Outpatient Management in Patients with Venous Thromboembolism with Edoxaban: A Post Hoc Analysis of the Hokusai-VTE Study

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Abstract

Direct oral anticoagulants (DOACs) facilitate the outpatient treatment of venous thromboembolism (VTE). However, the pivotal trials of DOACs have not reported outcomes separately for patients managed either as outpatients or in the hospital. We performed a subgroup analysis of the Hokusai-VTE study comparing efficacy and safety of edoxaban with warfarin in 8,292 patients with acute VTE. Patients received initial therapy with open-label enoxaparin or unfractionated heparin for $\geq$5 days in the hospital or as an outpatient at the discretion of the treating physician. Edoxaban or warfarin was then given for 3 to 12 months. The primary efficacy outcome was the cumulative incidence of symptomatic recurrent VTE at 12 months. The principal safety outcome was the incidence of clinically relevant bleeding (composite of major or clinically relevant non-major bleeding). Of the 5,223 consecutively enrolled patients with recorded hospital status and length of stay, 1,414 patients (27.1%) were managed as outpatients and 3,809 were managed in hospital. Among the outpatients, initial presentation was symptomatic deep-vein thrombosis (DVT) in 1,183 patients (83.7%)

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- direct oral anticoagulants
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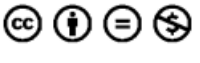

and pulmonary embolism (PE) in 231 patients (16.3%). Among the outpatients with DVT, recurrent VTE occurred in 18 (3.0%) given edoxaban and in 21 (3.6%) given warfarin (risk difference: −0.61, 95% confidence interval [CI]: −2.6 to 1.4). The principal safety outcome in outpatients occurred in 46 edoxaban patients (7.7%) and in 48 warfarin patients (8.3%; risk difference: −0.59, 95% CI: −3.7 to 2.5). Most outpatients had symptomatic DVT at presentation. In these patients, initial heparin followed by edoxaban had similar efficacy and safety to standard therapy with heparin and warfarin.

Introduction

The practical advantages of low-molecular-weight heparin (LMWH) over intravenous unfractionated heparin (UFH) have enabled outpatient treatment of patients with venous thromboembolism (VTE). The safety of this approach is supported by randomized trials in patients with deep-vein thrombosis (DVT) and in selected low-risk patients with pulmonary embolism (PE).[1–5] Evidence-based guidelines now recommend outpatient treatment or early discharge for these patients.[6,7] The direct oral anticoagulants (DOACs) further facilitate outpatient treatment for VTE. However, the pivotal trials comparing DOACs with conventional therapy for VTE treatment have not reported outcomes separately for patients managed either as outpatients or in the hospital.[8–12]

The Hokusai-VTE study was a randomized, double-blind trial comparing edoxaban with warfarin in patients with symptomatic VTE.[12,13] All patients received at least 5 days of treatment with LMWH or UFH. The decision for management in the hospital or as an outpatient was at the discretion of the treating physician. We performed a subgroup analysis of the Hokusai-VTE study comparing the efficacy and safety of edoxaban with warfarin, separately in outpatients and inpatients.

Methods

Study Design and Oversight

The design and methods of the Hokusai-VTE study have been reported in detail previously (ClinicalTrials.gov identifier: NCT00986154).[12,13] A coordinating committee in collaboration with the sponsor 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 center approved the protocol. All patients provided written informed consent.

Patients

Patients aged 18 years or older were eligible for study entry if they had been objectively diagnosed with acute symptomatic DVT involving the popliteal, femoral or iliac veins, or acute symptomatic PE with or without DVT.

The main exclusion criteria were contraindications to heparin or warfarin; prior treatment with more than 48 hours of therapeutic doses of heparin or with more than one dose of a vitamin K antagonist (VKA); use of thrombectomy, a caval filter, or a fibrinolytic agent to treat the current episode of DVT or PE; another indication for VKA therapy; continued treatment with aspirin at a dose of more than 100 mg daily or dual antiplatelet therapy or a creatinine clearance less than 30 mL/min. The full list of exclusion criteria is provided in the previously reported protocol.[12,13]

Randomization and Stratification

Randomization was performed with the use of an interactive web-based system, with stratification according to the qualifying diagnosis (DVT or PE), the presence or absence of temporary risk factors, the dose of edoxaban and geographic region of the study site. In all patients with PE, a blood sample was obtained and archived for later measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) in a core laboratory.

Initial Heparin Treatment and Hospitalization

All patients received initial therapy with open-label enoxaparin or UFH for at least 5 days. Treatment was given in the hospital or as an outpatient at the discretion of the treating physician. We recorded data on patients' hospital status and length of stay for the consecutive patients enrolled between June 2011 and the end of the study.

Long-term Anticoagulant Therapy

Edoxaban or warfarin was given using a double-blind method. Edoxaban (or placebo) was started after discontinuation of initial heparin. The edoxaban dose was 60 mg orally once daily, taken with or without food, or 30 mg once daily for patients with a creatinine clearance of 30 to 50 mL/min or body weight $\leq$60 kg, or taking concomitant treatment with the P-glycoprotein inhibitors verapamil or quinidine.

Warfarin (or placebo) was started concurrently with the study regimen of heparin. The warfarin dose was adjusted to maintain the international normalized ratio (INR) between 2.0 and 3.0. The parenteral anticoagulant was stopped when the INR was 2 or higher. Subsequent INR measurements were required at least monthly. To maintain blinding, sham INR measurements were provided for patients receiving edoxaban.

Treatment with edoxaban or warfarin was to be continued for at least 3 months in all patients. The duration of treatment beyond 3 months was determined by the treating physician based on the patient's clinical features and the patient's preference, up to a maximum of 12 months. Adherence to edoxaban was assessed with pill counts. Time in

therapeutic range for warfarin treatment was calculated as previously reported.[12,13]

Surveillance and Follow-up

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

Outcome Measures

The primary efficacy outcome was the incidence of adjudicated symptomatic recurrent VTE, which was defined as the composite of DVT or nonfatal or fatal PE. Death was adjudicated as related to VTE, other cardiovascular disease, bleeding or other causes. PE was considered the cause of death if there was objective documentation, or if death could not be attributed to a documented cause and PE could not be excluded.

The principal safety outcome was the incidence of adjudicated clinically relevant bleeding, which was defined as the composite of major or clinically relevant non-major bleeding (CRNM). Bleeding was defined as major if it was overt and associated with a decrease in haemoglobin of 2 g/dL or more, or required a transfusion of two or more units of whole blood or packed red blood cells, occurred in a critical site or contributed to death.[12,13] CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding, but associated with the need for medical intervention, contact with a physician, interruption of study drug, or discomfort or impairment of activities of daily life. Criteria for adjudication of outcomes have been reported previously.[12,13]

Statistical Analyses

The statistical hypotheses and sample size planning of the Hokusai-VTE trial have been reported previously.[12,13] The frequencies of baseline characteristics were calculated separately for outpatients and for inpatients. Inpatients were further categorized according to length of hospital stay using the categories of 1 to 2 days, 3 to 4 days, or 5 or more days.

The incidences and risk differences for recurrent VTE and bleeding between the edoxaban and warfarin groups were calculated separately for outpatients and all inpatients. The 95% confidence intervals (CIs) were calculated using the binomial distribution. The efficacy analysis is based on the modified intention-to-treat population, which included all patients who underwent randomization and received at least one dose of the study drug, regardless of the duration of treatment or whether the patient was receiving study medication at the time of a suspected recurrent thromboembolic event. The safety analysis is based on the safety population which included patients who received at least one dose of the study drug.

We also compared the incidences of bleeding between edoxaban and warfarin for clinically relevant bleeding and for major bleeding events occurring in the first 7 days after starting treatment separately for outpatients and inpatients. This time frame was chosen based on the median duration of hospital stay. Furthermore, bleeding events that occur after the first 7 days of treatment would unlikely be related to admission status.

Results

Patients and Hospital Status

From January 2010 through October 2012, a total of 8,292 patients were enrolled in 37 countries. Data on outpatient or in-hospital management were recorded for 5,223 consecutive patients enrolled between June 2011 and the end of the study. The flow of these patients through the study is shown in ►**Fig. 1**. The baseline characteristics and hospital status of the patients in the edoxaban and warfarin treatment groups are shown in ►**Table 1**. The median length of stay for the hospitalized patients was 7.5 and 8.0 days (IQR: 5–11 days) in the edoxaban and warfarin groups, respectively. The proportion of patients managed entirely as outpatients in the various countries participating in the study is shown in ►**Fig. 2**.

The mean duration of heparin treatment after randomization in days, for outpatients, was 7.0 (IQR: 5–8 days) and 8.0 (IQR: 6–10 days) in the edoxaban and warfarin groups, respectively. The corresponding mean heparin treatment durations for the inpatients was 7.0 (IQR: 6–8 days) and 7.0 (IQR: 6–9 days) days in the edoxaban and warfarin groups, respectively.

The mean duration of oral anticoagulant treatment in the outpatient group was 215.0 days for edoxaban and 235.0 days for warfarin. In the inpatient group, the mean duration of treatment was 256.0 and 243.0 days in the edoxaban and warfarin groups, respectively. Adherence to edoxaban was 80% or more in 685 (94.6%) of the outpatients and 1,753 (93.0%) of the inpatients. In the warfarin group, the mean time in therapeutic range was 63.7 and 64.7% for those initially managed as outpatients or inpatients, respectively.

Efficacy Outcomes

Among the patients treated as outpatients, recurrent VTE occurred in 23 patients (3.2%) who received edoxaban and 26 patients (3.8%) who received warfarin (risk difference: −0.59, 95% CI: −2.50 to 1.32). Of these recurrent VTE events, 10 (1.4%) in the edoxaban group and 16 (2.3%) in the warfarin group occurred after stopping anticoagulant treatment. The incidences of recurrent VTE in the outpatients in whom the initial presentation was symptomatic DVT alone or PE (with or without DVT) are shown in ►**Table 2**.

Among those managed as inpatients, recurrent VTE occurred in 54 patients (2.9%) who received edoxaban and 62 patients (3.2%) who received warfarin (risk difference: −0.36, 95% CI: −1.45 to 0.73). Of these recurrent VTE events, 38 patients (2.0%) in the edoxaban group and 37 patients (1.9%) in the warfarin group occurred after stopping anticoagulant treatment. The incidences of recurrent VTE in inpatients in whom the initial presentation was symptomatic DVT alone or PE (with or without DVT) are shown in ►**Table 2**.

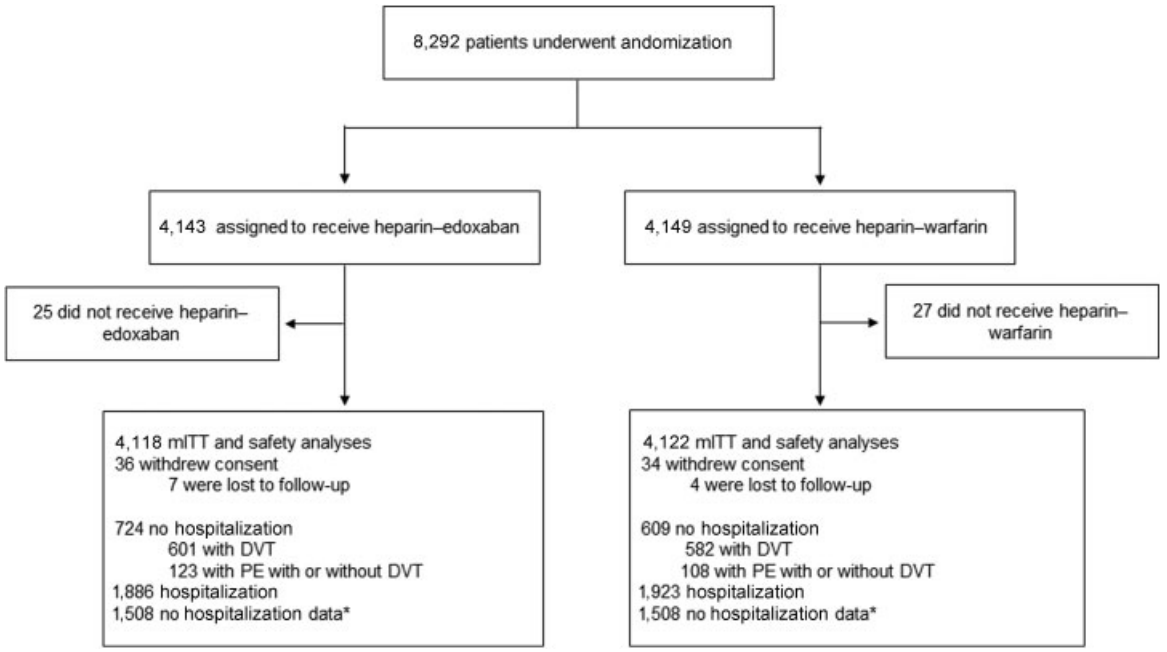

Fig. 1 Patient flow. DVT, deep-vein thrombosis; mITT, modified intention-to-treat; PE, pulmonary embolism.

Safety Outcomes

Among those treated as outpatients, clinically relevant bleeding (major or non-major) occurred in 65 of the 724 patients (9%) who received edoxaban and in 60 of the 690 patients (9%) who received warfarin (risk difference: 0.28, 95% CI: −2.68 to 3.24). Major bleeding occurred in 12 patients (1.7%) given edoxaban and in 10 patients (1.5%) given warfarin (risk difference: 0.21, 95% CI: −1.08 to 1.50). Within the first 7 days after beginning study treatment, clinically relevant bleeding occurred in six patients (0.8%) in the edoxaban group and in three patients (0.4%) in the warfarin group (risk difference: 0.39, 95% CI: −0.43 to 1.22).

Among those treated as inpatients, clinically relevant bleeding (major or non-major) occurred in 168 of the 1,886 patients (8.9%) who received edoxaban and 193 of the 1,923 patients (10.0%) who received warfarin (risk difference: −1.13, 95% CI: −2.99 to 0.73). Major bleeding occurred in 22 patients (1.2%) in the edoxaban group and 26 patients (1.4%) in the warfarin group. Within the first 7 days of treatment, clinically relevant bleeding occurred in 17 patients (0.9%) in the edoxaban group and in 33 patients (1.7%) in the warfarin group (risk difference: −0.81, 95% CI: −1.54 to −0.09). For both outpatients and inpatients, the incidences of these bleeding outcomes in whom the initial presentation was symptomatic DVT alone or PE (with or without DVT) are shown in ►**Table 2**.

Discussion

In this analysis, we found that for the outpatient treatment of DVT, edoxaban was as safe and effective as warfarin. Although there were fewer PE patients treated as outpatients, safety and efficacy outcomes were also comparable with edoxaban and warfarin. As expected, hospitalized patients tended to be older and sicker, particularly those who required admission lasting more than 5 days. The main driver for inpatient treatment was presentation with symptomatic PE. Other factors that affected the decision for inpatient treatment were geographic region and extent of VTE. There are country differences in treatment disposition trends (►**Fig. 2**), which likely reflect variations in national guidelines and institutional practice. For example, the majority of patients enrolled in Canada were treated as outpatients, while the majority of patients enrolled in the United States were treated as inpatients. In patients for whom early discharge or outpatient treatment is appropriate, the requirement for heparin lead-in for edoxaban should not preclude outpatient treatment even if preceded by a short inpatient stay (1–2 days), as the lead-in can be completed at home with LMWH. Our data further demonstrate the safety of outpatient treatment of DVT using heparin and edoxaban in the outpatient setting.

Current international treatment guidelines for DVT recommend home (outpatient) treatment for DVT in most patients (i.e. those with adequate home support and without uncontrolled comorbidities).[6] Guidelines for inpatient versus outpatient management of PE are less clearly defined.[7] Several scoring systems are used for the identification of low-risk PE patients who are eligible for home management, including the Pulmonary Embolism Severity Index (PESI) score and the Hestia score.[3,4] Patients who are haemodynamically stable, with a PESI score of I or II, or are negative by Hestia criteria and who have adequate home support are eligible for early discharge or outpatient treatment.[5,14–16] We show that in patients with DVT treated as outpatients, the risk of bleeding in the first week is similar with edoxaban and warfarin. Although some physicians may be concerned about using LMWH for outpatient treatment of VTE, we show

Table 1 Patient characteristics according to treatment as an outpatient or in the hospital

Characteristic	Outpatient		Hospitalized for ≥1 d		Hospitalized for 1–2 d		Hospitalized for 3–4 d		Hospitalized for ≥5 d	
	Edoxaban ($n = 724$)	Warfarin ($n = 690$)	Edoxaban ($n = 1,886$)	Warfarin ($n = 1,923$)	Edoxaban ($n = 184$)	Warfarin ($n = 213$)	Edoxaban ($n = 261$)	Warfarin ($n = 252$)	Edoxaban ($n = 1,441$)	Warfarin ($n = 1,458$)
Age										
Mean-year	54.9 ± 15.2	54.2 ± 15.3	56.0 ± 16.7	56.2 ± 16.5	53.2 ± 15.2	54.8 ± 16.1	52.1 ± 16.6	52.6 ± 16.3	57.1 ± 16.8	57.0 ± 16.5
≥75 y	82 (11.3)	65 (9.4)	268 (14.2)	270 (14.0)	14 (7.6)	19 (8.9)	29 (11.1)	25 (9.9)	225 (15.6)	226 (15.5)
Sex										
Male	436 (60.2)	413 (59.9)	1,066 (56.5)	1,073 (55.8)	105 (57.1)	122 (57.3)	151 (57.9)	145 (57.5)	810 (56.2)	806 (55.3)
Female	288 (39.8)	277 (40.1)	820 (43.5)	850 (44.2)	79 (42.9)	91 (42.7)	110 (42.1)	107 (42.5)	631 (43.8)	652 (44.7)
Weight	722	689	1,880	1,916	184	213	260	252	1,436	1,451
≤60 kg	54 (7.5)	56 (8.1)	229 (12.2)	230 (12.0)	14 (7.6)	13 (6.1)	25 (9.6)	26 (10.3)	190 (13.2)	191 (13.2)
> 100 kg	129 (17.9)	131 (19.0)	269 (14.3)	289 (15.1)	32 (17.4)	49 (23.0)	57 (21.8)	58 (23.0)	180 (12.5)	182 (12.5)
Creatinine clearance ≥30 to ≤50 mL/min	34 (4.7)	30 (4.3)	122 (6.5)	136 (7.1)	3 (1.6)	7 (3.3)	15 (5.7)	12 (4.8)	104 (7.2)	117 (8.0)
Dose reduction criteria met at randomization	82 (11.3)	81 (11.7)	340 (18.0)	333 (17.3)	19 (10.3)	21 (9.9)	36 (13.8)	37 (14.7)	285 (19.8)	275 (18.9)
Qualifying event at entry										
DVT	601 (83.0)	582 (84.3)	903 (47.9)	906 (47.1)	80 (43.5)	99 (46.5)	99 (37.9)	96 (38.1)	724 (50.2)	711 (48.8)
PE +/− DVT	123 (17.0)	108 (15.7)	983 (52.1)	1,017 (52.9)	104 (56.5)	114 (53.5)	162 (62.1)	156 (61.9)	717(49.8)	747 (51.2)
Anatomical extent of qualifying event (DVT only)										
Limited	194 (32.2)	205 (35.2)	190 (21.0)	180 (19.9)	20 (25.0)	30 (30.3)	34 (34.3)	23 (24.0)	136 (18.8)	127 (17.9)
Intermediate	218 (36.3)	200 (34.4)	268 (29.7)	281 (31.0)	33 (41.3)	33 (33.3)	30 (30.3)	25 (26.0)	205 (28.3)	223 (31.4)
Extensive	186 (30.9)	172 (29.6)	426 (47.2)	433 (47.8)	24 (30.0)	34 (34.3)	30 (30.3)	45 (46.9)	372 (51.4)	354 (49.8)
Not assessable	3 (0.5)	5 (0.9)	19 (2.1)	12 (1.3)	3 (3.8)	2 (2.0)	5 (5.1)	3 (3.1)	11 (1.5)	7 (1.0)
Anatomical extent of qualifying event (PE)										
Limited	11 (8.9)	12 (11.1)	67 (6.8)	67 (6.6)	10 (9.6)	6 (5.3)	13 (8.0)	25 (16)	44 (6.1)	36 (4.8)
Intermediate	53 (43.1)	43 (39.8)	374 (38.0)	406 (39.9)	50 (48.1)	55 (48.2)	74 (45.7)	60 (38.5)	250 (34.9)	291 (39.0)
Extensive	46 (37.4)	43 (39.8)	482 (49.0)	488 (48.0)	41 (39.4)	46 (40.4)	69 (42.6)	66 (42.3)	372 (51.9)	376 (50.3)
Not assessable	13 (10.6)	10 (9.3)	60 (6.1)	56 (5.5)	3 (2.9)	7 (6.1)	6 (3.7)	5 (3.2)	51 (7.1)	44 (5.9)
Baseline NT-proBNP										
Patients with measurement	119	99	944	986	98	112	157	151	689	723

Table 1 (*Continued*)

Characteristic	Outpatient		Hospitalized for ≥1 d		Hospitalized for 1–2 d		Hospitalized for 3–4 d		Hospitalized for ≥5 d	
	Edoxaban (*n* = 724)	Warfarin (*n* = 690)	Edoxaban (*n* = 1,886)	Warfarin (*n* = 1,923)	Edoxaban (*n* = 184)	Warfarin (*n* = 213)	Edoxaban (*n* = 261)	Warfarin (*n* = 252)	Edoxaban (*n* = 1,441)	Warfarin (*n* = 1,458)
Patients with level ≥500 pg/L	21 (17.6)	18 (18.2)	299 (32.0)	330 (33.4)	9 (9.2)	20 (17.9)	32 (20.3)	31 (20.5)	258 (37.4)	279 (38.6)
Right ventricular dysfunction	27 (38.6)	28 (45.2)	263 (45.8)	273 (44.2)	23 (34.8)	27 (32.9)	38 (35.2)	39 (36.8)	202 (50.5)	207 (48.1)
Causes of DVT or PE										
Unprovoked	492 (68.0)	495 (71.7)	1,239 (65.7)	1,219 (63.4)	112 (60.9)	119 (55.9)	149 (57.1)	150 (59.5)	978 (67.9)	950 (65.2)
Temporary risk factor	186 (25.7)	163 (23.6)	538 (28.5)	566 (29.4)	65 (35.3)	77 (36.2)	96 (36.8)	86 (34.1)	377 (26.2)	403 (27.6)
Cancer	66 (9.1)	47 (6.8)	156 (8.3)	190 (9.9)	15 (8.2)	27 (12.7)	24 (9.2)	23 (9.1)	117 (8.1)	140 (9.6)
Previous VTE	164 (22.7)	143 (20.7)	344 (18.2)	339 (17.6)	35 (19.0)	40 (18.8)	60 (23.0)	64 (25.4)	249 (17.3)	235 (16.1)
Comorbidities										
CV disease	68 (9.4)	57 (8.3)	281 (14.9)	316 (16.4)	13 (7.1)	26 (12.2)	22 (8.4)	32 (12.7)	246 (17.1)	258 (17.7)
Heart failure	6 (0.8)	6 (0.9)	48 (2.5)	49 (2.5)	2 (1.1)	3 (1.4)	3 (1.1)	5 (2.0)	43 (3.0)	41 (2.8)
Diabetes	66 (9.1)	61 (8.8)	213 (11.3)	209 (10.9)	16 (8.7)	19 (8.9)	27 (10.3)	20 (7.9)	170 (11.8)	170 (11.7)
Cerebrovascular disease	22 (3.0)	19 (2.8)	84 (4.5)	76 (4.0)	10 (5.4)	9 (4.2)	4 (1.5)	5 (2.0)	70 (4.9)	62 (4.3)
Hospitalization days (mean)			8.5 ± 6.32 (5–11)	8.50 ± 6.16 (5–11)						

Abbreviations: CV, cardiovascular; DVT, deep-vein thrombosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism.

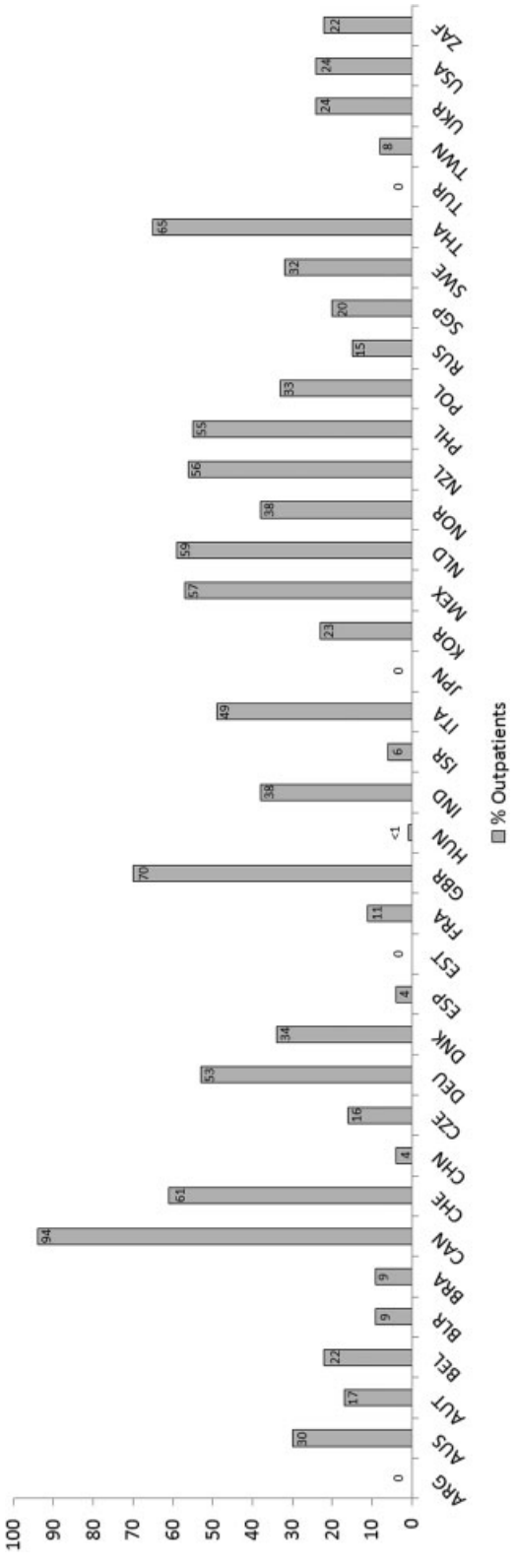

Fig. 2 Outpatients by country. ARG, Argentina; AUS, Australia; AUT, Austria; BEL, Belgium; BLR, Belarus; BRA, Brazil; CAN, Canada; CHE, Switzerland; CHN, China; CZE, Czech Republic; DEU, Germany; DNK, Denmark; ESP, Spain; EST, Estonia; FRA, France; GBR, United Kingdom; HUN, Hungary; IND, India; ISR, Israel; ITA, Italy; JPN, Japan; KOR, Korea; MEX, Mexico; NLD, the Netherlands; NOR, Norway; NZL, New Zealand; PHL, Philippines; POL, Poland; RUS, Russia; SGP, Singapore; SWE, Sweden; THA, Thailand; TUR, Turkey; TWN, Taiwan; UKR, Ukraine; USA, United States of America; ZAF, South Africa.

that it provides safe initial therapy lead-in to edoxaban in outpatients with DVT.

Outpatient treatment of DVT reduces health care costs as evidenced by multiple studies showing a cost reduction of 32 to 64% in DVT patients who were treated at home.[17–20] The cost-saving with outpatient treatment or early discharge of patients with PE is not as well established, but Aujesky et al have shown a cost reduction when low-risk PE patients were treated as outpatients or discharged early.[15,19,21] Further, reducing or eliminating time in the hospital also improves quality of life and physical activity.[2]

Our analysis has some limitations. First, patients considered at highest risk based on comorbidities such as concurrent cancer, severe renal impairment or those who required thrombolytics were excluded from the Hokusai-VTE trial. Because the sickest patients were excluded, the patients in the study would be more likely to be eligible for outpatient treatment. Second, it is possible that the double-blind study design and complexity of the protocol may have influenced the decision to admit the patient to the hospital in some centers. Third, we did not start collecting data on hospitalization status until about one-third of patients were already enrolled in the study. However, because we collected data on all subsequent consecutive patients, this should not affect the results of this analysis. Finally, we acknowledge that the practices at the centers of this study might not be representative of overall practices in the countries in which the centers are located.

DOACs further facilitate the outpatient treatment of VTE. Until now, the pivotal trials of DOACs have not reported outcomes separately for patients managed either as outpatients or in the hospital. In this analysis, we showed that most of the patients who were managed in the outpatient setting were those who presented with symptomatic DVT. In these patients, initial heparin followed by edoxaban had similar efficacy and safety to standard therapy with heparin and warfarin.

What is known about this topic?

- Direct oral anticoagulants (DOACs) are as effective and associated with less bleeding than vitamin K antagonists in patients with venous thromboembolism (VTE).
- It is common practice to treat many patients with deep-vein thrombosis (DVT) and selected patients with pulmonary embolism (PE) as an outpatient.
- However, the pivotal trials of DOACs have not reported outcomes separately for patients managed either as outpatients or in the hospital.

What does this paper adds

- For the outpatient treatment of DVT, initial heparin followed by edoxaban had similar efficacy and safety to standard therapy with heparin and warfarin.
- The main driver for inpatient treatment was presentation with symptomatic PE. Other factors that affected the decision for inpatient treatment were geographic region and extent of VTE.

Table 2 Primary efficacy and bleeding outcomes according to the patient's initial presentation with DVT and PE and hospital status

	Patients with DVT						Patients with PE					
	Outpatient			Hospitalized for ≥1 d			Outpatient			Hospitalized for ≥1 d		
	Edoxaban (n = 601)	Warfarin (n = 582)	Risk difference 95% CI	Edoxaban (n = 903)	Warfarin (n = 906)	Risk difference 95% CI	Edoxaban (n = 123)	Warfarin (n = 108)	Risk difference 95% CI	Edoxaban (n = 983)	Warfarin (n = 1017)	Risk difference 95% CI
Primary efficacy outcome: first recurrent VTE or VTE-related death	18 (3.0)	21 (3.6)	−0.61 (−2.65, 1.43)	26 (2.9)	24 (2.7)	0.23 (−1.28, 1.74)	5 (4.1)	5 (4.6)	−0.56 (−5.85, 4.72)	28 (2.9)	38 (3.7)	−0.89 (−2.45, 0.67)
Fatal PE	0 (0.0)	0 (0.0)	–	1 (0.1)	0 (0.0)	0.11 (−0.11, 0.33)	0 (0.0)	0 (0.0)	–	2 (0.2)	0 (0.0)	0.20 (−0.08, 0.49)
Death, with PE not ruled out	2 (0.3)	3 (0.5)	−0.18 (−0.93, 0.56)	4 (0.4)	3 (0.3)	0.11 (−0.46, 0.68)	0 (0.0)	1 (0.9)	−0.93 (−2.73, 0.88)	5 (0.5)	8 (0.8)	−0.28 (−0.98, 0.42)
Nonfatal PE with or without DVT	9 (1.5)	9 (1.6)	−0.05 (−1.45, 1.35)	9 (1.0)	13 (1.4)	−0.44 (−1.45, 0.57)	3 (2.4)	2 (1.9)	0.59 (−3.14, 4.32)	14 (1.4)	18 (1.8)	−0.35 (−1.44, 0.75)
DVT alone	7 (1.2)	9 (1.6)	−0.38 (−1.70, 0.94)	12 (1.3)	8 (0.9)	0.45 (−0.52, 1.41)	2 (1.6)	2 (1.9)	−0.23 (−3.61, 3.16)	7 (0.7)	12 (1.2)	−0.47 (−1.31, 0.38)
Primary safety outcome: first major or clinically relevant non-major bleeding	46 (7.7)	48 (8.3)	−0.59 (−3.68, 2.49)	63 (7.0)	79 (8.7)	−1.74 (−4.22, 0.73)	19 (15.5)	12 (11.1)	4.34 (−4.38, 13.05)	105 (10.7)	114 (11.2)	−0.5 (−3.26, 2.21)
Major bleeding	8 (1.3)	8 (1.4)	−0.04 (−1.36, 1.27)	7 (0.8)	11 (1.2)	−0.44 (−1.35, 0.48)	4 (3.3)	2 (1.9)	1.40 (−2.64, 5.44)	15 (1.5)	15 (1.5)	0.05 (−1.01, 1.12)
Clinically relevant non-major bleeding	38 (6.3)	42 (7.2)	−0.89 (−3.76, 1.97)	56 (6.2)	69 (7.6)	−1.41 (−3.75, 0.92)	16 (13.0)	10 (9.3)	3.75 (−4.33, 11.83)	91 (9.3)	101 (9.9)	−0.67 (−3.25, 1.91)
First major or clinically relevant non-major bleeding in the first week	0 (0.0)	2 (0.3)	−0.34 (−0.82, 0.13)	6 (0.6)	10 (1.1)	−0.44 (−1.30, 0.42)	6 (4.9)	1 (0.9)	3.95 (−0.26, 8.17)	11 (0.1)	23 (0.2)	−1.14 (−2.27, −0.02)
Fatal bleeding	0 (0.0)	1 (0.2)	−0.17 (−0.51, 0.16)	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	1 (0.1)	2 (0.2)	−0.09 (−0.43, 0.24)

Abbreviations: CI, confidence interval; DVT, deep-vein thrombosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; VTE, venous thromboembolism.

Declaration of Interests

Dr. Raskob reports personal fees from Daiichi Sankyo and Itreas during the conduct of the study and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Isis Pharmaceuticals, Janssen, Pfizer and Portola outside the submitted work. Dr. Ageno reports grants, personal fees and non-financial support from Bayer, Boehringer Ingelheim, Daiichi Sankyo and Stago, and personal fees from Bristol-Myers Squibb, Pfizer and Ono, outside the submitted work. Dr. Cohen reports grants from Daiichi Sankyo Pharma Development during the conduct of the study; grants and personal fees from Bayer, Bristol-Myers Squibb and Pfizer; and personal fees from Boehringer Ingelheim, Janssen, Johnson & Johnson, Portola, Sanofi, and XO1 outside the submitted work. Dr. Chen is an employee of Daiichi Sankyo, Inc. Dr. Grosso and Dr. Lin are employees of Daiichi Sankyo Pharma Development. Dr. Mercuri is an employee of Daiichi Sankyo Pharma Development and has a patent application pending for properties of edoxaban. Dr. Segers reports grants from Daiichi Sankyo Pharma Development during the conduct of the study and grants from Isis Pharmaceuticals outside the submitted work. Dr. Verhamme reports grants and personal fees from Daiichi-Sankyo Pharma Development during the conduct of the study and grants from Leo Pharma; grants and personal fees from Boehringer Ingelheim, Sanofi and ThromboGenics; and personal fees from Bayer outside the submitted work. Dr. Wells reports personal fees from Bayer and Daiichi Sankyo and grants from Bristol-Myers Squibb and Pfizer outside the submitted work. Ms. Winters was an employee of Daiichi Sankyo, Inc. Dr. Weitz reports personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Isis Pharmaceuticals, Janssen, Pfizer and Portola outside the submitted work. Dr. Büller reports grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Isis Pharmaceuticals, Pfizer, Roche, Sanofi and Thrombogenics outside the submitted work. Dr. Medina, Dr., Brekelmans and Dr. Vanassche have nothing to disclose.

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