Although these large studies show that the absolute number of bleeding events in patients treated with DOACs is low, little is known about the clinical impact of those bleeding episodes. There is a need for information about the severity of presentation and the course of DOAC- and VKA-associated bleeds. Furthermore, insights in optimal management of DOAC-associated bleeding and procedures in case of emergent interventions or surgery are wanted (12,13).

The aim of the present study is to assess the clinical relevance and management of major bleeding events associated with edoxaban. We therefore classified all major bleeding events of the Hokusai-VTE study in a blinded fashion with regard to clinical impact at the time of presentation and the clinical course. A comparison was made between edoxaban and VKA treated patients. Additionally, the interventions and treatment strategies used to manage bleeding were described.

Methods

Hokusai-VTE study

In the Hokusai-VTE study, edoxaban was compared to VKA (i.e. warfarin) in a double-blind, double-dummy fashion for the treatment of acute symptomatic DVT or PE. All patients received initial treatment with enoxaparin (LMWH) or unfractionated heparin (UFH) for at
least 5 days. After discontinuation of LMWH or UFH, edoxaban (or placebo) was started at a dose of 60 mg once daily. A lower dose of 30 mg once daily was prescribed in case of a creatinine clearance of 30-50 ml per minute, a bodyweight of ≤ 60 kg or when the patient received concomitant treatment with potent P-glycoprotein inhibitors. Simultaneously, warfarin (or placebo) was started. Target international normalized ratio (INR) was between 2.0 and 3.0 and was measured by point-of-care INR devices at least once a month. The treatment duration was between 3 and 12 months and was a decision of the treating physician. Additional information about the Hokusai-VTE study can be found in the original article (9).

The primary safety outcome was a composite of first major or clinically relevant non-major bleeding. Major bleeding was, according to the ISTH criteria (14), defined as overt and associated with a drop in haemoglobin level of ≥ 2 grams per decilitre or leading to blood transfusion of 2 or more units of red blood cells, appearing in a critical organ or site, or fatal. Patients were followed prospectively and were asked to report symptoms suggestive of bleeding. Appropriate diagnostic investigations were performed when needed.

Classification of presentation and course of major bleeding

All major bleeding events from the Hokusai-VTE study were classified blindly by three independent adjudicators (HB, AC, SM) using predefined criteria (Table 8.1). An extensive description of the adjudication process has been described previously (15). Briefly, the first classification assessed the severity of the clinical presentation of the bleeding. The second classification assessed the clinical course and evaluated applied measures and interventions to treat the major bleed and the outcome of the bleed. When the adjudicators differed in opinion, a thorough debate on the classification followed, taking all relevant information into consideration, in order to reach consensus. If no consensus was reached, the following rule applied: in case of doubt between categories, the more severe outcome was chosen (and the bleeding was adjudicated to the higher category). The investigators were not aware of the assigned treatment regimen at the time of adjudication of both classification schemes.

If a patient had experienced more than one major bleed at different anatomical sites or a recurrent major bleed at the same anatomical site, the first major bleed or the major bleed with the worst outcome was taken into account. Hence, for every patient only one major bleeding episode was considered for the final analysis.
Table 8.1. Classification of clinical presentation and course of major bleeding

A. Clinical presentation

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bleeding events presenting without any clinical emergency.</td>
</tr>
<tr>
<td>2</td>
<td>All bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency.</td>
</tr>
<tr>
<td>3</td>
<td>Bleeding events presenting with great medical emergency; e.g. with hemodynamic instability; or cerebral bleeding presenting with neurologic symptoms.</td>
</tr>
<tr>
<td>4</td>
<td>Bleeding events that are fatal before or almost immediately upon entering the hospital.</td>
</tr>
</tbody>
</table>

B. Clinical course

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bleeding events for which only measures were applied to treat discomfort, without transfusions of erythrocytes.</td>
</tr>
<tr>
<td>2</td>
<td>Bleeding events requiring only standard measures such as transfusions of erythrocytes, and straightforward interventions.</td>
</tr>
<tr>
<td>3</td>
<td>Life threatening bleeding events for which immediate and elaborate measures were used to avoid death. These bleedings could still be fatal after all interventions and could lead to persistent disability.</td>
</tr>
<tr>
<td>4</td>
<td>Bleeding events for which death was unavoidable, so that no lifesaving attempts were made.</td>
</tr>
</tbody>
</table>

Classifications of clinical presentation (A) and clinical course (B) of major bleeding events in the Hokusai-VTE study

Assessment of treatment of major bleeds

The protocol of the Hokusai-VTE study pre-specified treatment strategies that could be applied for bleeding events (9,16). To assess treatment strategies applied for major bleeds in both treatment groups, the focus was on patients with observed clinical course categories 2 and 3. Category 2 of the clinical course was defined as standard measures to treat the bleeding, for example administration of vitamin K, packed cells and/or fresh frozen plasma. Clinical course category 3 was defined as more elaborate measures to avoid serious morbidity and mortality, including administration of prothrombin complex concentrate (PCC) and procedures to stop the bleeding, such as surgical, radiological or endoscopic procedures.

Description of major bleeds included in the analysis

The major bleeds were assessed by means of time-to-first major bleed. Only major bleeds that occurred during the on-treatment period (period in which patients received the study drug or within 3 days after the study drug was stopped or interrupted) were eligible.

Statistical analysis

The results are presented as counts and percentages. Kaplan Meier curves were calculated for the cumulative rates of major bleeds in both treatment groups. Additional information
about the statistical analysis in the Hokusai-VTE study is described in the original article (9). A logistic regression model was applied for the analysis of the clinical presentation and course within the major bleeding group. Odds ratios (OR) were computed for the combined categories 3 and 4 between the edoxaban and VKA group for both classifications. In addition, a Cox proportional hazard regression analysis was performed. Outcome was defined as time to onset of major bleedings with combined clinical presentation or clinical course 3 and 4. Patients without clinical presentation or course in categories 3 and 4 were censored. All patients who received at least one dose of study medication were included in the analysis.

Results

Major bleeding in Hokusai-VTE study
A total of 8240 patients were included in the Hokusai-VTE study. Of these patients, 4118 were treated with edoxaban and 4122 patients received standard care with VKA. The primary safety outcome of first major and clinically relevant non-major bleeding occurred in 349 patients treated with edoxaban and in 423 patients assigned to VKA (hazard ratio [HR] 0.81, CI 0.71-0.94; p=0.004) (9). Major bleeds were observed in 56 of the edoxaban treated patients and in 66 of the VKA treated patients (HR 0.84, CI 0.59-1.21; p=0.35) (9). Kaplan Meier curves are shown in Figure 8.1.

Descriptive information of major bleeding events
Data of one patient with a major bleed from the VKA group was not available for the current analysis. In total, 56 major bleeds in patients receiving edoxaban and 65 major bleeds in patients treated with VKA were classified. The mean age in the edoxaban group was 64±15 years and in the VKA group 66±14 years and was not statistically different (p=0.58). The distribution of sex was also not different between the groups (edoxaban group 39% male and VKA group 52% male; p=0.15). In the edoxaban group 75% of patients had an index DVT compared to 79% in the VKA group (p=0.65). The median day of presentation was 38 in the edoxaban group (interquartile range [IQR] 9-93) and 77 in the VKA group (IQR 13-176; p=0.41). In edoxaban recipients, the distribution of bleeding type was 9% intracranial, 48% gastrointestinal (GI), 16% vaginal, 5% cutaneous/soft tissue and 22% other bleeds. For VKA recipients, 28% intracranial, 26% GI, 5% vaginal, 14% cutaneous/soft tissue and 27% other bleeds were observed.

Results clinical presentation
More than half of the patients with major bleeds in the edoxaban group presented in category 1 and 2 (54%) compared to 42% of the VKA treated group (Figure 8.2A). The
distribution of clinical presentation was similar, with a non-significant trend towards a milder presentation for the edoxaban treated patients. The most severe categories of clinical presentation (3+4) were observed in 46% of the edoxaban cases versus in 58% of the VKA treated patients (OR 0.62, 95%CI 0.30-1.27; p=0.19). The HR for time to onset of major bleeds with clinical presentation 3 or 4 was 0.68 (95%CI 0.41-1.12; p=0.13).

Results clinical course
The clinical course of the major bleeding events in the edoxaban group was categorised as 3 or 4 in 23% of patients and in 30% of VKA-related major bleeding events with an OR of 0.73 (95%CI 0.32-0.66; p=0.46) (Figure 8.2B). The accompanying HR for time to major bleeding event with clinical course 3 or 4 was 0.68 with a 95%CI of 0.34-1.38 (p=0.29).

From clinical presentation to clinical course
Table 8.2 shows the clinical course for patients presenting with a major bleeding event classified with categories 2 or 3 for both treatment groups.
Chapter 8

Of the edoxaban treated patients who presented with a category 2 major bleeding event (50%), category 1 clinical course was present in 14% of the patients, while 79% was categorized as category 2 clinical course and 7% as category 3. Of the edoxaban treated patients who had a category 3 bleeding at presentation (44%), clinical course category 1 or 2 was found in 60% of the patients; the remainder of patients had a clinical course 3 (36%) or 4 (4%).

For VKA treated patients presenting with a category 2 major bleed (31%), clinical course were categorized as 1 in 10%, as 2 in 85% and as 3 in 5% of the patients. Of the VKA recipients who had a category 3 bleed at presentation (57%), category 1 or 2 of clinical course was applied in 54% of the patients, while the remaining 46% had a clinical course category 3 or 4.

Table 8.2. From clinical presentation to clinical course

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Clinical Presentation Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edoxaban</td>
</tr>
<tr>
<td>Category 1</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Category 2</td>
<td>22 (79%)</td>
</tr>
<tr>
<td>Category 3</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Category 4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
</tr>
</tbody>
</table>

Figure 8.2. Clinical presentation and course of major bleeding episodes

Clinical presentation (A) and clinical course (B) of all major bleeding events that occurred in the on treatment period with edoxaban or VKA in the Hokusai-VTE study.

Of the edoxaban treated patients who presented with a category 2 major bleeding event (50%), category 1 clinical course was present in 14% of the patients, while 79% was categorized as category 2 clinical course and 7% as category 3. Of the edoxaban treated patients who had a category 3 bleeding at presentation (44%), clinical course category 1 or 2 was found in 60% of the patients; the remainder of patients had a clinical course 3 (36%) or 4 (4%).

For VKA treated patients presenting with a category 2 major bleed (31%), clinical course were categorized as 1 in 10%, as 2 in 85% and as 3 in 5% of the patients. Of the VKA recipients who had a category 3 bleed at presentation (57%), category 1 or 2 of clinical course was applied in 54% of the patients, while the remaining 46% had a clinical course category 3 or 4.
Clinical presentation category 3

<table>
<thead>
<tr>
<th>Clinical Presentation Category 3</th>
<th>Edoxaban</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>1 (4%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Category 2</td>
<td>14 (56%)</td>
<td>16 (43%)</td>
</tr>
<tr>
<td>Category 3</td>
<td>9 (36%)</td>
<td>15 (41%)</td>
</tr>
<tr>
<td>Category 4</td>
<td>1 (4%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>37</td>
</tr>
</tbody>
</table>

Clinical course for major bleeding events classified as clinical presentation 2 (A) and 3 (B), to give an indication of the dynamics in the clinical impact of major bleeding events

Treatment of major bleeds

Vitamin K was administered to none of the edoxaban treated patients and to 4 patients (6%) with a VKA-associated major bleeding. Thirteen patients (23%) with an edoxaban-related major bleed and 19 patients (29%) with a VKA-related major bleed received fresh frozen plasma. Packed cells were administered in 34 (61%) versus 27 (42%) patients treated with edoxaban and VKA respectively. Only 1 patient (2%) in the edoxaban and 2 patients (3%) in the VKA treated group received PCC. All three patients receiving PPC had an intracranial bleed. In the edoxaban group, FFP was administered to 13 patients and in the VKA group to 19 patients. FFP was mainly given for retroperitoneal, intracranial and gastro-intestinal bleeds. One (2%) of the major bleeding events in the edoxaban group and 5 (8%) in the VKA group were fatal. Interventions applied to control the bleeding include endoscopy with clip placement for GI bleeds, burr holes for subdural hematomas, drainage of pericardial and joint bleeds and curettage for vaginal bleeds. None of the applied interventions differed significantly between the treatment groups (Table 8.3).

Table 8.3. Interventions to treat the major bleeding

<table>
<thead>
<tr>
<th>Prohaemostatic intervention</th>
<th>LMWH/Edoxaban N=56</th>
<th>LMWH/VKA N=65</th>
<th>P-value (chi square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>0 (0)</td>
<td>4 (6%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Prothrombin complex concentrate</td>
<td>1 (2%)</td>
<td>2 (3%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>13 (23%)</td>
<td>19 (29%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Packed cells</td>
<td>34 (61%)</td>
<td>27 (42%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Procedure to stop bleeding</td>
<td>18 (32%)</td>
<td>15 (23%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Fatality</td>
<td>1 (2%)</td>
<td>5 (8%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Applied interventions to treat the major bleeding episodes
Discussion

The results from our analysis of the major bleeding events from the Hokusai-VTE study suggest that edoxaban-associated major bleeding events have a similar presentation and course when compared to major bleeding events with VKA in patients treated for venous thromboembolism, although we observed a non-significant trend towards a milder presentation and a milder course in the edoxaban recipients. Major bleeding events with a presentation in category 2 or 3 had a comparable distribution on the subsequently classified clinical course between edoxaban and VKA. The treatment of major bleeding events did not differ between edoxaban and VKA treated patients; half of the patients in both treatment groups received packed cells and about a quarter of the patients got FFP administered. Other prohaemostatic interventions were only applied in a small proportion of the patients in both treatment groups. These results contribute to the insight in severity of presentation, clinical relevance, course or outcome and management of major bleeding episodes. Besides the fact that major bleeding complications occur less often in DOAC treated patients (11), we showed that the clinical presentation and course of those bleeds is in general similar to and potentially less severe than with VKA treatment. It should be realized that at the time of this study, no specific antidote for edoxaban was available. Whether such an antidote would influence the clinical course is speculative.

A possible explanation for the observed trend towards a less severe presentation for the edoxaban group could be the relative unstable anticoagulant effect of VKA (17). Patients using VKA may not be safely and effectively anticoagulated all the time because of unpredictability of VKA anticoagulant properties, interactions with food and concomitant medication and intra- and inter-individual variability. Patients therefore may experience episodes of overtreatment, which can contribute to more severe bleeding. Warfarin is a VKA with a longer half-life than edoxaban. Hence, bleeding complications may be prolonged or stimulated when the drug is present in the system for a prolonged period of time (18). Edoxaban has a stable pharmacological profile and is therefore postulated to have a more predictable anticoagulant effect, leading to fewer severe bleeding events. Another possible explanation is the observed higher number of ICH in the VKA group compared to edoxaban in the Hokusai-VTE study (9). There were no fatal ICH in the edoxaban group versus 5 in the VKA group. Nonfatal ICH were observed in 5 edoxaban treated patients and 12 VKA treated patients. This difference in ICH likely plays a role in the observed numbers of major bleeds with severe presentation and course, because ICH are almost always severe and therefore fall in category 3 or 4 of both classifications.

The current observation that edoxaban leads to fewer major bleeds with a possible milder presentation is supported by earlier studies with dabigatran. Dabigatran is an oral direct thrombin inhibitor and has been shown to cause less intracranial bleeds than
Clinical impact of bleeding with edoxaban

treatment with VKA (19,20). Furthermore, bleeding complications with dabigatran had a milder course and were associated with a shorter length of stay in hospital, in a non-randomized comparison (21). Results from the Einstein studies where rivaroxaban was compared to VKA in treatment of VTE, showed that rivaroxaban-associated major bleeding events had a less severe presentation and had a milder course than VKA bleeding episodes (15). For the sub-analysis of the major bleeds in the Einstein studies, the same classification schemes regarding clinical presentation and course were used as in the present study.

Strengths of our analysis and the previous analysis of the Einstein studies are the use of predefined criteria, the long term follow-up and the fact that information on major bleeds was recorded prospectively on case report forms. Comprehensive medical information was available about symptoms, hemodynamic parameters, laboratory results and interventions to control the bleeding, and could be applied to classify the event according to severity of presentation and course. As a result, our analysis is not just a typical retrospective data collection study. Another strength of the current study is the double-blind design (9), hence the treating physician was unaware of treatment allocation and the bleeding episode was treated using clinical judgment. The findings are robust because all bleeding events were adjudicated by three independent experienced clinicians who were unaware of the assigned treatment regimen at the time of adjudication. A final aspect is that we only adjudicated a single most severe event per patient. From a methodological point of view one should always take one event, since other events are not independent observations in a single patient. Including those latter events could bias the results.

The present analysis has several limitations. One limitation is that the current classification schemes lack in validation and have only been used on data from the Einstein and Hokusai studies. Further research is needed to confirm the results and the quality and reproducibility of the classification schemes. It would be of interest to further validate these scores in other DOAC trials, as well as in other settings, such as in trials of patients with atrial fibrillation. A second limitation is the modest sample size. Although the Hokusai-VTE study included 8240 patients with DVT, PE or both, major bleeding only occurred in 56 edoxaban and 65 VKA treated patients (9). The results from this study should therefore be confirmed with data from other phase III studies with as a results more major bleeding events. In addition, although the protocol did provide pre-specified guidance for the treatment of bleeding events, the final decision of the applied strategy was made by the treating physician. The limited use of vitamin K, fresh frozen plasma and PCC is remarkable. While it is uncertain that PCC work for DOACs and edoxaban in particular, vitamin K and PCC have been shown to be effective for VKA-associated bleeding (22,23). The fact that these agent have not been used frequently is therefore to the disadvantage of VKA treated patients. This may have influenced the results. Another limitation is the potential for overlap and interdependence between the two classification schemes, since presentation is likely to influence clinical course.
For example, if all or most category 4 clinical presentations would also have a category 4 clinical course. But as shown in the result section, 56% of the edoxaban treated patients that presented with a category 3 bleeding had a category 2 clinical course. A comparable observation was made for VKA treated patients. So events with a severe presentation can have a mild clinical course, and the other way round. Therefore, the two classifications are largely independent. We also minimized the potential for overlap by first presenting the adjudicators with relevant information to categorize the event for severity of presentation and then, in a separate session and in random order, relevant information about the course was presented. In this way the adjudicators could not be influenced by their own adjudication of the presentation. Finally, the current classification of major bleeding events according to the ISTH criteria (14) has been standardized and used in all phase III DOAC trials. However, we observed that major bleeding events are quite heterogeneous with large variation in clinical severity and course, indicating that all major bleeds do not have the same clinical significance.

In conclusion, edoxaban-associated major bleeding events have at least a similar presentation and course as major bleeding events with VKA in patients treated for venous thromboembolism. These results provide insight in the characteristics of bleeding in edoxaban treated patients and may assure physicians that it is safe to prescribe this medication. Should a major bleeding occur, its clinical presentation and clinical course are not worse than in VKA treated patients.
References


