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Edoxaban for 12 Months Versus 3 Months in Cancer Patients With Isolated Distal Deep Vein Thrombosis (ONCO DVT study): An Open-label, Multicenter, Randomized Clinical Trial

Running title: *Yamashita et al.; Edoxaban in cancer-associated isolated distal DVT*

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Abstract

Background: The optimal duration of anticoagulation therapy for isolated distal deep vein thrombosis (DVT) in patients with cancer is clinically relevant, but the evidence is lacking. The prolonged anticoagulation therapy could have a potential benefit for prevention of thrombotic events, however, it could also increase the risk of bleeding.

Methods: In a multicenter, open-label, adjudicator-blinded, randomized clinical trial at 60 institutions in Japan, we randomly assigned cancer patients with isolated distal DVT, in a 1-to-1 ratio, to receive either a 12-month or 3-month edoxaban treatment. The primary endpoint was a composite of a symptomatic recurrent venous thromboembolism (VTE) or VTE-related death at 12 months. The major secondary endpoint was major bleeding at 12 months, according to the criteria of the International Society on Thrombosis and Hemostasis. The primary hypothesis was that a 12-month edoxaban treatment was superior to a 3-month edoxaban treatment with respect to the primary endpoint.

Results: From April 2019 through June 2022, 604 patients were randomized, and after excluding 3 patients who withdrew consent, 601 patients were included in the intention-to-treat population: 296 patients in the 12-month edoxaban group and 305 patients in the 3-month edoxaban group. The mean age was 70.8 years, 28% of the patients were men, and 20% of the patients had symptoms of DVT at baseline. The primary endpoint of a symptomatic recurrent VTE event or VTE-related death occurred in 3 of the 296 patients (1.0%) in the 12-month edoxaban group and in 22 of the 305 (7.2%) in the 3-month edoxaban group (odds ratio, 0.13; 95% CI, 0.03 to 0.44). The major secondary endpoint of major bleeding occurred in 28 of the 296 patients (9.5%) in the 12-month edoxaban group and in 22 of the 305 (7.2%) in the 3-month edoxaban group (odds ratio, 1.34; 95% CI, 0.75 to 2.41). The prespecified subgroups did not affect the estimates on the primary endpoint.

Conclusions: In cancer patients with isolated distal DVT, 12 months was superior to 3 months for an edoxaban treatment with respect to the composite outcome of a symptomatic recurrent VTE or VTE-related death.

Clinical Trial Registration: ClinicalTrials.gov, NCT03895502.

Key words: Deep vein thrombosis; Cancer; Anticoagulant; Edoxaban; Recurrence

Clinical Perspective

What is new?

- This study demonstrated that 12 months of edoxaban treatment was superior to 3 months of edoxaban treatment for patients with active cancer and newly diagnosed isolated distal deep vein thrombosis (DVT) with respect to the composite outcome of symptomatic recurrent venous thromboembolism (VTE) event or VTE-related death.
- There was no statistically significant difference in the risk of major bleeding between 12 months and 3 months of edoxaban treatment, although 12 months of edoxaban treatment showed a numerically slightly higher incidence of major bleeding.

What are the clinical implications?

- The risk of symptomatic recurrent VTE in cancer patients with isolated distal DVT could be high without anticoagulation therapy, which could be effectively prevented by anticoagulation therapy.
- The longer duration of anticoagulation therapy had a potential benefit for prevention of thrombotic events in cancer patients with isolated distal DVT.
- Considering the risk of bleeding associated with anticoagulation therapy, physicians should make the decision of anticoagulation strategies for these patients based on risk-benefit balance with anticoagulation therapy in individual patient.

Introduction

Venous thromboembolism (VTE) has a long-term risk of recurrence, and the prevention of a recurrent VTE by anticoagulation therapy is essential for patients with VTE[1]. Isolated distal deep vein thrombosis (DVT) is a common presentation of DVT, which is reported to account for about half of all diagnoses of DVT[2]. The current international guidelines weakly recommend anticoagulation therapy for patients with severe symptoms or with risk factors for a thrombus extension including cancer, and extended duration beyond 3 months for isolated distal DVT patients with active cancer[3, 4]. Cancer is a strong risk factor for the development of VTE[5]. Recently, many cancer patients are surviving longer because of the progress in the diagnosis and treatment of cancer, and thus, VTE during the treatment course of cancer is becoming more clinically relevant in terms of cardio-oncology[6]. A previous study reported that approximately 4.6% of cancer patients had distal DVT[7]. Despite the relatively high frequency of isolated distal DVT in patients with cancer[8-10], previous clinical trials evaluating isolated distal DVT excluded cancer patients[11-13], which resulted in a huge uncertainty of the optimal management strategies including the duration of the anticoagulation therapy and subtypes of distal DVT[14]. However, a previous observational study showed that cancer patients with isolated distal DVT were usually treated with a limited duration period of anticoagulation therapy and were at a relatively high risk of recurrent VTE after discontinuation of the anticoagulation therapy[15], which suggested that those might benefit from prolonged anticoagulation therapy. Given there are no randomized clinical trials on this issue, we conducted the ONCO DVT study to compare the 2 different

treatment durations of the oral factor Xa inhibitor edoxaban for isolated distal DVT in patients with cancer.

Methods

Study design

The ONCO DVT study was an investigator-initiated, multicenter, open-label, adjudicator-blinded, superiority, randomized clinical trial at 60 institutions in Japan designed to compare a 12-month edoxaban treatment with a 3-month edoxaban treatment in cancer patients with isolated distal DVT. Funding was provided by Daiichi Sankyo Co., Ltd., which had no role in the study design, data collection, analysis, interpretation, or writing of the report. The trial was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Kyoto University Institutional Review Board, along with the institutional review boards of all participating institutions. Data were reviewed by an independent data and safety monitoring committee. The protocol and accompanying documents are available with the full text (Supplement). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study population

Adult patients with active cancer who were newly diagnosed with isolated distal DVT confirmed by ultrasonography were eligible for inclusion. Active cancer was defined as cancer which satisfies one of the following criteria; newly diagnosed with cancer within 6 months of randomization; cancer

treatment (surgery, chemotherapy, radiotherapy, etc.) performed within 6 months of randomization; currently receiving cancer treatment (surgery, chemotherapy, radiotherapy, etc.); has recurrence, local invasion, or distant metastases; patients with hematopoietic malignancy who have not achieved complete remission[16].

All patients are evaluated by whole leg ultrasonography using a high-frequency (5-10MHz) linear probe. The examination observes the veins from the inferior vena cava to the ankle level with the patient in a supine position. In addition to imaging diagnostics using a color Doppler, the compression method will also be used to check for thrombi. If evaluation with the patient in a supine position is insufficient for examination of the veins of the lower limbs, then the examination may be conducted with the patient in a seated position with their feet on the floor, at the discretion of the expert sonographer. The calf veins were evaluated using the anteromedial, posterior, and posterolateral views. Several veins were scanned in the transverse plane over their entire length: anterior tibial, posterior tibial, and fibular (axial veins), medial and lateral gastrocnemius, and soleal veins (muscular veins). The diagnostic criteria for isolated distal DVT are the presence of thrombi or lack of blood flow with distal compression, in addition to non-collapse with compression.

The key exclusion criteria were patients on anticoagulation therapy at the time of the diagnosis, patients with a contraindication for edoxaban, patients with pulmonary embolism (PE), and patients who were expected to have a life prognosis of 3 months or less by the treating physicians. All patients provided written informed consent. The full detailed inclusion and exclusion criteria are provided in

e-Appendix 3.

Randomization and treatment

Eligible patients were randomly assigned, in a 1-to-1 ratio, either to the 12-month edoxaban treatment group or to the 3-month edoxaban treatment group in an open-label design. Randomization was performed centrally through the electronic data capture system with a stochastic minimization algorithm for adaptive randomization to balance the treatment assignments within the institutions.

Edoxaban was administered after an appropriate initial treatment after the diagnosis, in accordance with the policies at each institution, however, no restrictions were set for the policies, providing the treatment did not contravene the exclusion criteria. Edoxaban was administered orally at a fixed dose of 60 mg once daily and 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.

Follow-up

The mandatory follow-up visits were planned at 3 months and 12 months, with additional assessments for routine clinical care as needed. At the 3-month visit after the diagnosis (between 61 days and 119 days), the 3-month edoxaban treatment group stopped edoxaban, while the 12-month edoxaban treatment group continued edoxaban. In addition to the baseline visit, ultrasonography of the lower limb venous system and laboratory tests were repeated at 3 months and 12 months. During the follow-up period, the anticoagulation status was obtained including the discontinuation and initiation of

anticoagulants with the reasons and types of anticoagulants. Persistent edoxaban discontinuation was defined as a discontinuation of edoxaban according to the study protocol or lasting for more than 14 days for any reason. A full detailed follow-up methodology is provided in e-Appendix 5.

Primary and secondary endpoints

The primary endpoint was a composite of symptomatic recurrent VTE or VTE-related death at 12 months. Symptomatic recurrent VTE was defined as new or newly worsening PE or DVT symptoms, and new thrombi found on imaging tests, or thrombi that had worsened over time as compared to the most recent image. Symptomatic VTE recurrence is not determined solely based on the appearance or worsening of thrombus images on imaging without new or worsening symptoms. Similarly, if the patient had a thrombus in the index vein and new symptoms, we did not count it as symptomatic recurrent VTE if there was no thrombus extension. VTE-related death was diagnosed at autopsy, death followed a clinically severe PE, or death unexplained by something other than a PE.

The major secondary endpoint was a major bleeding event at 12 months. Major bleeding was defined according to the definition of the International Society on Thrombosis and Haemostasis (ISTH) criteria, which consisted of fatal bleeding, symptomatic bleeding in a critical area or organ, and bleeding causing a reduction in the hemoglobin level by at least 2 g/dL or leading to a transfusion of at least 2 units of whole blood or red cells[17]. Other secondary endpoints were symptomatic VTE recurrence events, VTE-related deaths, new or worsening thrombus images in any imaging tests during the follow-up without any symptoms, all clinically relevant bleeding events, and deaths from all causes

at 12 months. New or worsening thrombus images in any imaging tests during the follow up without any symptoms were defined as appearance of new or worsening thrombus images in the pulmonary arteries and deep veins on imaging tests that did not match the definition of a symptomatic VTE recurrence, and were not associated with new or worsening symptoms. A list of the prespecified secondary endpoints and criteria for adjudication of all the outcomes is provided in e-Appendix 6.

The members of an independent clinical events committee who were unaware of the study-group assignments adjudicated all the suspected outcome events and causes of death, as well as the severity of the major bleeding events, with the use of a prespecified criteria[18].

Statistical analysis

The primary hypothesis was that the 12-month edoxaban treatment group was superior to the 3-month edoxaban treatment group in terms of the rate of the primary endpoint at 12 months. A detailed calculation of the trial sample size is provided in e-Appendix 7. We assumed a 6% event rate in the 12-month edoxaban group and 13% event rate in the 3-month edoxaban group based on the previous studies[15, 16]. To demonstrate the superiority of a 12-month versus 3-month edoxaban treatment with a power of 80% and a 2-sided α=0.05, 550 participants were required, and we enrolled 600 participants considering the potential dropouts.

The analysis of the primary endpoint was performed in the intention-to-treat population, which included all the patients who had undergone randomization after excluding those patients who withdrew consent. For patients who did not experience an event, the time to the first event was

censored at day 365, or the last day the patient had a complete assessment for the study outcomes, whichever came first. Patients lost to follow-up and patients who died because of reasons other than VTE before the end of the 12-month treatment period and who did not have the primary endpoint, were censored on the last day when the patient had a complete assessment for the study outcomes. We also performed per-protocol and as-treated analysis to avoid bias of an open-label assigned group as the sensitivity analyses (e-Appendix 8). We performed subgroup analyses with interaction tests in the prespecified clinically relevant subgroups. Furthermore, because the presence of symptoms for isolated distal DVT at diagnosis might have some influence on thrombotic tendency, we conducted a post-hoc stratified analysis according to the symptoms at diagnosis. The detailed statistical analysis plans are available with the full text (Supplement).

We compared the rates of patients with the primary and secondary endpoints between the 2 treatment groups in the intention-to-treat population, and calculated the odds ratios (OR), using the logistic regression models with the corresponding 95% confidence intervals (CI). We estimated the persistent discontinuation rates of edoxaban and cumulative incidences of the primary and major secondary endpoints with the Kaplan-Meier method, and the difference for the primary endpoint was assessed by the log-rank test. We constructed the same logistic regression models to estimate the P-values for any interaction in the subgroup analyses. A physician (Y.Y.) and a statistician (T.M.) performed all statistical analyses using JMP version 15.2.0 (SAS Institute Inc., Cary, NC, USA) and SAS version 9.4 (SAS Institute Inc) software. The reported P-values were 2-tailed, and a $P<0.05$ was

considered statistically significant. Because there was no plan for adjustment of the widths of CIs and interaction P-values of subgroup analyses for multiple comparisons, these data should be interpreted as exploratory. In addition, because variations in the effectiveness of the interventions and other managements were less likely, an adjustment of the stratification variable was not planned.

Results

Patient enrollment and characteristics

From April 1, 2019 through June 30, 2022, a total of 605 patients were screened and enrolled, and after excluding 1 patient who withdrew consent before randomization, 604 patients were randomized (Figure 1). After excluding 3 patients who withdrew consent, 601 patients were included in the intention-to-treat population: 296 patients in the 12-month edoxaban group and 305 patients in the 3-month edoxaban group. The clinical characteristics of the patients at baseline are shown in Table 1. The mean age was 70.8 years, 28% of the patients were men, and 20% of the patients had symptoms of DVT at baseline. The most common type of cancer was gynecologic cancer (28%), followed by lung cancer (11%) and colon cancer (10%) (Table S1). The most common reason for conducting ultrasonography was due to a high-risk status with elevated D-dimer levels (38%), followed by elevated D-dimer levels before surgery (24%) and suspected DVT based on the symptoms (20%) (Table S2).

Edoxaban treatment

The median (interquartile range) duration of the edoxaban treatment was 92 (74-104) days in the 3-month edoxaban group and 365 (131-365) days in the 12-month edoxaban group. The cumulative 120-day incidences of a persistent discontinuation of edoxaban were 20.6% in the 12-month edoxaban group and 86.3% in the 3-month edoxaban group, respectively (Figure 2). Among 305 patients in the 3-month edoxaban group, 46 (15%) discontinued edoxaban prematurely within 60 days and 49 (16%) continued edoxaban beyond 120 days. The common reasons for a persistent edoxaban discontinuation in the 12-month edoxaban group were due to bleeding events (26%) and cancer progression (25%), whereas those in the 3-month edoxaban group were per-protocol discontinuations (78%) (Table S3).

Primary endpoint

The primary endpoint of symptomatic recurrent VTE or VTE-related death occurred in 3 of the 296 patients (1.0%) in the 12-month edoxaban group and in 22 of the 305 patients (7.2%) in the 3-month edoxaban group (OR, 0.13; 95% CI, 0.03 to 0.44) (Table 2). There were no VTE-related deaths in either group. Symptomatic recurrent VTE consisted of 3 PEs including 2 PEs with hypoxia, and 22 DVTs including 7 proximal DVTs and 14 isolated distal DVTs (Table S4). Among the 22 patients with symptomatic recurrent VTE in the 3-month edoxaban group, 13 (59%) developed a recurrence as isolated distal DVT. The time to the occurrence of the primary endpoint is shown in Figure 3. The results of the per-protocol and as-treated analysis were consistent with the results of the primary analysis (Tables S5 and S6, and Figures S1, S2, S3, and S4).

Secondary endpoints

The major secondary endpoint of major bleeding occurred in 28 of the 296 patients (9.5%) in the 12-month edoxaban group and in 22 of the 305 patients (7.2%) in the 3-month edoxaban group (OR, 1.34; 95% CI, 0.75 to 2.41) (Table 2, and Figure 4). The most common site of major bleeding was the lower gastrointestinal tract (48%), and the vast majority of the severity of the major bleeding was category 2 (78%) (Table S3). The results of the per-protocol and as-treated analysis were consistent with the results of the primary analysis (Table S5 and S6).

The incidence of other secondary endpoints in the 2 groups are provided in Table 2. New or worsening thrombus images in any imaging tests during follow up without any symptoms occurred in 23 patients (7.8%) in the 12-month edoxaban group and in 46 (15%) in the 3-month edoxaban group (OR, 0.47; 95% CI, 0.28 to 0.80). All clinically relevant bleeding events occurred in 53 patients (18%) in the 12-month edoxaban group and in 41 (13%) in the 3-month edoxaban group (OR, 1.40; 95% CI, 0.90 to 2.19). Deaths from all causes occurred in 66 patients (22%) in the 12-month edoxaban group and in 77 (25%) in the 3-month edoxaban group (OR, 0.85; 95% CI, 0.58 to 1.24). Patients with symptomatic recurrent VTE during the follow-up period had a numerically higher incidence rate of deaths from all causes than those without (with symptomatic recurrent VTE: 32% and without symptomatic recurrent VTE: 23%), although it was not statistically significant.

Subgroup analysis

There were no differences of effect between the pre-specified subgroup and treatment for the primary endpoint (Figure 5). The stratified analysis by the presence of symptoms at the time of the diagnosis

is shown in Table S7. Generally, patients with symptoms had numerically higher event rates of the primary endpoint (Symptomatic DVT at diagnosis: 11%, and asymptomatic DVT at diagnosis: 2.5%). Among the patients with symptomatic DVT at the time of the diagnosis, the primary endpoint occurred in 3 of the 53 patients (5.7%) in the 12-month edoxaban group and in 10 of the 69 patients (14%) in the 3-month edoxaban group (OR, 0.35; 95% CI, 0.09 to 1.36), whereas among the patients with asymptomatic DVT at the time of the diagnosis, there were no patients with the primary endpoint in the 12-month edoxaban group and 12 patients (5.1%) with the primary endpoint in the 3-month edoxaban group.

Discussion

The ONCO DVT study, which enrolled patients with active cancer and newly diagnosed isolated distal DVT, showed that 12 months of edoxaban treatment was superior to 3 months of edoxaban treatment with respect to the composite outcome of symptomatic recurrent VTE event or VTE-related death, whereas the longer duration of edoxaban treatment showed a numerically slightly higher incidence of major bleeding, although not significant.

The clinical relevance of isolated distal DVT remains debatable. Historically, isolated distal DVT is considered as a more benign condition of DVT than a proximal DVT, whereas some previous studies reported that isolated distal DVT had a similar long-term risk of recurrence as a proximal DVT[19, 20]. Due to the lack of solid evidence, the optimal management strategies for isolated distal DVT

remain controversial, which leads to wide variations in the diagnostic and therapeutic strategies across the institutions[2, 21]. A previous randomized clinical trial, the CACTUS trial, showed that low-molecular-weight heparin was not superior to placebo in reducing the risk of a proximal extension or venous thromboembolic events in patients with a symptomatic distal DVT[11]. Another recent randomized clinical trial, the RIDTS study, showed that rivaroxaban administered for 6 additional weeks in patients with isolated distal DVT who had an uneventful 6-week treatment course reduced the risk of recurrent VTE[13]. However, these studies excluded patients with active cancer, who were considered as high-risk patients for thrombotic events. The American College of Chest Physicians (ACCP) 2021 guidelines weakly recommend that isolated distal DVT patients with active cancer should receive anticoagulation therapy and anticoagulation strategy should be same as that for patients with proximal DVT, which means that an extended duration of anticoagulation therapy might be recommended[3]. Similarly, the European Society for Vascular Surgery (ESVS) 2021 guidelines weakly recommend that anticoagulation therapy beyond 3 months should be considered for symptomatic isolated distal DVT patients with active cancer[4]. In addition, the current study included a dominant proportion of asymptomatic isolated distal DVT, of which the clinical relevance might be further debatable. Considering the frequent detection of asymptomatic isolated distal DVT among cancer patients in daily clinical practice[7], we allowed the inclusion of asymptomatic isolated distal DVT in the current study.

A previous observational study showed that patients with isolated distal DVT complicated

with active cancer were usually treated with a limited duration period of anticoagulation therapy and were at a relatively high risk of recurrent VTE (13.2% per year), with about two-thirds of events occurring after discontinuation of the anticoagulation therapy[15], which suggested that isolated distal DVT patients with active cancer might benefit from prolonged anticoagulation therapy. However, there have been no randomized clinical trials specifically evaluating the optimal duration of anticoagulation therapy for isolated distal DVT patients with active cancer, and it remains uncertain whether anticoagulation therapy should be extended beyond 3 months. The current randomized clinical trial demonstrated that a longer duration of anticoagulation therapy with edoxaban was superior to a limited duration of anticoagulation therapy with 3 months of edoxaban in terms of symptomatic thrombotic events. Although a certain number of recurrent VTEs were PEs with hypoxia and proximal DVTs, more than half of recurrent VTE were recurrent distal DVTs. The clinical relevance of recurrent distal DVT might be lower than that of recurrent proximal DVT, whereas development of recurrent distal DVT with symptoms could lead to additional anticoagulation therapy. When physicians consider the potential benefit of extended anticoagulation therapy beyond 3 months, it should be taken into consideration that most of the favorable effects could be based on the prevention of recurrent distal DVT.

For the decision-making of the optimal duration of anticoagulation therapy, the risk of bleeding associated with anticoagulation therapy should be taken into account[22]. Especially, patients with cancer-associated VTE have been reported to have a markedly higher risk of bleeding, compared

with those without active cancer, leading to difficulty in achieving a good risk-benefit balance with anticoagulation therapy. The Hokusai VTE Cancer trial showed the rate of major bleeding was 6.9% at 1 year in the edoxaban treatment group of cancer-associated VTE[16]. The current study showed that the rate of major bleeding was 9.5% in the 12-month edoxaban group, however, there was no statistically significant difference as compared to the 3-month edoxaban group (7.2%). The time-to-event curves for major bleeding events demonstrated that the occurrence of major bleeding seemed to be more common in the first 3 months in both groups, and the risk of major bleeding did not significantly differ beyond 3 months, suggesting that the major bleeding risk associated with edoxaban might be more remarkable in the early period after the initiation of edoxaban and continuation of edoxaban beyond that phase might not necessarily increase the risk of major bleeding. However, considering the numerically higher incidence of major bleeding including intracranial bleeding in 12-month edoxaban group, clinicians should still be cautious for the risk of bleeding. Considering the risk of bleeding associated with anticoagulation therapy, physicians should make the decision of anticoagulation strategies for these patients based on risk-benefit balance with anticoagulation therapy in individual patient.

Some limitations of the current study should be noted. First, the open-label design had the potential to introduce bias including ascertainment bias. Although all the clinical endpoints were adjudicated by the members of an independent committee who were unaware of the study-group assignments, the diagnostic testing strategies could have been influenced by the open-label design,

which could have had a certain influence on the primary endpoint. On the other hand, to decrease the influence of the diagnostic testing strategies on the primary endpoint due to the open-label design, we evaluated symptomatic recurrent VTE as the primary endpoint, not asymptomatic recurrent VTE, which could have been more influenced by the diagnostic testing strategies. Second, the current study population included a high proportion of asymptomatic isolated distal DVT. In the daily clinical practice in Japan, physicians do not usually conduct a screening strategy for DVT in the case of a low pretest probability or low D-dimer level, which is recommended in the current guidelines[3]. However, if there is suspicion or concern for acute thrombosis such as an acute elevation of the D-dimer levels in high-risk patients, patients could be evaluated by ultrasonography based on the discretion of the physicians. In the current study, the majority of patients received ultrasonography due to suspicion of acute thrombosis such as an acute elevation of the D-dimer level. Although the current study population was basically expected to consist of acute DVT, isolated distal DVT without major symptoms could reflect a more minor thrombus, which should be interpreted cautiously. Third, there were patients with withdrawal of consent and loss to follow-up. However, those patients consisted of approximately 2% of the total cohort, and the influence could have been minimal. Fourth, the number reaching the primary endpoint was lower than expected. This could be partly because the estimated event rates in both groups were calculated based on different study populations than the current study population. Especially, the estimated event rates of 6% in the 12-month edoxaban group was calculated based on patients with PE and proximal DVT in the Hokusai VTE Cancer trial, which were thought to

be at a higher risk of recurrent VTE than isolated distal DVT[16]. In addition, the majority of the patients in the current study had asymptomatic isolated distal DVT, which could be at a lower risk of recurrent VTE than that symptomatic. Actually, patients with symptomatic isolated distal DVT showed numerically higher event rates of the primary endpoint among both 12-month and 3-month edoxaban group compared with those with asymptomatic. Despite this limitation, the superiority was established. Fifth, adherence to edoxaban treatment was relatively low according to the study protocol. Especially, some of the patients in the 12-month edoxaban group discontinued edoxaban prematurely due to bleeding events or cancer progression. This issue could have underestimated the risk of major bleeding in the 12-month edoxaban group by the intention-to-treat analysis. However, the sensitivity analysis of the per-protocol population and as-treated population confirmed the results of the primary analysis including major bleeding. Finally, there could be racial differences including the prevalence of hereditary thrombophilia and low body weight, and practice differences depending on the regions including the ultrasonography methodology. In addition, the current study included a variety of cancer patients including a relatively high proportion of patients with gynecologic cancers. Furthermore, the influence of the detailed thrombus site including axial and muscular distal DVT was not evaluated in the current study. The generalizability of the current results should be carried out carefully.

Conclusions

In the ONCO DVT study enrolling isolated distal DVT patients with active cancer, a 12-month

edoxaban treatment was superior to a 3-month edoxaban treatment with respect to the composite outcome of symptomatic recurrent VTE or VTE-related death.

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Supplemental Materials

e-Appendix 1-8

Table S1-7

Figure S1-4

Original protocol, final protocol, summary of changes

Original statistical analysis plan, final statistical analysis plan, summary of changes

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Tables

Table 1. Clinical Characteristics of the Patients at Baseline (Intention-to-treat Population)*

	12-month edoxaban (N=296)	3-month edoxaban (N=305)
Baseline characteristics		
Age, years	71.6±9.4	70.1±10.3
Age ≥75 years, No. (%)	131 (44)	114 (37)
Male sex, No. (%)	94 (32)	73 (24)
Body weight, kg	56.3±12.1	54.8±11.6
Body weight <60 kg, No. (%)	199 (67)	222 (73)
Body mass index, kg/m^2	22.7±4.0	22.4±4.1
Symptoms at baseline, No. (%)	53 (18)	69 (23)
Site of thrombosis, No. (%)		
Bilateral side, No. (%)	118 (40)	105 (34)
Right side, No. (%)	73 (25)	81 (27)
Left side, No. (%)	105 (35)	119 (39)
Standard dose of edoxaban (60 mg per day), No. (%)†	80 (27)	71 (23)
Lower dose of edoxaban (30 mg per day), No. (%) †	216 (73)	234 (77)
Cancer status		
Newly diagnosed with cancer within 6 months, No. (%)	184 (62)	205 (67)
Chemotherapy performed within 6 months, No. (%)	142 (48)	141 (46)
Radiotherapy performed within 6 months, No. (%)	20 (6.8)	32 (10)
Recurrent cancer, No. (%)	31 (10)	34 (11)
Metastatic disease, No. (%)	67 (23)	80 (26)
ECOG performance status, No. (%)‡		
0	161 (54)	150 (49)
1	78 (26)	103 (34)
≥2	57 (19)	52 (17)
Comorbidities		
Hypertension, No. (%)	133 (45)	130 (43)
Diabetes, No. (%)	54 (18)	47 (15)
Heart failure, No. (%)	7 (2.4)	3 (1.0)
History of stroke, No. (%)	14 (4.7)	13 (4.3)

History of venous thromboembolism, No. (%)	20 (6.8)	13 (4.3)
History of major bleeding, No. (%)	7 (2.4)	16 (5.3)
Transient risk factors for venous thromboembolism, No. (%)§	80 (27)	71 (23)
Recent surgery within 2 months, No. (%)	41 (14)	44 (14)
Laboratory tests at diagnosis		
Creatinine clearance ≤50 ml/min, No. (%)	69 (23)	62 (20)
Anemia, No. (%)‖	199 (67)	203 (67)
Platelet count <100,000 per μl, No. (%)	12 (4.1)	19 (6.2)
D-dimer, μg/mL**	5.2 (2.2-10.8)	4.7 (2.3-11.3)
Concomitant medication		
Antiplatelet, No. (%)	27 (9.1)	21 (6.9)
Steroid, No. (%)	34 (11)	43 (14)
Statin, No. (%)	71 (24)	63 (21)

*Plus–minus values are means ±standard deviation.

†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.

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

§Transient risk factors for venous thromboembolism included recent surgery, recent immobilization, long-distance travel, central venous catheter use, pregnancy or puerperium, recent leg trauma, fracture or burn, severe infection, and estrogen use.

‖Anemia was diagnosed if the value of hemoglobin was <13 g/dL for men and <12 g/dL for women.

**Data are missing for 19 patients in the 3-month edoxaban group and 15 patients in the 12-month edoxaban group. Values (continuous variables) are presented as the median and interquartile range.

Table 2. Clinical Outcomes at 12 Months*

	12-month edoxaban (N=296)	3-month edoxaban (N=305)	Odds ratio (95% CI)
Primary endpoint			
Symptomatic recurrent venous thromboembolism or venous thromboembolism-related death, No. (%)	3 (1.0)	22 (7.2)	0.13 (0.03-0.44)
Major secondary endpoint			
Major bleeding, No. (%)†	28 (9.5)	22 (7.2)	1.34 (0.75-2.41)
Other secondary endpoints			
Symptomatic venous thromboembolism recurrence events, No. (%)	3 (1.0)	22 (7.2)	0.13 (0.03-0.44)
Venous thromboembolism-related deaths, No. (%)‡	0 (0)	0 (0)	-
New or worsening thrombus images in any imaging tests during follow up without any symptoms, No. (%)§	23 (7.8)	46 (15)	0.47 (0.28-0.80)
All clinically relevant bleeding events, No. (%)‖	53 (18)	41 (13)	1.40 (0.90-2.19)
Clinically relevant non-major bleeding, No. (%)	28 (9.5)	22 (7.2)	1.34 (0.75-2.41)
Deaths from all causes, No. (%)	66 (22)	77 (25)	0.85 (0.58-1.24)

*The analyses were performed for the full analysis set based on the intention-to-treat approach, which included all the patients who had undergone randomization after excluding patients who withdrew consent. For patients who did not experience an event, the time to the first event was to be censored at day 365, or the last day the patient had a complete assessment for study outcomes, whichever comes first. We calculated the odds ratios, computed using the logistic regression model along with the corresponding 95% confidence intervals for all clinical endpoints, which have not been adjusted for multiple comparisons.

†Major and nonmajor bleeding events were classified according to the criteria of the International Society on Thrombosis and Hemostasis.

‡Death due to pulmonary embolism diagnosed prior to death or at autopsy, or death unexplained by other than pulmonary embolism.

§Appearance of new or worsening thrombus images in the pulmonary arteries and deep veins on imaging tests (ultrasonography of lower limb vein system, computed tomography examination, pulmonary perfusion

scintigraphy, pulmonary angiography, venography) that do not match the definition of a symptomatic venous thromboembolism recurrenc and are not associated with new or worsening symptoms.
||For patients who had more than one event, only the first was counted.

Figure Legends

Figure 1. Enrollment, Randomization, and Follow-up.

Patients were randomly assigned in a 1:1 ratio to receive a 3-month edoxaban treatment or a 12-month edoxaban treatment. Randomization was performed centrally through the electronic data capture system with a stochastic minimization algorithm to balance the treatment assignment within the centers. The intention-to-treat population included all patients who had undergone randomization.

Figure 2. Kaplan–Meier Curves for a Persistent Edoxaban Discontinuation.

The time-to-event curves over 1-year after the diagnosis of persistent edoxaban discontinuation. Persistent edoxaban discontinuation was defined as discontinuation of edoxaban according to the study protocol or lasting for more than 14 days for any reason. The analyses were performed for the full analysis set based on the intention-to-treat approach.

Figure 3. Kaplan–Meier Curves for the Primary Endpoint.

The time-to-event curves over 1-year after the diagnosis of the primary endpoint (symptomatic recurrent VTE or VTE-related death).

VTE, venous thromboembolism.

Figure 4. Kaplan–Meier Curves for the Major Secondary Endpoint.

The time-to-event curves over 1-year after the diagnosis of the major secondary endpoint (major bleeding). Major bleeding was defined according to the definition of the International Society on Thrombosis and Haemostasis criteria, which consisted of fatal bleeding, symptomatic bleeding in a critical area or organ, and bleeding causing a reduction in the hemoglobin level by at least 2 g/dL or leading to a transfusion of at least 2 units of whole blood or red cells.

Figure 5. Subgroup Analyses for the Primary Endpoint.

The ORs for the primary endpoint in the 2 groups are described according to the pre-defined subgroups. The 95% CIs have not been adjusted for multiple comparisons.

OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism

Figure 1

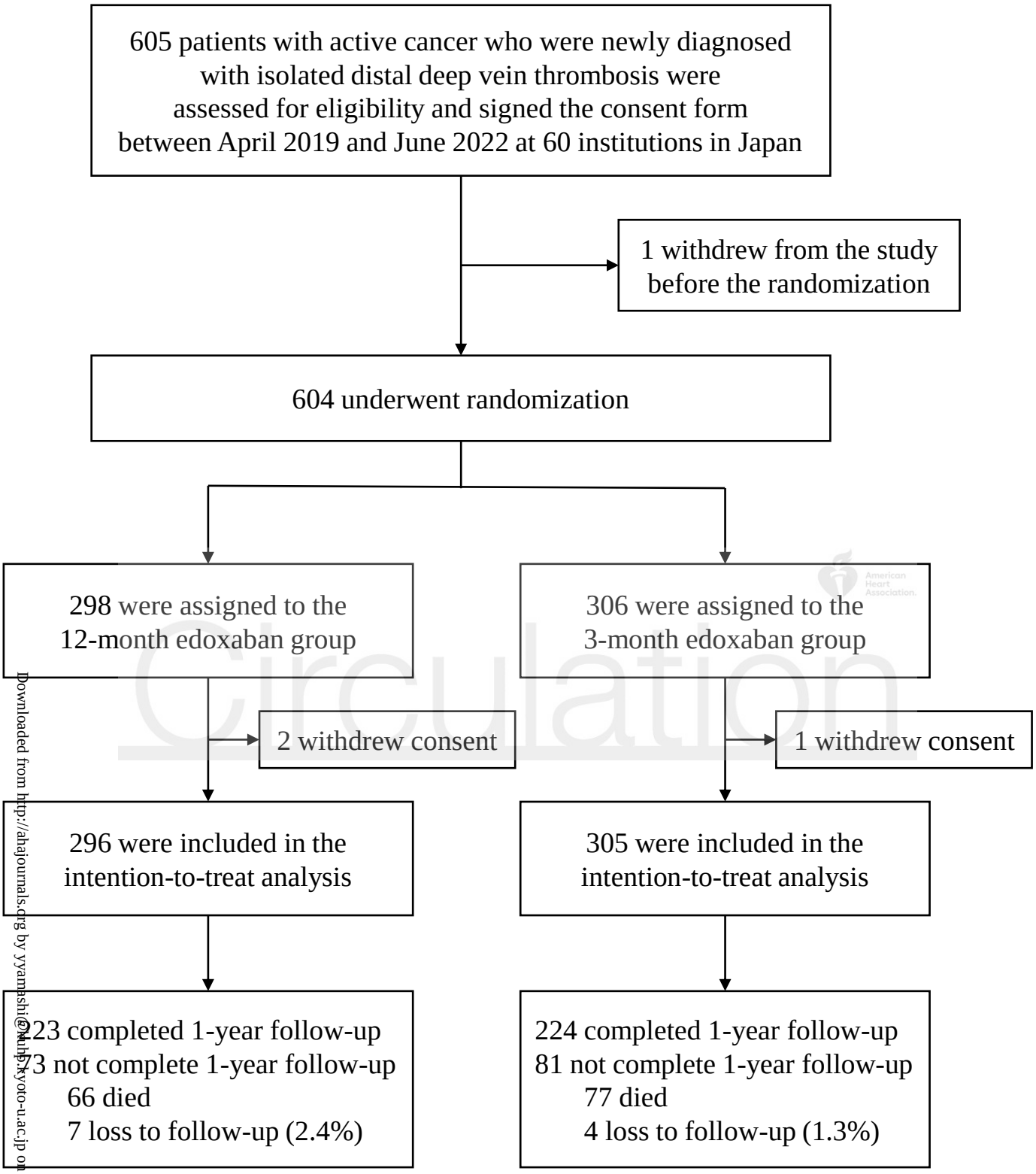
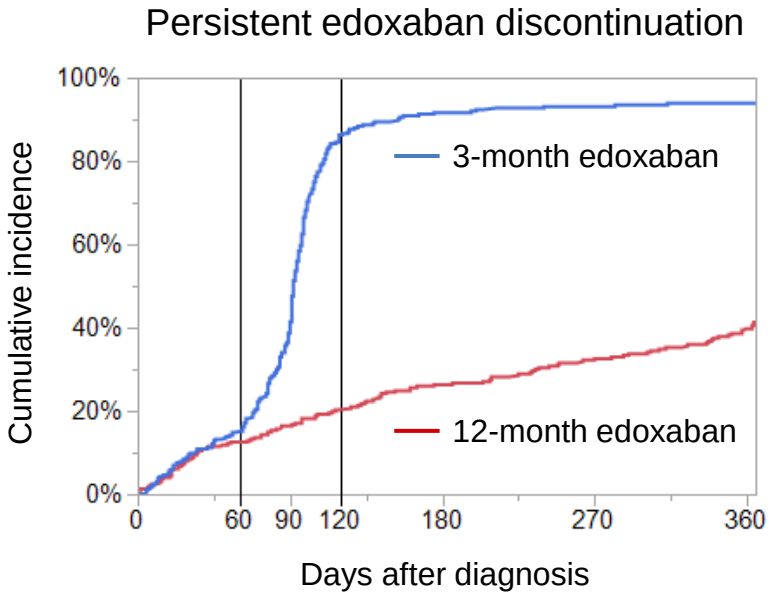
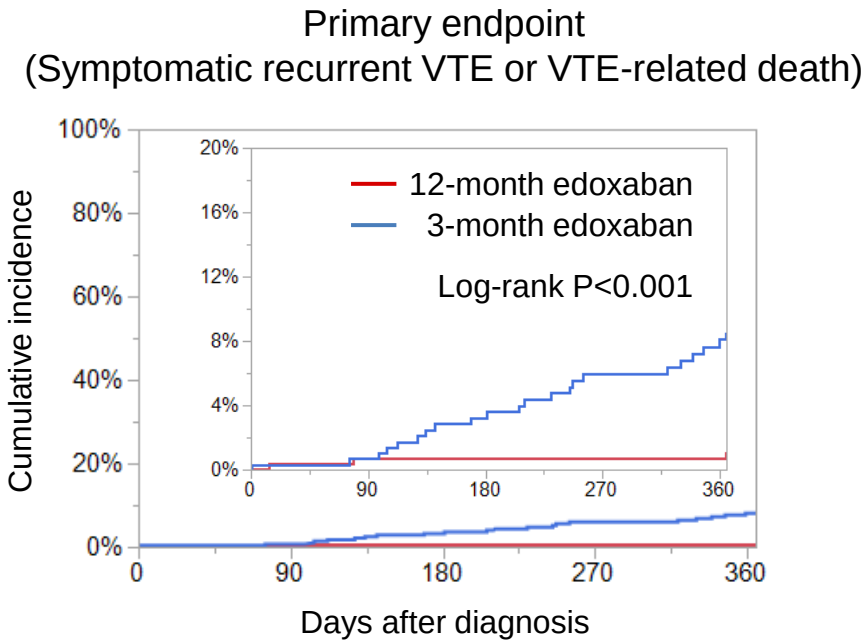


Figure 2



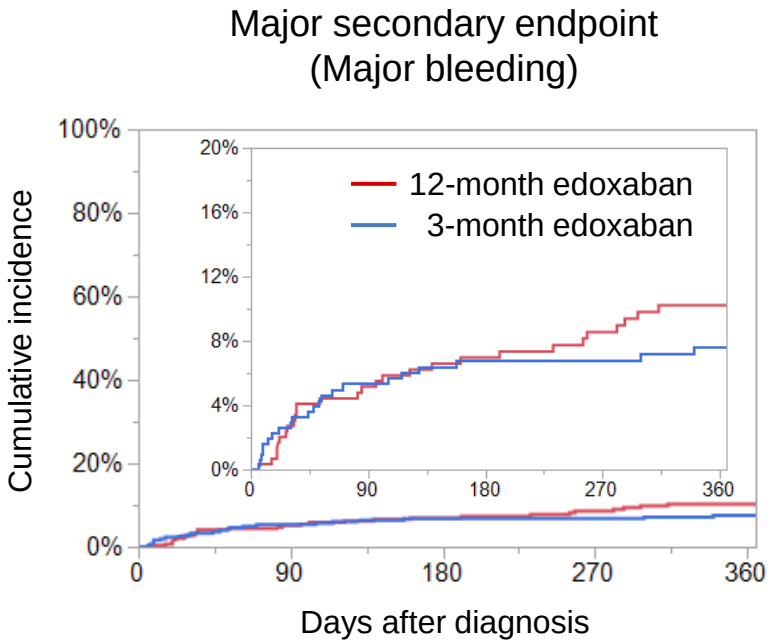
	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban						
N of patients with discontinuation		37	48	60	76	116
N of patients on edoxaban	296	253	240	224	202	151
Cumulative incidence		12.6%	16.4%	20.6%	26.3%	41.3%
3-month edoxaban						
N of patients with discontinuation		46	124	256	271	277
N of patients on edoxaban	305	255	173	40	23	15
Cumulative incidence		15.2%	41.4%	86.3%	91.6%	93.9%

Figure 3



	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban						
N of patients with event		1	2	2	2	3
N of patients at risk	296	283	274	269	253	222
Cumulative incidence		0.3%	0.7%	0.7%	0.7%	1.2%
3-month edoxaban						
N of patients with event		1	2	5	9	22
N of patients at risk	305	289	280	275	256	210
Cumulative incidence		0.3%	0.7%	1.8%	3.2%	8.5%

Figure 4



	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban						
N of patients with event		13	15	17	20	28
N of patients at risk	296	273	267	261	245	210
Cumulative incidence		4.4%	5.2%	5.9%	7.0%	10.2%
3-month edoxaban						
N of patients with event		14	16	18	20	22
N of patients at risk	305	279	271	264	250	217
Cumulative incidence		4.7%	5.3%	6.1%	6.8%	7.6%

Figure 5