ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

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ABSTRACT

BACKGROUND

Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

METHODS

In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS

Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P=0.006 for noninferiority; P=0.87 for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

CONCLUSIONS

Oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparin. (Funded by Daiichi Sankyo; Hokusai VTE Cancer ClinicalTrials.gov number, NCT02073682.)

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Venous thromboembolism is a common complication of cancer and its therapy.[1,2] Treatment of cancer-associated venous thromboembolism is challenging, and the risks of recurrent thrombosis and bleeding are higher among patients with cancer than among those without cancer.[3] These two complications are important because they contribute to mortality and morbidity and may interfere with cancer treatment and increase the risk of hospitalization.

In previous studies involving patients with cancer who had venous thromboembolism, the rate of recurrent thrombosis was lower with a 6-month course of low-molecular-weight heparin than with vitamin K antagonists, and the risk of bleeding was similar with the two treatments.[4,5] Therefore, guidelines recommend treatment with low-molecular-weight heparin.[6-8] However, whether this therapy has a benefit beyond 6 months is unknown, and the therapy is burdensome because it requires daily subcutaneous injections, which limits its adoption.[9,10]

Direct oral anticoagulant agents are as effective as vitamin K antagonists for the treatment of venous thromboembolism and are associated with less frequent and less severe bleeding.[11,12] However, the efficacy and safety of direct oral anticoagulants as compared with long-term low-molecular-weight heparin for the treatment of cancer-associated venous thromboembolism have not been established. We conducted the Hokusai VTE Cancer trial to compare the oral factor Xa inhibitor edoxaban with subcutaneous dalteparin for the treatment of patients with cancer-associated venous thromboembolism. The trial assessed for a composite outcome of recurrent venous thromboembolism or major bleeding, which are the two most prominent complications of these therapies. Our objective was to compare these two regimens for at least 6 months and up to 12 months to provide needed guidance on treatment beyond 6 months.

Methods

Trial Oversight

The rationale and design of this randomized, open-label trial have been reported previously.[13] A coordinating committee, in collaboration with the sponsor (Daiichi Sankyo), was responsible for the trial design, protocol, and oversight. The institutional review board at each participating center approved the protocol.

The sponsor was responsible for collection and maintenance of the data. An independent data and safety monitoring committee periodically reviewed trial outcomes. The sponsor performed the statistical analysis in collaboration with the writing committee, which included all the authors. The members of the writing committee wrote all drafts of the manuscript and made the decision to submit the manuscript for publication; they also verified the data and vouch for the completeness of the data, the accuracy of the analyses, and the fidelity of the trial to the protocol. The protocol and accompanying documents are available with the full text of this article at NEJM.org.

Patients

Adult patients with cancer were eligible for inclusion in the trial if they had acute symptomatic or incidentally detected deep-vein thrombosis involving the popliteal, femoral, or iliac vein or the inferior vena cava; acute symptomatic pulmonary embolism that was confirmed by means of diagnostic imaging; or incidentally detected pulmonary embolism involving segmental or more proximal pulmonary arteries. An independent clinical events committee, whose members were unaware of the treatment assignments, confirmed the qualifying diagnosis of venous thromboembolism. The protocol also required that the treating physician intended to administer low-molecular-weight heparin for at least 6 months.

Patients had to have cancer other than basal-cell or squamous-cell skin cancer that was active or had been diagnosed within the previous 2 years and was objectively confirmed. Active cancer was defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 months before randomization; or hematologic cancer that was not in complete remission. A single independent physician (the second author), who was unaware of the treatment assignments, reviewed the data for all the enrolled patients to confirm the diagnosis of cancer and to verify the status of cancer as active or inactive.

A list of the exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

RANDOMIZATION AND TRIAL TREATMENT

Eligible patients were randomly assigned, in a 1:1 ratio, to receive either edoxaban or dalteparin. Randomization was performed with the use of an interactive Web-based system, with stratification according to whether risk factors for bleeding were present and whether the patient met the criteria to receive a lower dose of edoxaban. Risk factors for bleeding were surgery within the previous 2 weeks, the use of antiplatelet agents, a primary or metastatic brain tumor, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer that had been diagnosed within the previous 6 months, or treatment with bevacizumab within the previous 6 weeks.

Edoxaban was started after a course of therapeutic-dose low-molecular-weight heparin was given subcutaneously for at least 5 days. This lead-in low-molecular-weight heparin was not required to be dalteparin; the choice of heparin and therapeutic regimen were at the discretion of the treating physician. Edoxaban was administered orally at a fixed dose of 60 mg once daily, with or without food. It was administered at a lower dose (30 mg once daily) in patients with a creatinine clearance of 30 to 50 ml per minute or a body weight of 60 kg or less or in those receiving concomitant treatment with potent P-glycoprotein inhibitors.

Dalteparin was given subcutaneously at a dose of 200 IU per kilogram of body weight once daily for 30 days,[4] with a maximum daily dose of 18,000 IU. Thereafter, dalteparin was given at a dose of 150 IU per kilogram once daily.[4] If the platelet count declined to less than 100,000 per microliter during treatment, the dose of dalteparin was temporarily reduced.

In all the patients, treatment with edoxaban or dalteparin was to be continued for at least 6 months and up to 12 months. The duration beyond 6 months was determined by the treating physician.

OUTCOME MEASURES

The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. Recurrent venous thromboembolism was defined as symptomatic new deep-vein thrombosis or pulmonary embolism, incidental new deep-vein thrombosis or pulmonary embolism involving segmental or more proximal pulmonary arteries, or fatal pulmonary embolism or unexplained death for which pulmonary embolism could not be ruled out as the cause. Incidental venous thromboembolism was defined as thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of venous thromboembolism.[14] In accordance with the criteria of the International Society on Thrombosis and Haemostasis (ISTH), major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death.[15]

Death was adjudicated to be caused by venous thromboembolism, bleeding, cancer, cardiovascular disease, or other causes. Pulmonary embolism was considered to be the cause of death if there was objective documentation that pulmonary embolism caused the death or if the death could not be attributed to a documented cause and pulmonary embolism could not be ruled out.

A list of prespecified secondary outcomes and the criteria for adjudication of all the outcomes are provided in the Supplementary Appendix. The clinical events committee adjudicated all the suspected outcome events and causes of death, as well as the severity of the major bleeding events, with the use of prespecified criteria.[12]

SURVEILLANCE AND FOLLOW-UP

All the patients were followed for 12 months or until the end of the trial (minimum follow-up, 9 months). Patients underwent assessment, in the clinic or by telephone, on day 31 after randomization and at months 3, 6, 9, and 12. Patients were instructed to report symptoms that were suggestive of recurrent venous thromboembolism or bleeding. Appropriate diagnostic tests, laboratory tests, or both were required in patients with suspected outcome events. The following adverse events were reported: suspected outcome events, serious adverse events that were not related to the underlying cancer or its treatment, and combined elevations in aminotransferase and bilirubin levels.

STATISTICAL ANALYSIS

The trial hypothesis was that edoxaban would be noninferior to dalteparin with respect to the rate of primary-outcome events (recurrent venous

thromboembolism or major bleeding), with an upper limit of the 95% confidence interval for the hazard ratio of less than 1.5 and a two-sided alpha level of 0.05. The margin of 1.5 was chosen as the maximum difference that may be potentially clinically acceptable because of the unmet need for an alternative to parenteral low-molecular-weight heparin and the advantages of oral therapy. Assuming equal effectiveness of edoxaban and dalteparin (i.e., a hazard ratio of 1.0) and a rate of primary-outcome events at 12 months of 20%, we estimated that a sample of approximately 1000 patients would be required to observe an expected total of 191 primary-outcome events and would give the trial 80% power to show the noninferiority of edoxaban. When the number of patients who were enrolled in the trial approached 1000, we set the date for the end of the trial such that the last patient enrolled would complete 9 months of follow-up.

The analysis of the primary outcome was performed in the modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of the assigned treatment. The primary analysis included any primary-outcome events that had occurred from randomization through the end of 12 months or the end of the trial (overall trial period), regardless of the duration of treatment for each patient. The time to the first primary-outcome event was analyzed with the use of a Cox proportional-hazards model to compare the hazards between treatment groups. The stratification factors were used as covariates. Time-to-event curves were calculated with the use of the Kaplan–Meier method. Analyses of secondary safety outcomes were performed in the safety population, which was the same as the modified intention-to-treat population.

Two sensitivity analyses were planned for the primary outcome. The first was an analysis of primary-outcome events that occurred during the first 6 months, which was the minimum intended duration of the assigned treatment and corresponds with the treatment duration used in previous trials.[4,5] The second was an analysis of outcomes that occurred during treatment (i.e., during or within 3 days after discontinuation of the assigned treatment) in the per-protocol population. This population excluded patients who had not received at least one dose of edoxaban or dalteparin after randomization and patients in whom the qualifying diagnosis of venous thromboembolism had not been confirmed.

RESULTS

PATIENTS AND TREATMENT

From July 2015 through December 2016, a total of 1050 patients were enrolled at 114 centers in 13 countries (Fig. 1). The baseline characteristics of the patients were similar in the two trial groups (Table 1). The types of cancer and the categories of anticancer drugs given during the course of the trial are shown in Tables S1 and S2, respectively, in the Supplementary Appendix. The median duration of the assigned treatment was 211 days (interquartile range, 76 to 357) in the edoxaban group and 184 days (interquartile range, 85 to 341) in the dalteparin group (P=0.01). Details about the duration of the assigned treatment and reasons for discontinuation are provided in Table S3 in the Supplementary Appendix. The counts of pills and syringes indicated that 447 patients (85.6%) in the edoxaban group and 465 patients (88.7%) in the dalteparin group had received at least 80% of the prescribed treatment before permanent discontinuation.

PRIMARY OUTCOME

The primary outcome of recurrent venous thromboembolism or major bleeding occurred in 67 of the 522 patients (12.8%) in the edoxaban group and in 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P=0.006 for noninferiority; P=0.87 for superiority) (Table 2). The time to the occurrence of primary-outcome events is shown in Figure 2. Characteristics of the primary-outcome events are shown in Table S4 in the Supplementary Appendix.

The results of the two prespecified sensitivity analyses were similar to the results of the primary analysis and also met the criteria for noninferiority (Tables S5 and S6 in the Supplementary Appendix). In the analysis of events that occurred during the first 6 months, a primary-outcome event occurred in 55 patients (10.5%) in the edoxaban group and in 56 patients (10.7%) in the dalteparin group (hazard ratio, 1.01; 95% CI, 0.69 to 1.46; P=0.02 for noninferiority). In the analysis of events that occurred during treatment in the per-

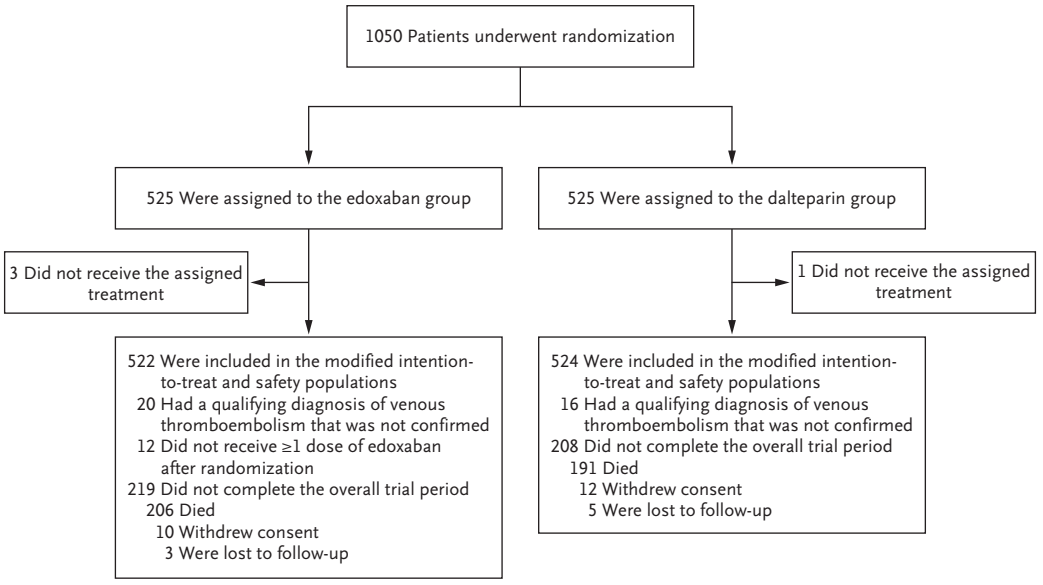

Figure 1. Randomization and Follow-up.

The modified intention-to-treat and safety populations included all the patients who had undergone randomization and received at least one dose of the assigned treatment. Of the 303 patients in the edoxaban group and the 316 in the dalteparin group who completed the overall trial period, 72 and 69 patients, respectively, had their follow-up truncated to between 9 and 12 months because they were enrolled less than 12 months before the end of the trial.

protocol population, a primary-outcome event occurred in 51 of 490 patients (10.4%) in the edoxaban group and in 53 of 508 patients (10.4%) in the dalteparin group (hazard ratio, 0.99; 95% CI, 0.68 to 1.46; P=0.02 for noninferiority).

SECONDARY OUTCOMES

The secondary outcomes are shown in Table 2. Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, −3.4 percentage points [95% CI, −7.0 to 0.2]; hazard ratio, 0.71 [95% CI, 0.48 to 1.06; P=0.09]). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points [95% CI, 0.1 to 5.6]; hazard ratio, 1.77 [95% CI, 1.03 to 3.04; P=0.04]).

The time to the occurrence of recurrent venous thromboembolism and major bleeding during the overall trial period is shown in Figure 3. Sensitivity analyses for the secondary outcomes are shown in Tables S5 and S6, data on bleeding events that occurred during treatment in the safety population are shown in Table S7, and data on event-free survival are shown in Figure S1 — all in the Supplementary Appendix.

Death occurred in 206 patients (39.5%) in the edoxaban group and in 192 patients (36.6%) in the dalteparin group. The causes of death are shown in Table S8 in the Supplementary Appendix. The majority of deaths were related to cancer; six deaths in each group were related to either venous thromboembolism or bleeding.

SUBGROUP ANALYSES

Subgroup analyses for the primary outcome, and for recurrent venous thromboembolism and major bleeding separately, are shown in Figures S2 through S5 in the Supplementary Appendix. There were no statistically significant interactions between subgroup and treatment, except for the subgroups defined according to whether the patient had gastrointestinal cancer at the time of randomization. Patients with gastrointestinal cancer were more likely to have an increase in the risk of bleeding during treatment with edoxaban than

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Edoxaban (N=522)	Dalteparin (N=524)
Age — yr	64.3±11.0	63.7±11.7
Male sex — no. (%)	277 (53.1)	263 (50.2)
Weight		
Mean — kg	78.8±17.9	79.1±18.1
≤60 kg — no. (%)	83 (15.9)	78 (14.9)
Creatinine clearance of 30–50 ml/min — no. (%)	38 (7.3)	34 (6.5)
Platelet count of 50,000–100,000 per μl — no. (%)	32 (6.1)	23 (4.4)
Met criteria to receive lower dose of edoxaban — no. (%)†	122 (23.4)	117 (22.3)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without deep-vein thrombosis	328 (62.8)	329 (62.8)
Deep-vein thrombosis only	194 (37.2)	195 (37.2)
Symptomatic deep-vein thrombosis or pulmonary embolism	355 (68.0)	351 (67.0)
Incidental deep-vein thrombosis or pulmonary embolism‡	167 (32.0)	173 (33.0)
Active cancer — no. (%)	513 (98.3)	511 (97.5)
Metastatic disease — no. (%)	274 (52.5)	280 (53.4)
Recurrent cancer — no. (%)	163 (31.2)	152 (29.0)
Cancer treatment within previous 4 wk — no. (%)§	374 (71.6)	383 (73.1)
ECOG performance status — no. (%)¶		
0	155 (29.7)	148 (28.2)
1	243 (46.6)	246 (46.9)
2	123 (23.6)	124 (23.7)
Previous venous thromboembolism — no. (%)	49 (9.4)	63 (12.0)
Risk factors for bleeding — no. (%)‖		
0	92 (17.6)	92 (17.6)
1	148 (28.4)	151 (28.8)
2	174 (33.3)	159 (30.3)
≥3	108 (20.7)	122 (23.3)

* Plus–minus values are means ±SD. Some percentages may not total 100 because of rounding. None of the numerical differences between the two groups were statistically significant at an alpha level of 0.05.

† Edoxaban was administered at a dose of 30 mg once daily (instead of 60 mg once daily) in patients with a creatinine clearance of 30 to 50 ml per minute or a body weight of 60 kg or less or in those receiving concomitant treatment with potent P-glycoprotein inhibitors.

‡ Incidental venous thromboembolism (deep-vein thrombosis or pulmonary embolism) was defined as thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of venous thromboembolism.

§ Cancer treatment includes anticancer drug therapy (cytotoxic, hormonal, targeted, or immunomodulatory), radiotherapy, surgery, or a combination of these therapies.

¶ Eastern Cooperative Oncology Group (ECOG) performance status values range from 0 to 4, with higher values indicating greater disability.

‖ Risk factors for bleeding include surgery within 2 weeks before randomization, the use of antiplatelet agents, a primary or metastatic brain tumor at randomization, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer that was present at randomization or had been diagnosed within 6 months before randomization, and treatment with bevacizumab within the 6-week period before randomization.

Table 2. Clinical Outcomes during the Overall Trial Period.*

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority
Secondary outcomes				
Recurrent venous thromboembolism — no. (%)	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)	0.09
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)	
Recurrent pulmonary embolism — no. (%)†	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Severity of major bleeding among those with major bleeding — no./total no. (%)‡				
Category 1	0	0		
Category 2	24/36 (66.7)	8/21 (38.1)		
Category 3	12/36 (33.3)	12/21 (57.1)		
Category 4	0	1/21 (4.8)		
Clinically relevant nonmajor bleeding — no. (%)§	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Major or clinically relevant nonmajor bleeding — no. (%)§¶	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)	
Death from any cause — no. (%)	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)	
Event-free survival — no. (%)‖	287 (55.0)	296 (56.5)	0.93 (0.77–1.11)	

* The overall trial period was the time from randomization through the end of 12 months or the end of the trial, regardless of the duration of treatment for each patient.
† No patient in either group had confirmed fatal pulmonary embolism. A total of six patients in the edoxaban group and four patients in the dalteparin group had unexplained death for which pulmonary embolism could not be ruled out as the cause.
‡ The severity of major bleeding at clinical presentation was adjudicated by an independent clinical events committee (whose members were unaware of the treatment assignments) according to the following prespecified categories: category 1 included bleeding events that were not considered to be a clinical emergency; category 2 included bleeding events that could not be classified in any of the other categories because they led to some treatment but were not considered to be a clinical emergency; category 3 included bleeding events that were considered to be a clinical emergency, such as bleeding with hemodynamic instability or intracranial bleeding with neurologic symptoms; and category 4 included bleeding events that led to death before or almost immediately after the patient entered the hospital.[12]
§ Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the use of medical intervention, contact with a physician, interruption of the assigned treatment, discomfort, or impairment of activities of daily living.
¶ For patients who had more than one event, only the first was counted.
‖ Event-free survival was defined as the absence of recurrent venous thromboembolism, major bleeding, and death.

with dalteparin (P=0.02 for interaction in the safety population).

ADVERSE EVENTS

The adverse events reported in the trial are shown in Tables S9, S10, and S11 in the Supplementary Appendix. The most common adverse events were progression of neoplasm and pneumonia; for each of these events, the rate was similar in the two treatment groups.

DISCUSSION

The Hokusai VTE Cancer trial, which involved patients with predominantly advanced cancer and acute symptomatic or incidental venous thromboembolism, showed that treatment with a fixed once-daily dose of oral edoxaban for up to 12 months was noninferior to treatment with subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboem-

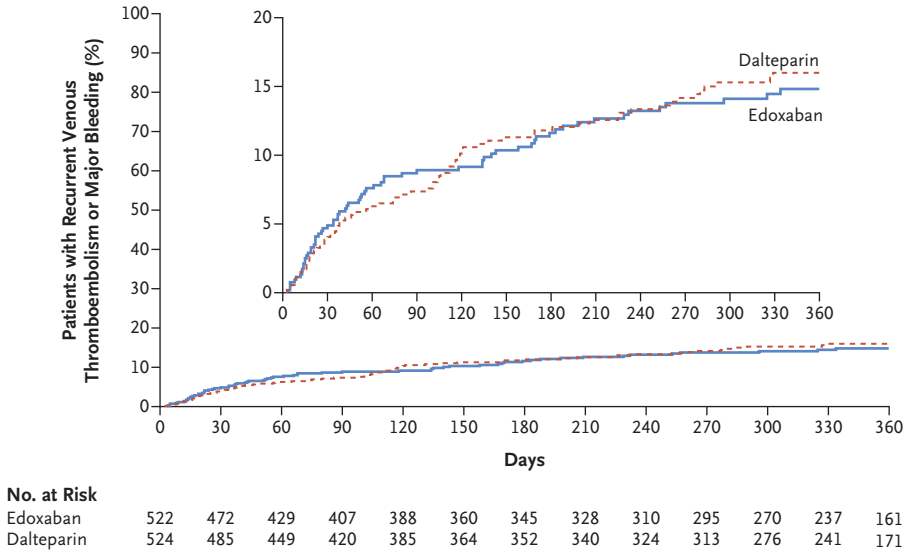

Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.
The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. The inset shows the same data on an enlarged y axis.

bolism or major bleeding. The rate of recurrent venous thromboembolism was numerically lower with edoxaban than with dalteparin (7.9% and 11.3%, respectively; hazard ratio, 0.71; 95% CI, 0.48 to 1.06; P=0.09) because of the lower rate of recurrent symptomatic deep-vein thrombosis with edoxaban (Table 2). The 8.8% rate of recurrent venous thromboembolism at 6 months in the dalteparin group in this trial is consistent with rates reported with dalteparin in previous studies involving patients with cancer.[4,16]

The rate of major bleeding was significantly higher with edoxaban than with dalteparin (6.9% and 4.0%, respectively; hazard ratio, 1.77; 95% CI, 1.03 to 3.04; P=0.04). This difference was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban. This finding is consistent with results of previous studies of direct oral anticoagulants.[11] The increase in upper gastrointestinal major bleeding occurred mainly in patients who had entered the trial with gastrointestinal cancer. However, the frequency of severe major bleeding (category 3 or 4; see Table 2) was similar with edoxaban and dalteparin. The 3.2% rate of major bleeding at 6 months in the dalteparin group in this trial is lower than previously reported rates with dalteparin.[4,16]

Our trial has some limitations. First, the use of an open-label design is a potential weakness, but long-term administration of placebo injections was not considered to be appropriate. To mitigate potential bias, all events were adjudicated by a committee whose members were unaware of the treatment assignments. Second, the number of primary-outcome events was lower than expected; despite this limitation, noninferiority was established. Third, the median duration of the assigned treatment was shorter with dalteparin than with edoxaban, which may have influenced the relative efficacy of the two treatments. However, this difference was primarily due to the inconvenience of the use of subcutaneous dalteparin as compared with oral edoxaban, thus demonstrating the desirability of oral therapy in this context. In addition, the sensitivity analysis of events that occurred during treatment in the per-protocol population confirmed the results of the primary analysis. Finally, the trial included a broad spectrum of patients with cancer who had received a wide array of cyto-

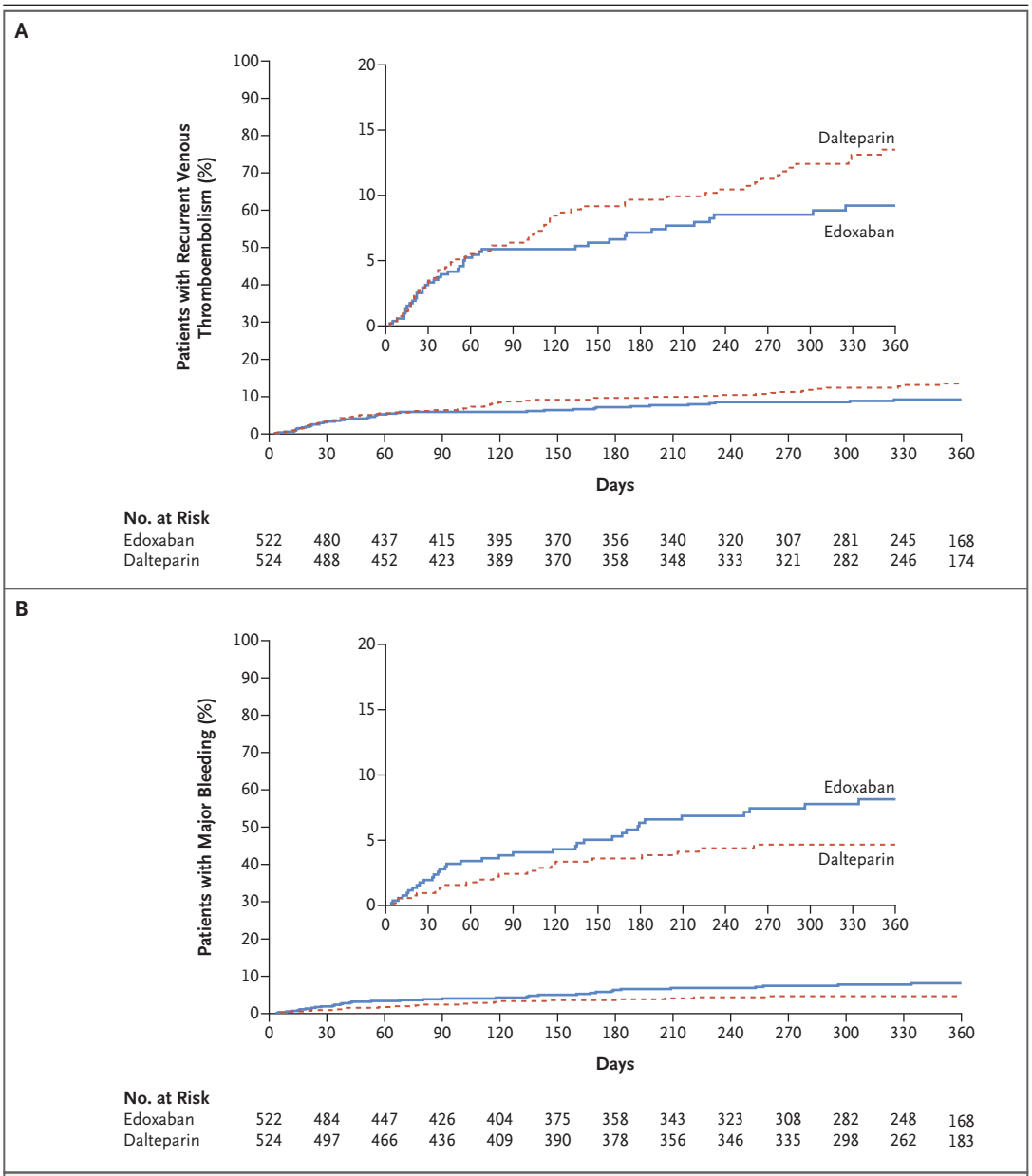

Figure 3. Kaplan–Meier Cumulative Event Rates for Secondary Outcomes.

Shown are cumulative event rates for recurrent venous thromboembolism (Panel A) and major bleeding (Panel B). The insets show the same data on an enlarged y axis.

toxic and biologic therapies, but the sample size limits our ability to make definitive conclusions about outcomes associated with individual tumor types.

In conclusion, in this trial involving patients with cancer-associated venous thromboembolism, edoxaban was noninferior to dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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