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CHAPTER 13

EDOXABAN FOR TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER: RATIONALE AND DESIGN OF THE HOKUSAI VTE-CANCER STUDY

Nick van Es, Marcello Di Nisio, Suzanne M. Bleker, Annelise Segers, Michele F. Mercuri, Lee Schwocho, Ajay Kakkar, Jeffrey I. Weitz, Jan Beyer-Westendorf, Zoltan Boda, Marc Carrier, Jaromir Chlumsky, Hervé Décosus, David Garcia, Harry Gibbs, Pieter W. Kamphuisen, Manuel Monreal, Paul Ockelford, Ingrid Pabinger, Peter Verhamme, Michael A. Grosso, Harry R. Büller, and Gary E. Raskob

Thrombosis and Haemostasis, 2017
ABSTRACT

BACKGROUND Direct oral anticoagulants may be effective and safe for treatment of venous thromboembolism (VTE) in cancer patients, but they have not been compared with low-molecular weight-heparin (LMWH), the current recommended treatment for these patients.

OBJECTIVE AND METHODS The Hokusai VTE-cancer study is a randomized, open-label, clinical trial to evaluate whether edoxaban, an oral factor Xa inhibitor, is non-inferior to low-molecular-weight heparin for treatment of VTE in patients with cancer. We present the rationale and some design features of the study. One such feature is the composite primary outcome of recurrent VTE and major bleeding during a 12-month study period. These two complications occur frequently in cancer patients receiving anticoagulant treatment and have a significant impact. The evaluation beyond 6 months will fill the current gap in the evidence base for the long-term treatment of these patients. Based on the observation that the risk of recurrent VTE in patients with active cancer is similar to that in those with a history of cancer, the Hokusai VTE-cancer study will enrol patients whose cancer was diagnosed within the past 2 years. In addition, patients with incidental VTE are eligible because their risk of recurrent VTE is similar to that in patients with symptomatic disease.

CONCLUSION The unique design features of the Hokusai VTE-cancer study should lead to enrolment of a broad spectrum of cancer patients with VTE who could benefit from oral anticoagulant treatment.
INTRODUCTION

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in cancer patients, and cancer patients with VTE are at increased risk of recurrent thromboembolism. Current international guidelines recommend low-molecular-weight heparin (LMWH) monotherapy over vitamin K antagonists (VKAs) for the treatment of cancer-associated VTE based on the lower risk of VTE recurrence in LMWH-treated patients. This better efficacy of LMWH is, in part, explained by the often problematic anticoagulation control of VKAs in cancer patients due to frequent gastrointestinal disturbances and drug-drug interactions. In contrast, LMWH offers stable pharmacokinetics and pharmacodynamics, but is a burden for patients because it requires daily subcutaneous injections.

Like LMWH, direct oral anticoagulants (DOACs), which include inhibitors of factor Xa or thrombin, have minimal food or drug interactions allowing for fixed dosing without routine coagulation monitoring. In the setting of VTE treatment in the general population, a meta-analysis indicates that DOACs are as effective as VKAs for VTE treatment, but are associated with less bleeding. Although the subgroup analysis of cancer patients showed encouraging results, the use of DOACs in cancer patients is currently not recommended, mainly because patients for whom long-term LMWH therapy was anticipated were excluded. Therefore, the cancer patients enrolled in the DOAC trials may have had a more favourable prognosis compared with the broader population of cancer patients with VTE. Last and most importantly, the efficacy and safety of DOACs have not been evaluated directly against LMWH, the currently recommended treatment for VTE in cancer patients.

Edoxaban is an oral, direct factor Xa inhibitor that has recently been approved for the treatment of acute VTE based on the results of the Hokusai-VTE study. This was a phase 3 randomized double-blind trial, in which edoxaban was shown to be non-inferior to traditional VKA therapy for preventing recurrent symptomatic VTE while causing significantly less bleeding. The analysis of the a priori defined subgroup of cancer patients suggested that edoxaban may be effective and safe in these patients. The Hokusai VTE-cancer study is designed to examine this possibility; this phase 3b clinical trial will compare the effectiveness and safety of edoxaban and LMWH for the treatment of VTE associated with cancer (clinicaltrials.gov; NCT02073682). The goal of this article is to summarize the rationale and design of the Hokusai VTE-cancer study and to provide a background for various innovative study design features.
STUDY OVERVIEW

Hokusai VTE-cancer is a multinational, prospective, randomized, open-label, blinded endpoint (PROBE), non-inferiority study comparing edoxaban with dalteparin for the prevention of the combined outcome of recurrent VTE or major bleeding in cancer patients with acute VTE. One thousand subjects will be randomized after informed consent to receive either a short course of LMWH followed by edoxaban or dalteparin monotherapy and observed during a 12-month study period (Figure 1). Before randomization, subjects will be stratified by bleeding risk and by the need for edoxaban dose adjustment (Panel 1). The intention is to treat patients for 12 months with the allocated study treatment, but continuation of anticoagulation beyond 6 months will be based on the risk-benefit assessment of the treating physician and/or on patient preference. This approach is consistent with current evidence-based guideline recommendations.2,3

Figure 1. Overview of the design of the Hokusai VTE-cancer study

Abbreviations: IU, international units; LMWH, low-molecular-weight heparin; od, once daily; PROBE, prospective randomized open blinded endpoint; R, randomization; VTE, venous thromboembolism.

* Dose adjustment to edoxaban 30 mg od in patients with a body weight of 60 kg or less, a creatinine clearance between 30 and 50 mL/min inclusive, or concomitant use of P-glycoprotein inhibitors.
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Panel 1. Stratification factors

**Increased bleeding risk (assessed at time of randomization):**
- body weight 60 kg or less;
- surgery within 2 weeks prior to randomization;
- use of antiplatelet agents (e.g., aspirin 100 mg/day or less) that will continue during the study
- brain tumour or brain metastases present at the time of randomization;
- metastatic disease present at the time of randomization;
- regionally advanced cancer present at the time of randomization;
- gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization;
- urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization;
- bevacizumab use at randomization or given within the 6-week period prior to randomization.

**Need for dose adjustment:**
- body weight 60 kg or less;
- creatinine clearance between 30 and 50 mL/min inclusive;
- concomitant use of P-glycoprotein inhibitors.

Patient population and eligibility

Adult cancer patients with symptomatic or incidental proximal lower extremity DVT (i.e. popliteal, femoral, or iliac vein thrombosis), or symptomatic or incidental PE (involving segmental or more proximal pulmonary arteries), or both, confirmed by diagnostic imaging are eligible for the study. Cancer must be other than basal-cell or squamous cell carcinoma of the skin, be active or diagnosed within 2 years prior to randomization, and objectively confirmed. Active cancer is defined by any of the following: (a) diagnosis of cancer within the past 6 months, (b) recurrent, regionally advanced, or metastatic disease, (c) currently receiving treatment or having received any treatment for cancer during the 6 months prior to randomization, or (d) a hematologic malignancy not in complete remission. The treating physician should have an intention to treat the subject for at least 6 months with parenteral LMWH. Exclusion criteria are listed in Panel 2.

LMWH/edoxaban regimen

In the LMWH/edoxaban group, therapeutic doses of LMWH will be administered subcutaneously for at least 5 days. The choice of the LMWH type and lead-in duration will be left to the treating physician. Thereafter, oral edoxaban will be given at a dose of 60 mg once daily for the remainder of the treatment period. A reduced edoxaban dose is used for patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min), or a body
weight of 60 kg or less, or who are receiving strong P-glycoprotein inhibitors. The edoxaban regimen was selected based on the Hokusai-VTE study.⁸

**Panel 2. Exclusion criteria**

| 1. | Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of deep vein thrombosis and/or pulmonary embolism; |
| 2. | More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (low-molecular-weight heparin, unfractionated heparin, and fondaparinux per local labelling), direct oral anticoagulant, or vitamin K antagonist prior to randomization to treat the current (index) episode; |
| 3. | Treatment with therapeutic doses of an anticoagulant other than that used for pre-treatment of the current (index) venous thromboembolism episode prior to randomization; |
| 4. | Active bleeding or any contraindication for treatment with low-molecular-weight heparin/dalteparin or edoxaban; |
| 5. | Indication for dalteparin other than deep vein thrombosis and/or pulmonary embolism; |
| 6. | An Eastern Cooperative Oncology Group performance status of 3 or 4 at the time of randomization; |
| 7. | Calculated creatinine clearance less than 30 mL/min; |
| 8. | History of heparin associated thrombocytopenia; |
| 9. | Acute hepatitis, chronic active hepatitis, liver cirrhosis; |
| 10. | Hepatocellular injury with concurrent transaminase (alanine transaminase/aspartate transaminase more than 3 x upper limit of normal) and bilirubin (more than 2 x upper limit of normal) elevations in the absence of a clinical explanation; |
| 11. | Life expectancy less than 3 months; |
| 12. | Platelet count less than 50,000/mL; |
| 13. | Uncontrolled hypertension as judged by the Investigator (e.g. systolic blood pressure more than 170 mmHg or diastolic blood pressure more than 100 mmHg despite antihypertensive treatment); |
| 14. | Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding; |
| 15. | Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs including both cyclooxygenase-1 and cyclooxygenase-2 inhibitors for ≥ 4 days/week anticipated to continue during the study; |
| 16. | Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any two antiplatelet agents including aspirin plus any other oral or intravenous antiplatelet drug) anticipated to continue during the study; |
| 17. | Treatment with the P-glycoprotein inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study; |
| 18. | Systemic use of the P-glycoprotein inhibitors ketoconazole,itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use is permitted; |
| 19. | Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study. |
Dalteparin regimen

In the standard of care group, dalteparin will be administered subcutaneously at a dose of 200 IU/kg for 30 days, with a maximal daily dose of 18,000 IU. Thereafter, the dalteparin dose will be reduced to 150 IU/kg for the remainder of the study period. In this way, patients are maximally protected against recurrent VTE in the initial treatment period when the incidence of recurrent VTE is expected to be highest. The reduced dalteparin dose for long-term treatment should offer adequate protection, but is associated with a lower risk of bleeding, which is especially important in cancer patients who are intrinsically at a higher risk of bleeding than those without cancer. Moreover, dalteparin is approved in many parts of the world for VTE treatment in cancer patients following the results of the CLOT trial in which an identical dalteparin regimen was used, although other LMWH are registered in other countries as well.

Outcomes

The primary study outcome is the composite of recurrent VTE and major bleeding. Recurrent VTE is defined as (a) symptomatic confirmed (new) DVT or (new) PE, (b) incidental (new) proximal DVT of the legs or incidental (new) PE located in segmental or more proximal pulmonary arteries, or (c) fatal PE including unexplained death for which PE cannot be ruled out. Incidental VTE is defined as thrombi that are detected during imaging tests performed for other reasons than VTE suspicion, such as cancer staging and treatment response evaluation. The definition of major bleeding will follow the criteria of the International Society of Hemostasis and Thrombosis and includes overt bleeding that is fatal, occurs in a critical area or organ, causes a fall in haemoglobin of 2 g/dL (or 1.24 mmol/L) or more, or leads to transfusion of two or more units of whole blood or packed red blood cells. An important secondary outcome is event-free survival, defined as the proportion of subjects who remain free of recurrent VTE, bleeding events, and death, since minimizing the number of these events is the ultimate goal of antithrombotic therapy. Other secondary and exploratory outcomes are listed in Panel 3. All suspected clinical outcomes and all deaths during the 12-month study period will be adjudicated by a clinical events committee whose members are unaware of treatment allocation.
Panel 3. Secondary and exploratory outcomes

Secondary outcomes
- Recurrent venous thromboembolism;
- Major bleeding;
- Clinically relevant non-major bleeding;
- Major and clinically relevant non-major bleeding;
- Event-free survival, defined as the proportion of subjects over time free of recurrent venous thromboembolism, bleeding events, and death;
- Death related to venous thromboembolism;
- Mortality from all causes;
- Recurrent deep vein thrombosis;
- Recurrent pulmonary embolism;
- Healthcare resource utilization for potential recurrent venous thromboembolism and bleeding events.

Exploratory outcomes
- Cardiovascular events (myocardial infarction, stroke, and systemic embolic events);
- Thrombotic events at other locations;
- Reason for permanent early discontinuation of study drug.

Sample size and statistical analysis

The study hypothesis is that edoxaban will be non-inferior to dalteparin with respect to the occurrence of recurrent VTE or major bleeding, with a non-inferiority margin for the hazard ratio (HR) of 1.5 and a type I error of 0.05 (two-sided). Assuming a HR of 1.0, approximately 1,000 patients will be required to observe an expected total of 200 overall primary events, which will ensure at least 80% power for confirming non-inferiority.

The primary outcome analysis will be based on the modified intention-to-treat population, and includes all randomized patients who have received at least one dose of study drug. The time to the first event of the composite primary outcome during the 12-month study period will be analysed using a Cox proportional hazards model including treatment group and the stratification factors as covariates. Secondary analyses will be performed for events occurring during the first 6 months of treatment (the minimum recommended duration in all patients), since study physicians may decide to switch or stop anticoagulant treatment after 6 months. A secondary analysis using the per-protocol population will also be done.
INNOVATIVE FEATURES AND UNIQUE ASPECTS

The Hokusai VTE-cancer study incorporates various innovative design features that warrant explanation. In the following paragraphs, a scientific basis is provided for some of these aspects based on available literature and individual data from the cancer population enrolled in the Hokusai-VTE study. Furthermore, the expected results are discussed and put in perspective with results from published trials which have evaluated VTE treatment in cancer patients.

Rationale for expanding eligibility to patients with a history of cancer within 2 years

The definition of ‘active cancer’ in the setting of VTE is not universal. Although this classification can be readily applied to cancer patients with measurable disease or a haematological malignancy that is not in remission, many patients are more difficult to categorize. The two largest VTE trials to date have enrolled patients diagnosed with cancer or receiving any treatment for cancer during the previous 6 months. As a consequence, a patient diagnosed with VTE 5 months after curative surgery for colon cancer is regarded as a patient with ‘active cancer’, despite being tumour-free and not receiving antineoplastic treatment for 5 months. The same holds true for women developing VTE while on long-term hormonal therapy for up to 5 years after breast cancer surgery. From an oncological perspective, many patients are not truly considered cancer-free until the end of this 5-year post-surgery period. Considering LMWH as the primary treatment option in these subgroups of cancer patients would be justified if they have a similar risk of recurrence and bleeding following a VTE diagnosis as patients with evident active cancer. However, at present it is unknown whether the arbitrary period beyond 6 months from cancer diagnosis or the end of cancer treatment to the occurrence of VTE properly classifies all patients with seemingly cured cancer who may benefit from LMWH.

In the Hokusai-VTE study, 778 patients were enrolled who were classified by the treating physician as having ‘active cancer’ or a ‘history of cancer’ at randomization. Using individual patient data, 165 of these 778 patients were classified as having active cancer (e.g. solid measurable disease or haematological malignancy not in remission) and 507 patients with cancer that was curatively treated 2, 2 to 5, or more than 5 years before the current VTE diagnosis. The remaining 106 patients were excluded from the analysis due to a diagnosis of non-melanoma skin cancer or a benign condition erroneously classified as cancer. Among all 672 cancer patients, the cumulative incidence of recurrent VTE at the end of the 12-month
period was 5.8% in the active cancer group and 5.1% in the history of cancer group (Gray’s test P=0.7; Figure 2A). The rates of recurrent VTE in patients with cancer that was treated within 2 years, 2 to 5 years, or more than 5 years were comparable (Figure 2B). These findings suggest that patients with acute VTE and a history of cancer have a risk of recurrent VTE that is comparable to the risk of patients with a more narrow definition of active cancer. In addition, the risk of recurrent VTE in patients with a history of cancer does not appear to be dependent on the time since cancer cure, suggesting that a broader spectrum of cancer patients may benefit from LMWH therapy. Based on these findings, the Hokusai VTE-cancer study will allow patients to be enrolled when the cancer is active or was diagnosed within 2 years prior to randomization, thereby providing insight into the potential benefit of LMWH or edoxaban for patients with a more remote history of cancer.

Rationale for combined outcome of recurrent VTE and major bleeding

Cancer patients with VTE are at increased risk of both recurrent VTE and anticoagulation-related bleeding compared with non-cancer patients.13 These complications occur frequently in cancer patients10,12,14 and have a significant impact on the patient’s well-being. Recurrent VTE and major bleeding are potentially life-threatening conditions with a case-fatality rate within the first 3 to 6 months of 11% for both in the general population.15 Similarly, in the 165 patients with active cancer in the Hokusai-VTE trial, 1 of 9 (11%) recurrent VTE and 1 of 8 (13%) major bleeding events were fatal. The anticoagulant treatment of VTE should aim to prevent recurrent VTE with a minimal risk of major bleeding. As a consequence, it is more realistic to consider these two outcomes equally in a study evaluating a new treatment option. Furthermore, these outcomes are often correlated during or after antithrombotic treatment. For example, a bleeding event may lead to cessation of anticoagulant therapy, thereby increasing the risk of recurrent VTE. Conversely, recurrent VTE is often managed by a change in anticoagulant treatment, which may increase the risk of bleeding. Therefore, the primary outcome of the Hokusai VTE-cancer study is the composite of recurrent VTE and major bleeding. Although a primary outcome combining efficacy and safety has been used before in the setting of cancer-associated VTE,16 the Hokusai VTE-cancer study is the first to adopt it in a randomized controlled trial this large.
Rationale and design of Hokusai VTE-cancer

The rates of recurrent VTE in patients with cancer that was treated within 2 years, 2 to 5 years, or more than 5 years were comparable (Figure 2B). These findings suggest that patients with acute VTE and a history of cancer have a risk of recurrent VTE that is comparable to the risk of patients with a more narrow definition of active cancer. In addition, the risk of recurrent VTE in patients with a history of cancer does not appear to be dependent on the time since cancer cure, suggesting that a broader spectrum of cancer patients may benefit from LMWH therapy. Based on these findings, the Hokusai VTE-cancer study will allow patients to be enrolled when the cancer is active or was diagnosed within 2 years prior to randomization, thereby providing insight into the potential benefit of LMWH or edoxaban for patients with a more remote history of cancer.

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Figure 2. Cumulative incidence of recurrent venous thromboembolism in Hokusai-VTE during the overall study period

(A) Patients with active cancer (N=165) and patients with a history of cancer (N=507), and (B) patients with a history of cancer 0 to 2 years (N=101), 2 to 5 years (N=67), 5 years or more (N=135), or unknown (N=204) time since cancer curation.
**Rationale for including incidental DVT or PE as inclusion criterion and as a component of the primary outcome**

Up to half of all PE events in cancer patients are not clinically suspected at the time of diagnosis but rather incidentally detected on imaging tests.\(^\text{17}\) Although the term incidental PE implies that the episode is asymptomatic, many of these patients do report signs and/or symptoms consistent with PE, such as fatigue or shortness of breath.\(^\text{18}\) These symptoms are, however, non-specific and may have been erroneously attributed to the effects of the cancer or cancer therapy. Incidental PE is not harmless which is underscored by the fact that half of all clots are located in the main or lobar pulmonary arteries and that the outcome in terms of recurrence, anticoagulation-related bleeding, and overall mortality appears to be comparable to the outcomes in patients with symptomatic events.\(^\text{19}\) As a consequence, in the absence of trials evaluating treatment options for incidental VTE, international guidelines recommend that these patients receive similar initial and long-term treatment as for symptomatic VTE.\(^\text{2,3}\) Therefore, in the Hokusai VTE-cancer study, incidental PE and lower extremity DVT will be considered as an inclusion criterion and also as a component of the primary outcome.

**Rationale for study duration of 12 months**

The recommended treatment duration for VTE in patients with cancer is at least 6 months.\(^\text{2,3,5}\) Indefinite treatment needs to be strongly considered in patients in whom cancer is not cured.\(^\text{3}\) However, after 6 months of treatment, physicians are often faced with a dilemma due to the absence of data from studies comparing LMWH with VKAs beyond 6 months. Hence, in clinical practice, the choice of anticoagulant for the remainder of the treatment duration varies among physicians and is mainly based on patient and physician preference.\(^\text{20}\) However, the recent DALTECAN cohort study has demonstrated that LMWH therapy for 6 to 12 months is associated with similar rates of VTE recurrence and major bleeding compared with treatment for 2 to 6 months; findings that highlight the need for evaluation of VTE treatment beyond 6 months in these patients.\(^\text{14}\) Therefore, in the Hokusai VTE-cancer study, it is the intent to treat all subjects for 12 months, which will add significantly to the evidence of anticoagulant treatment beyond 6 months. In addition, all subjects will be followed for 12 months after randomization irrespective of the actual treatment duration. This is important because bleeding, including clinically relevant non-major bleeding events, may lead to discontinuation or interruption of anticoagulant therapy which increases the risk of subsequent recurrent VTE events; such events would not be captured using traditional on-treatment analyses. The Hokusai VTE-cancer study aims to provide that information with
the longer follow-up, and will fill a current gap in the evidence base for clinical decision making.\textsuperscript{3,21}

**Feasibility**

Approximately 20\% of all VTE cases are related to cancer\textsuperscript{1} and cancer patients with VTE have a three-fold higher risk of recurrent VTE and a two- to six-fold higher incidence of anticoagulation-related major bleeding compared to non-cancer patients.\textsuperscript{13,22} Evaluating a new VTE treatment in this population is challenging, because the primary focus is obviously on treating their cancer. To enrol a broad spectrum of patients and improve the external validity, the Hokusai VTE-cancer study implemented patient- and investigator-friendly features. First, the study has an open-label design since double-blinding would require daily subcutaneous injections of a placebo drug in the edoxaban recipients, which is difficult to justify. As a consequence, half of patients will receive an oral drug in a fixed dose, which may increase the willingness to participate. Second, the study burden will be kept as low as possible by minimizing the number of study visits to month 1 and 3 and every 3 months thereafter until study completion. This is important because many cancer patients, especially those with active cancer, already have multiple clinic visits for their care. Lastly, to minimize the work load, hospitalizations for (a) pre-planned procedures or diagnostic tests (including cancer staging), (b) cancer treatment, (c) diagnostic work-up or treatment of worsening cancer, or (d) complications of cancer treatment (e.g. work-up for febrile neutropenia or blood transfusion for anemia) are regarded as clinically anticipated and will therefore not be reported as serious adverse events. In this way, the feasibility of the Hokusai VTE-cancer study is enhanced by making it a practical and pragmatic study for both patients and investigators.

**Expected results and sample size considerations**

The Hokusai VTE-cancer study will be the first to directly compare LMWH with a DOAC for VTE treatment in patients with cancer. Hence, considerations regarding the anticipated results can only be guided by indirect comparisons available from published literature. We therefore performed a frequentist network meta-analysis\textsuperscript{23} to quantify the expected relative difference between Xa-inhibitors and LMWH with respect to the composite of recurrent VTE and major bleeding. Data were used from studies comparing VKAs with LMWH for treatment of cancer-associated VTE that were included in the latest Cochrane review on this topic\textsuperscript{10,16,24–26} supplemented by the recent CATCH trial.\textsuperscript{12} In addition, data were used from the
A subgroup of cancer patients enrolled in phase 3 trials comparing VKAs with a factor Xa-inhibitor for VTE treatment. A combined outcome of recurrent VTE and major bleeding was calculated for each study by adding numbers of the separate outcomes. In the traditional random effects meta-analysis, both LMWH and factor Xa inhibitors were associated with a significantly reduced risk of recurrent VTE or major bleeding compared with VKAs with an odds ratio (OR) of 0.72 (95% confidence interval [CI], 0.57 to 0.89) and 0.60 (95% CI, 0.41 to 0.88), respectively (Figures 3 and 4). In the subsequent frequentist network meta-analysis, treatment with factor Xa inhibitors was associated with a non-significant lower risk of the combined outcome of recurrent VTE or major bleeding compared with LMWH (OR 0.83; 95% CI, 0.54 to 1.29; Figure 5). These results suggest that one might expect a comparable risk of recurrent VTE or major bleeding with LMWH and factor Xa inhibitors in future trials. The point estimate is non-significantly in favour of factor Xa inhibitors, which is reassuring for confirming non-inferiority of edoxaban to dalteparin in the treatment of cancer-associated VTE, especially given the non-inferiority margin for the HR of 1.5.

**Figure 3. Direct meta-analysis of studies comparing low-molecular-weight heparin with vitamin K antagonists for treatment of venous thromboembolism in cancer patients: combined outcome of recurrent venous thromboembolism and major bleeding**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LMWH Events</th>
<th>VKA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td>Meyer 2002 (CANTHANOX)</td>
<td>7</td>
<td>67</td>
<td>16</td>
<td>71</td>
<td>0.70 (0.57 to 0.89)</td>
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<tr>
<td>Lee 2003 (CLOT)</td>
<td>46</td>
<td>336</td>
<td>66</td>
<td>336</td>
<td>0.50 (0.41 to 0.61)</td>
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<tr>
<td>Deitche 2006 (ONCENOX)</td>
<td>10</td>
<td>53</td>
<td>10</td>
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<td>Hull 2006 (Main-LITE)</td>
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<td>100</td>
<td>23</td>
<td>100</td>
<td>0.51 (0.33, 0.80)</td>
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<tr>
<td>Lee 2014 (CATCH)</td>
<td>44</td>
<td>449</td>
<td>57</td>
<td>451</td>
<td>0.78 (0.54, 1.12)</td>
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<tr>
<td>Total (95% CI)</td>
<td>1005</td>
<td>990</td>
<td>100.0%</td>
<td>0.72 (0.58, 0.90)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4. Direct meta-analysis of studies comparing a Xa-inhibitor with vitamin K antagonists for treatment of venous thromboembolism in cancer patients: combined outcome of recurrent venous thromboembolism and major bleeding**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Xa-inhibitor Events</th>
<th>VKA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td>AMPHISTEIN 2013</td>
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<td>81</td>
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<td>78</td>
<td>12.9%</td>
</tr>
<tr>
<td>EINSTEIN-DVT 2010</td>
<td>6</td>
<td>118</td>
<td>10</td>
<td>89</td>
<td>14.9%</td>
</tr>
<tr>
<td>EINSTEIN-PED 2012</td>
<td>6</td>
<td>114</td>
<td>6</td>
<td>109</td>
<td>11.7%</td>
</tr>
<tr>
<td>Hokusai 2013</td>
<td>24</td>
<td>378</td>
<td>41</td>
<td>393</td>
<td>60.5%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>691</td>
<td>669</td>
<td>100.0%</td>
<td>0.60 (0.41, 0.88)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $T^2 = 0.00$; $Q_{df} = 1.06$, df = 3 (P = 0.79); $I^2 = 0\%$

Test for overall effect: $Z = 2.63$ (P = 0.009)
Rationale and design of Hokusai VTE-cancer

A combined outcome of recurrent VTE and major bleeding was calculated for each study by adding numbers of the separate outcomes. In the traditional random effects meta-analysis, both LMWH and factor Xa inhibitors were associated with a significantly reduced risk of recurrent VTE or major bleeding compared with VKAs with an odds ratio (OR) of 0.72 (95% confidence interval [CI], 0.57 to 0.89) and 0.60 (95% CI, 0.41 to 0.88), respectively (Figures 3 and 4). In the subsequent frequentist network meta-analysis, treatment with factor Xa inhibitors was associated with a non-significant lower risk of the combined outcome of recurrent VTE or major bleeding compared with LMWH (OR 0.83; 95% CI, 0.54 to 1.29; Figure 5). These results suggest that one might expect a comparable risk of recurrent VTE or major bleeding with LMWH and factor Xa inhibitors in future trials. The point estimate is non-significantly in favour of factor Xa inhibitors, which is reassuring for confirming non-inferiority of edoxaban to dalteparin in the treatment of cancer-associated VTE, especially given the non-inferiority margin for the HR of 1.5.

POSSIBLE IMPLICATIONS OF THE DESIGN OF THE HOKUSAI VTE-CANCER STUDY

The Hokusai VTE-cancer study has the potential to change the practice of VTE treatment in cancer patients. Superiority of edoxaban over LMWH is not expected based on the findings of the network meta-analysis. However, if edoxaban proves to be as effective and safe as LMWH, then the therapeutic management of cancer patients with VTE could be simplified and rendered less burdensome for patients. Moreover, the Hokusai VTE-cancer study will provide unique data on the clinical outcome of cancer patients treated for incidental VTE and valuable information regarding the risk of recurrent VTE in patients with a history of cancer compared with those with active cancer. Last, by using a composite outcome of the patient-relevant outcomes – recurrent VTE and major bleeding – this is the first large trial that aims to directly evaluate the net clinical benefit in the setting of VTE treatment, both during and after stopping anticoagulant treatment.

In conclusion, the Hokusai VTE-cancer study combines traditional clinical trial methodology with some innovative design features with the goal of improving VTE treatment in a broad range of cancer patients. The characteristic aspects aim to optimize the internal and external validity while keeping the study integrity high and the burden as low as possible for both patients and investigators. The experience gained from this study could provide a basis for updating current guidelines and for the design of future trials evaluating anticoagulant treatment in cancer-associated VTE.
REFERENCES


