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ORIGINAL RESEARCH ARTICLE

Rivaroxaban for 18 Months Versus 6 Months in Patients With Cancer and Acute Low-Risk Pulmonary Embolism: An Open-Label, Multicenter, Randomized Clinical Trial (ONCO PE Trial)

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BACKGROUND: The optimal duration of anticoagulation therapy for patients with cancer and acute low-risk pulmonary embolism (PE) is clinically relevant, but evidence is lacking. 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 32 institutions in Japan, we randomly assigned patients with cancer and acute low-risk PE of the simplified version of the Pulmonary Embolism Severity Index score of 1, in a 1:1 ratio, to receive either an 18-month or a 6-month rivaroxaban treatment. The primary end point was recurrent venous thromboembolism (VTE) at 18 months. The major secondary end point was major bleeding at 18 months according to the criteria of the International Society on Thrombosis and Hemostasis. The primary hypothesis was that an 18-month treatment was superior to a 6-month treatment in terms of the primary end point.

RESULTS: From February 2021 to March 2023, 179 patients were randomized, and after the exclusion of one patient who withdrew consent, 178 were included in the intention-to-treat population: 89 patients in the 18-month rivaroxaban group and 89 in the 6-month rivaroxaban group. The mean age was 65.7 years; 47% of the patients were men, and 12% had symptoms of PE at baseline. The primary end point of recurrent VTE occurred in 5 of the 89 patients (5.6%) in the 18-month rivaroxaban group and in 17 of the 89 (19.1%) in the 6-month rivaroxaban group (odds ratio, 0.25 [95% CI, 0.09–0.72]; *P*=0.01). Among 22 recurrent VTE, 5 patients presented with a symptomatic recurrent VTE; recurrent PE occurred in 11 patients, including 2 with main and 4 with lobar PEs; and recurrent deep vein thrombosis was seen in 11 patients, including 3 with proximal deep vein thromboses. The major secondary end point of major bleeding occurred in 7 of the 89 patients (7.8%) in the 18-month rivaroxaban group and in 5 of the 89 patients (5.6%) in the 6-month rivaroxaban group (odds ratio, 1.43 [95% CI, 0.44–4.70]; *P*=0.55).

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CONCLUSIONS: In patients with cancer and acute low-risk PE of the simplified version of the Pulmonary Embolism Severity Index score of 1, the 18-month rivaroxaban treatment was superior to the 6-month rivaroxaban treatment with respect to recurrent VTE events.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04724460.

Key Words: anticoagulants ■ cardio-oncology ■ neoplasms ■ pulmonary embolism ■ recurrence ■ rivaroxaban

Clinical Perspective

What Is New?

- This trial demonstrated that 18 months of rivaroxaban treatment was superior to 6 months of rivaroxaban treatment for patients with cancer and acute low-risk pulmonary embolism of the simplified version of the Pulmonary Embolism Severity Index score of 1 with respect to recurrent venous thromboembolism events.
- There was no statistically significant difference in the risk of major bleeding between 18 months and 6 months of rivaroxaban treatment.

What Are the Clinical Implications?

- The risk of recurrent venous thromboembolism beyond 6 months in patients with cancer and acute low-risk pulmonary embolism could be high without anticoagulation therapy; this risk could be effectively prevented by anticoagulation therapy.
- The longer duration of anticoagulation therapy had a potential benefit for the prevention of thrombotic events in patients with cancer and acute low-risk pulmonary embolism.
- Considering the potential risk of bleeding associated with anticoagulation therapy in specific patients with a high bleeding risk, physicians should base anticoagulation strategy decisions for these patients on the risk-benefit balance with anticoagulation therapy in individual patients.

Nonstandard Abbreviations and Acronyms

CT	computed tomography
DVT	deep vein thrombosis
ONCO PE	Optimal Duration of Anticoagulation Therapy for Low-Risk Pulmonary Embolism Patients With Cancer
OR	odds ratio
PE	pulmonary embolism
sPESI	simplified version of the Pulmonary Embolism Severity Index
VTE	venous thromboembolism

Many patients with cancer can live longer as a result of advancements in the early diagnosis and treatment of cancer, and complications during the course of cancer treatment have become increasingly clinically important from the perspective of cardio-oncology.[1] Pulmonary embolism (PE) is one of the major complications in patients with cancer.[2] PE has been reported to be found in 3.6% of routine computed tomography (CT) scans of the chest for the evaluation of cancer,[3] and patients with cancer and acute low-risk PE, including incidental and minor PE, have become quite common in the current daily clinical practice. PE has a long-term risk of recurrent venous thromboembolism (VTE), which could be prevented by anticoagulation therapy.[4] However, data are limited on patients with cancer and acute low-risk PE, and the optimal anticoagulation strategies for these patients have been a matter of active debate.

The current international guidelines recommend extended anticoagulation therapy beyond 6 months for patients with PE with active cancer.[5–7] However, several guidelines weakly recommend the same management strategies for patients with incidental PE[5,6] and minor PE[8] as for patients with an evidence level of uncertainty. A previous observational study showed that patients with cancer and acute low-risk PE such as incidental PE were at a relatively high risk of recurrent VTE,[9] which suggested that these patients might benefit from prolonged anticoagulation therapy. Given that there has been no randomized clinical trial on this issue, we conducted the ONCO PE trial (Optimal Duration of Anticoagulation Therapy for Low-Risk Pulmonary Embolism Patients With Cancer) to investigate the efficacy and safety of anticoagulation therapy beyond 6 months by comparing the 2 different treatment durations of the oral factor Xa inhibitor rivaroxaban for patients with cancer and acute low-risk PE.

METHODS

Study Design

The ONCO PE trial (NCT04724460) was an investigator-initiated, multicenter, open-label, adjudicator-blinded, superiority, randomized clinical trial at 32 institutions in Japan designed to compare an 18-month rivaroxaban treatment with a 6-month rivaroxaban treatment in patients with cancer and acute low-risk

PE. We evaluated clinical end points at 18 months according to a previous extension trial in which the outcomes were evaluated at 12 months after the implementation of different treatments strategies.[10] Funding was provided by Bayer Yakuhin Co, Ltd, which had no role in the study design; data collection, analysis, or interpretation; or writing of the report. The design of the trial has previously been reported in detail.[11] The data were reviewed by an independent data and safety monitoring committee (Supplemental Appendix 1). 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 (Supplemental Appendix 2). The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Because there has been no established definition of acute low-risk PE, in the current trial, we used the simplified version of the Pulmonary Embolism Severity Index (sPESI) score as a standard risk stratification model for PE,[12] and PE with an sPESI score of 1 (no score component of the sPESI score other than cancer) was defined as acute low-risk PE. Adult patients with active cancer who were newly diagnosed with acute low-risk PE confirmed by a contrast CT examination were eligible for inclusion. Active cancer was defined as cancer meeting one of the following criteria: newly diagnosed cancer within 6 months of randomization; cancer treatment (surgery, chemotherapy, radiotherapy, etc) performed within 6 months of randomization; current cancer treatment (surgery, chemotherapy, radiotherapy, etc); recurrence, local invasion, or distant metastases; or a hematopoietic malignancy that has not achieved complete remission.[13] The key exclusion criteria were patients on anticoagulation therapy at the time of the diagnosis, patients with a contraindication to rivaroxaban, and patients who were expected to have a life prognosis of ≤6 months by the treating physicians. All patients provided written informed consent. The full detailed inclusion and exclusion criteria are provided in Supplemental Appendix 3.

Randomization and Treatment

Eligible patients were randomly assigned in a 1:1 ratio either to the 18-month rivaroxaban treatment group or to the 6-month rivaroxaban 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.

Rivaroxaban was administered in accordance with the policies at each institution, and no restrictions were set for the policies, providing that the treatment did not contravene the exclusion criteria. Treatment with a parenteral anticoagulant was allowed before enrollment, but after enrollment in the study, patients received the first dose of rivaroxaban according to the label of the marketed product for the treatment of acute PE in Japan; it consisted of 15 mg twice daily for the first 3 weeks followed by 15 mg once daily thereafter. The decision not to give the initial intensive dose of 30 mg/d was at the discretion of the treating physician in patients who were considered at high risk of bleeding.

Definition of the Baseline Characteristics

The sPESI score consisted of 6 variables, including an age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate of ≥110 bpm, systolic blood pressure <100 mm Hg, and arterial oxygen saturation <90% at the time of the diagnosis, and it ranged from 0 to 6 (0 is the lowest, and 6 is the highest mortality risk at 30 days).[12] Chronic cardiopulmonary disease included heart failure and chronic lung disease. Heart failure was diagnosed if the patient had a history of a hospitalization for heart failure, if the patient had symptoms attributable to heart failure (New York Heart Association functional class ≥2), or if the left ventricular ejection fraction was <40%. Chronic lung disease was defined as persistent if a lung disorder such as asthma, chronic obstructive pulmonary disease, or restrictive lung disease was seen. Detailed definitions of the other patient characteristics are given in Supplemental Appendix 4.

Follow-Up

The mandatory follow-up visits were planned at 3, 6, and 18 months, with additional assessments for routine clinical care as needed. At the 6-month visit after the diagnosis (between 151 and 209 days), the 6-month rivaroxaban treatment group stopped rivaroxaban, and the 18-month rivaroxaban treatment group continued rivaroxaban. During the follow-up period, the anticoagulation status was obtained, including the discontinuation and initiation of anticoagulants, along with the reasons and types of anticoagulants. Persistent rivaroxaban discontinuation was defined as a discontinuation of rivaroxaban according to the study protocol or lasting for >14 days for any reason. To evaluate the potential difference in the frequency of conducting contrast CT scans between the 2 groups, we collected all contrast CT scans studies during the follow-up period. To ensure compliance with rivaroxaban, the study protocol had predetermined the detailed follow-up methodology at each institution (Supplemental Appendix 5). A full detailed follow-up methodology is provided in Supplemental Appendix 5.

Primary and Secondary End Points

The primary end point was recurrent VTE at 18 months. Recurrent VTE included PE with or without deep vein thrombosis (DVT), which was defined as the appearance of new or worsening thrombus images in the pulmonary arteries and deep veins on imaging tests (ultrasonography of lower-limb vein system, CT examinations, pulmonary perfusion scintigraphy, pulmonary angiography, and venography) regardless of symptoms.[14] Recurrent VTE included incidentally diagnosed PE or DVT when imaging examinations were performed, usually for follow-up of cancer.[15] In the study protocol, follow-up imaging examinations for VTE were not recommended unless recurrent VTE was clinically suspected.

The major secondary end point was a major bleeding event at 18 months. 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 ≥2 g/dL or leading to a transfusion of ≥2 units of whole blood or red cells.[16] Other secondary end points were death resulting from all causes, symptomatic recurrent VTE events, and all clinically relevant

bleeding events at 18 months. A list of the prespecified secondary end points and criteria for adjudication of all the outcomes is provided in Supplemental 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, using a prespecified criteria.[17]

Statistical Analysis

The primary hypothesis was that the 18-month rivaroxaban treatment group was superior to the 6-month rivaroxaban treatment group in terms of the primary end point at 18 months. A detailed calculation of the trial sample size is provided in Supplemental Appendix 7. We assumed a 10% event rate in the 18-month rivaroxaban group and a 22% event rate in the 6-month rivaroxaban group on the basis of previous studies.[15,18] To demonstrate the superiority of an 18-month over a 6-month rivaroxaban treatment with a power of 80% and a 2-sided α=0.05, 292 participants were required, and we planned to enroll 330 participants considering the potential dropouts.

Analysis of the primary end point was performed in the intention-to-treat population, which included all the patients who had undergone randomization after the exclusion of those patients who withdrew consent. For patients who did not experience an event, the observation time was censored at 545 days or the last day the patient had a complete assessment for the study outcomes, whichever came first. Patients lost to follow-up before the end of the 18-month treatment period and patients who did not have the primary end point 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 analyses as sensitivity analyses (Supplemental Appendix 8). We performed subgroup analyses with interaction tests in the prespecified clinically relevant subgroups. Because a certain number of clinical end points occurred during the first 6 months when both groups were planned to receive rivaroxaban, we conducted a landmark analysis at 180 days for the primary and major secondary end points as a post hoc analysis. In this post hoc analysis, we excluded patients who died within 180 days and those who experienced clinical end points within 180 days. Furthermore, to confirm the robustness of the current trial among patients without either symptoms of PE or right ventricular dysfunction, we conducted another post hoc analysis after excluding those with symptomatic PE or right ventricular dysfunction. The detailed statistical analysis plans are available with the full text (Supplemental Material).

We compared the rates of patients with the primary and secondary end points between the 2 treatment groups in the intention-to-treat population and calculated the odds ratios (ORs) and the corresponding 95% CIs using the logistic regression models. We also estimated the first persistent discontinuation rates of rivaroxaban and cumulative incidences of the primary and major secondary end points with the Kaplan-Meier method, and the differences for the primary and major secondary end points were 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 14.0.0 (SAS Institute Inc, Cary, NC) and SAS version 9.4 (SAS Institute Inc) software. The reported *P* values were 2-tailed, and a value of $P<0.05$ was considered statistically significant. Because there was no plan for an adjustment of the widths of the CIs and interaction *P* values of the subgroup analyses for multiple comparisons, these data should be interpreted as exploratory. In addition, because variations in the efficacy of the interventions and other managements were less likely, an adjustment of the stratification variable was not planned.

RESULTS

Patient Enrollment and Characteristics

From February 2021 to March 2023, a total of 179 patients were enrolled and randomized (Figure 1). The steering committee prematurely terminated the trial when 54% of the estimated sample size had been included because of the slow enrollment during the COVID-19 pandemic. After the exclusion of 1 patient who withdrew consent, 178 patients were included in the intention-to-treat population: 89 patients in the 18-month rivaroxaban group and 89 patients in the 6-month rivaroxaban group.

The clinical characteristics of the patients at baseline were well balanced between the 2 groups (Table 1). The mean age was 65.7 years; 47% of the patients were men; and 12% of the patients had symptoms of PE at baseline. As for the thrombus location, central, main, lobar, segmental, and subsegmental PE accounted for 13%, 12%, 30%, 30%, and 20% of the patients, respectively. The most common type of cancer was colon cancer (12%), followed by uterine cancer (12%) and ovarian cancer (11%; Table S1).

Rivaroxaban Treatment and CT Scans During the Follow-Up Period

The median (interquartile range) duration of the rivaroxaban treatment was 482 days (169–545 days) in the 18-month rivaroxaban group and 182 days (157–194 days) in the 6-month rivaroxaban group. The cumulative 210-day incidences of a first persistent discontinuation of rivaroxaban were 23.6% in the 18-month rivaroxaban group and 87.9% in the 6-month rivaroxaban group (Figure 2). Among 89 patients in the 6-month rivaroxaban group, 12 patients (13%) discontinued rivaroxaban prematurely within 150 days, and 10 patients (11%) continued rivaroxaban beyond 210 days. The common reasons for the first persistent rivaroxaban discontinuation in the 18-month rivaroxaban group were bleeding events (29%) and cancer progression (26%), whereas those in the 6-month rivaroxaban group were per-protocol discontinuations (79%; Table S2).

Contrast CT scans were performed 309 times in the 18-month rivaroxaban group and 305 times in the 6-month rivaroxaban group within 18 months regardless of the primary purposes for the CT scans (Table S3). The median (interquartile range) numbers of CT scan were 3 (2–5) per patient in the 18-month rivaroxaban group and

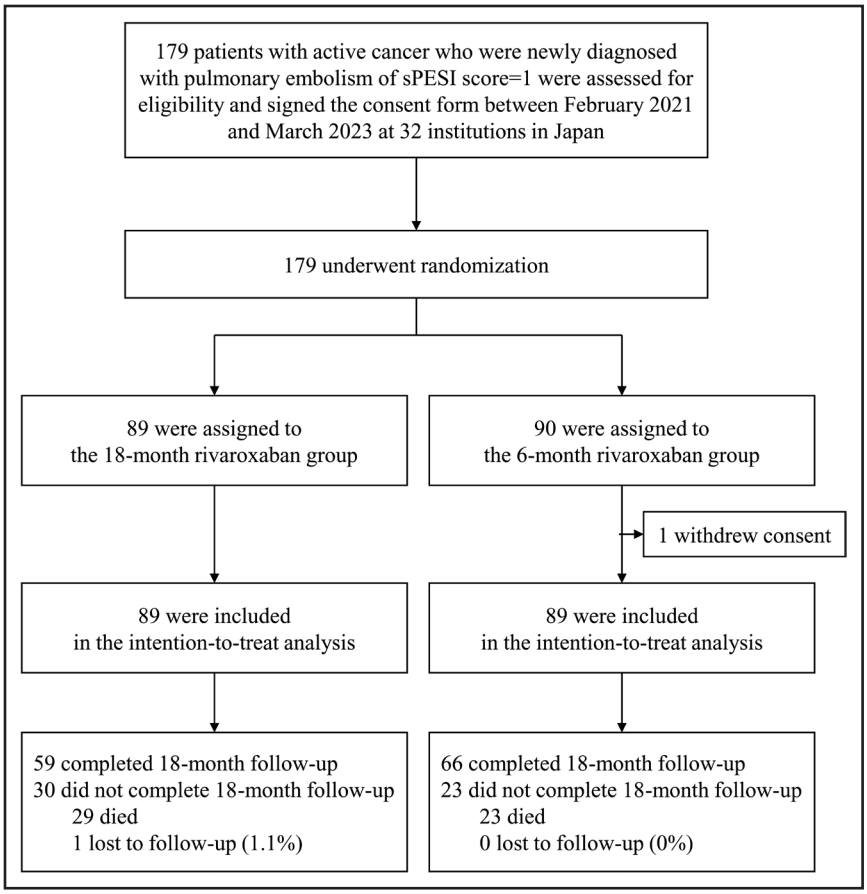

Figure 1. Enrollment, randomization, and follow-up.
Patients were randomly assigned in a 1:1 ratio to receive an 18-month rivaroxaban treatment or a 6-month rivaroxaban treatment. Randomization was performed centrally through the electronic data capture system with a stochastic minimization algorithm to balance the treatment assignment within the centers. sPESI indicates simplified version of the Pulmonary Embolism Severity Index.

3 (1–5) per patient in the 6-month rivaroxaban group. The incidences of CT scans were 2.90 per patient-year in the 18-month rivaroxaban group and 2.70 per patient-year in the 6-month rivaroxaban group.

Primary End Point

The primary end point of recurrent VTE occurred in 5 of the 89 patients (5.6%) in the 18-month rivaroxaban group and in 17 of the 89 patients (19.1%) in the 6-month rivaroxaban group (OR, 0.25 [95% CI, 0.09–0.72]; *P*=0.01; Table 2). The time to the occurrence of the primary end point is shown in Figure 3. Recurrent VTE consisted of 11 PEs, including 2 main and 4 lobar PEs, and 11 DVTs, including 3 proximal DVTs (Table S4). Among 22 recurrent VTE events, 5 patients presented with symptomatic recurrent VTE, including 3 with symptomatic PEs and 2 with symptomatic DVTs. Among 17 asymptomatic recurrent VTE events, 13 events (76%) consisted of development of new thrombus (Table S4). The results of the per-protocol and as-treated analyses were consistent with the results in the primary analysis (Tables S5 and S6; Figures S1 through S4).

Secondary End Points

The major secondary end point of major bleeding occurred in 7 of the 89 patients (7.8%) in the 18-month rivaroxaban group and in 5 of the 89 patients (5.6%) in the 6-month rivaroxaban group (OR, 1.43 [95% CI, 0.44–4.70]; *P*=0.55; Table 2). The time to the occurrence of the major secondary end point is shown in Figure 4. The most common site of major bleeding was the lower gastrointestinal tract (33%), and the severity of the major bleeding was mainly category 2 (92%; Table S4). The results of the per-protocol and as-treated analyses are presented in Tables S5 and S6.

The incidences of other secondary end points in the 2 groups are provided in Table 2. Deaths resulting from all causes occurred in 29 of the 89 patients (32.6%) in the 18-month rivaroxaban group and in 23 of the 89 patients (25.8%) in the 6-month rivaroxaban group (OR, 1.39 [95% CI, 0.72–2.66]). Symptomatic recurrent VTE occurred in 1 of the 89 patients (1.1%) in the 18-month rivaroxaban group and in 4 of the 89 patients (4.5%) in the 6-month rivaroxaban group (OR, 0.24 [95% CI, 0.03–2.20]). All clinically relevant bleeding events occurred in 20 of the 89 patients (22.5%) in the 18-month rivaroxaban group and in 18 of the 89 patients (20.2%) in the 6-month rivaroxaban group (OR, 1.14 [95% CI, 0.56–2.34]).

Subgroup and Sensitivity Analyses

Point estimates for the primary end point favored the 18-month rivaroxaban treatment in all the subgroups

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Table 1. Clinical Characteristics of the Patients at Baseline

	18-mo rivaroxaban (N=89)	6-mo rivaroxaban (n=89)
Baseline characteristics		
Age, y	66.3±10.4	65.2±10.5
Age ≥75 y, n (%)	23 (26)	17 (19)
Male sex, n (%)	42 (47)	41 (46)
Body weight, kg	60.5±11.2	59.7±11.6
Body weight ≤60 kg, n (%)	47 (53)	52 (58)
Body mass index, kg/m^2	23.0±4.1	23.0±3.5
Presentation at diagnosis		
Systolic blood pressure, mm Hg	127.6±17.3	125.4±16.5
Diastolic blood pressure, mm Hg	75.8±11.2	78.2±12.4
Heart rate, bpm	80.7±11.8	81.6±12.6
Oxygen saturation, %	97.1±1.6	97.3±1.3
Symptoms for PE at baseline, n (%)	13 (15)	9 (10)
Place of onset, n (%)		
Out-of-hospital onset	52 (58)	45 (51)
Home treatment	36 (40)	30 (34)
In-hospital onset after surgery	13 (15)	16 (18)
In-hospital onset other than after surgery	24 (27)	28 (31)
PE characteristics, n (%)		
Thrombus location		
Central	8 (9)	6 (7)
Main	12 (13)	10 (11)
Lobar	27 (30)	27 (30)
Segmental	25 (28)	28 (31)
Subsegmental	17 (19)	18 (20)
RV dysfunction*	11 (12)	4 (4)
RV/LV ≥0.9	8 (9)	4 (4)
Concomitant DVT	50 (56)	54 (61)
Cancer status, n (%)		
Newly diagnosed with cancer within 6 mo	57 (64)	45 (51)
Chemotherapy performed within 6 mo	56 (63)	51 (57)
Radiotherapy performed within 6 mo	3 (3)	10 (11)
Recurrent cancer	6 (7)	21 (24)
Metastatic disease	34 (38)	33 (37)
ECOG performance status†		
0	37 (42)	42 (47)
1	42 (47)	40 (45)
≥2	10 (11)	7 (8)
Comorbidities, n (%)		
Hypertension	30 (34)	37 (42)
Diabetes	15 (17)	12 (13)
Dyslipidemia	18 (20)	20 (22)
History of stroke	1 (1)	0 (0)
History of venous thromboembolism	2 (2)	5 (6)
History of major bleeding	7 (8)	3 (3)
Autoimmune disorder	6 (7)	6 (7)
Transient risk factors for venous thromboembolism‡	19 (21)	23 (26)
Recent surgery within 2 mo	14 (16)	15 (17)
Laboratory tests at diagnosis		
Creatinine, mg/dL	0.70±0.17	0.73±0.22
Creatinine clearance, mL/min	85.8±27.5	84.2±30.2
Creatinine clearance ≤50 mL/min, n (%)	6 (7)	5 (6)
Hemoglobin, g/dL	11.2±1.9	11.6±2.1
Anemia, n. (%)§	65 (73)	53 (60)
Platelet count, ×100 000/μL	22.8±9.9	23.6±11.7
Platelet count <100 000/μL, n (%)	5 (6)	6 (7)
D-dimer (n=166), μg/mL	8.6 (4.1–16.6)	8.0 (3.1–13.9)
BNP (n=59), pg/mL	15.5 (7.9–31.1)	21.5 (10.9–38.1)
NT-proBNP (n=48), pg/mL	132.5 (62.0–258.0)	68.1 (52.0–122.5)
Troponin I (n=53), ng/dL	0.010 (0.005–10.000)	0.022 (0.010–10.000)
Troponin T (n=38), ng/dL	0.010 (0.010–0.013)	0.010 (0.007–0.013)
Concomitant medication, n (%)		
Antiplatelet	3 (3)	2 (2)
Steroid	11 (12)	13 (15)
Statin	12 (13)	9 (10)
Proton pump inhibitor	46 (52)	35 (39)

BNP indicates brain natriuretic peptide; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; LV, left ventricular; PE, pulmonary embolism; RV, right ventricular.

Clinical characteristics of the patients at baseline are presented in the intention-to-treat population. Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean±SD or the median (interquartile range) based on their distributions.

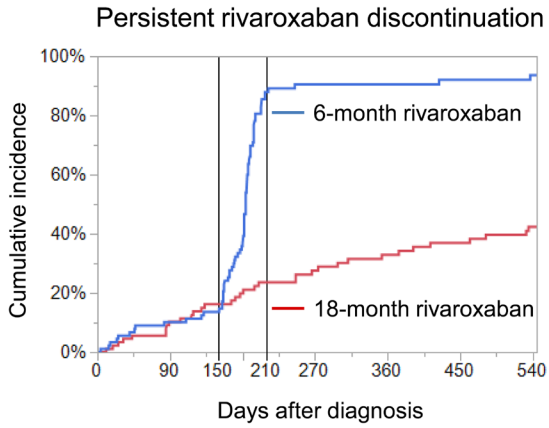
*RV dysfunction was defined as the presence of enlarged RV findings (RV/LV ≥0.9) on computed tomography or the existence of estimated systolic pulmonary arterial pressure of ≥40 mm Hg by echocardiography. Echocardiography was evaluated in 111 patients.

†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.

(Figure 5). The landmark analysis at 180 days for the primary and major secondary end points showed fully consistent results with the main results (Figures S5 and S6). The sensitivity analysis for the primary and major secondary end points after the exclusion of patients with symptomatic PE or right ventricular dysfunction showed generally consistent results with the main results (Figures S7 and S8).



	0-day	150-day	180-day	210-day	365-day	545-day
18-month rivaroxaban						
N of patients with discontinuation		14	17	20	27	34
N of patients on rivaroxaban	89	71	66	62	51	42
Cumulative incidence		16.2%	19.9%	23.6%	32.9%	42.4%
6-month rivaroxaban						
N of patients with discontinuation		12	32	74	76	78
N of patients on rivaroxaban	89	75	55	12	7	4
Cumulative incidence		13.6%	37.0%	87.9%	90.5%	93.6%

Figure 2. Kaplan-Meier curves for the first persistent rivaroxaban discontinuation.
The time-to-event curves of the first persistent rivaroxaban discontinuation over 18 months after the diagnosis. Persistent rivaroxaban discontinuation was defined as discontinuation of rivaroxaban according to the study protocol or lasting for >14 days for any reason. The analyses were performed for the full analysis set with the intention-to-treat approach.

DISCUSSION

The ONCO PE trial, which enrolled patients with active cancer who were newly diagnosed with acute low-risk PE without other score components of sPESI than cancer, showed that 18 months of rivaroxaban treatment was superior to 6 months of rivaroxaban treatment with respect to recurrent VTE events, whereas the longer duration of rivaroxaban treatment was not associated with a higher incidence of major bleeding.

The incidence of acute low-risk PE, including incidental PE, in patients with cancer was reported to be increasing over time partly as a result of the frequent use of CT for the diagnosis and monitoring of cancer and improvements in the CT scanning technology.[19–21] A recent study reported that approximately half of PEs in patients with cancer were diagnosed incidentally through routine CT scanning for cancer staging or the evaluation of the cancer treatment response.[21] The clinical relevance of acute low-risk PE, including incidental and minor PE, could still remain debatable. Historically, acute low-risk PE has been considered a more benign condition of PE than symptomatic or nonminor PE. However, several previous observational studies have reported that incidental PE has a risk of recurrent VTE similar to that of symptomatic PE,[22,23] suggesting a potentially higher risk of thrombosis events in patients with than in those without incidental PE. Based on those findings, current international guidelines weakly recommend the same anticoagulation strategies for incidental PE and minor PE as for symptomatic PE.[5,6,8] However, because of the lack of solid evidence from randomized clinical trials, the optimal anticoagulation strategies for patients with cancer and acute low-risk PE have remained controversial, leading to wide variations in anticoagulation strategies. No randomized clinical trials have evaluated the optimal duration of anticoagulation therapy for these patients, and it remains uncertain whether anticoagulation therapy should be extended beyond 6 months.

The current randomized clinical trial included patients with PE of sPESI score of 1 as potential acute low-risk PE, and 88% of the patients had asymptomatic PE. In terms of thrombotic events, a longer duration of anticoagulation therapy with rivaroxaban was significantly superior to a limited duration of anticoagulation therapy with 6 months of rivaroxaban, which demonstrated the potential benefit of extended anticoagulation beyond 6 months for those patients. A previous meta-analysis from observational studies reported that the 6-month incidence of recurrent VTE was 5.8% in patients with cancer and incidental PE, and that increased up to 12% among patients without anticoagulation therapy.[24] In line with the previous report, the current randomized clinical trial demonstrated that the 18-month incidence of recurrent VTE was 19.1% in patients with a limited duration of anticoagulation therapy for 6 months, and the event rate increased beyond 6 months presumably after the discontinuation of the anticoagulation therapy. It is notable that the current trial also showed that a certain number of the recurrent VTEs were PE, including main and lobar PE and proximal DVT, which were supposed to be clinically

Table 2. Clinical Outcomes at 18 Months

	18-mo rivaroxaban (n=89), n (%)	6-mo rivaroxaban (n=89), n (%)	OR (95% CI)
Primary end point			
Recurrent VTE	5 (5.6)	17 (19.1)	0.25 (0.09-0.72)
Major secondary end point			
Major bleeding	7 (7.8)	5 (5.6)	1.43 (0.44-4.70)
Other secondary end points			
Deaths resulting from all causes	29 (32.6)	23 (25.8)	1.39 (0.72-2.66)
Death attributable to PE	0 (0)	0 (0)	…
Death attributable to bleeding events	0 (0)	0 (0)	…
Death attributable to cancer	26 (29.2)	20 (22.5)	…
Symptomatic recurrent VTE	1 (1.1)	4 (4.5)	0.24 (0.03–2.20)
All clinically relevant bleeding events	20 (22.5)	18 (20.2)	1.14 (0.56–2.34)

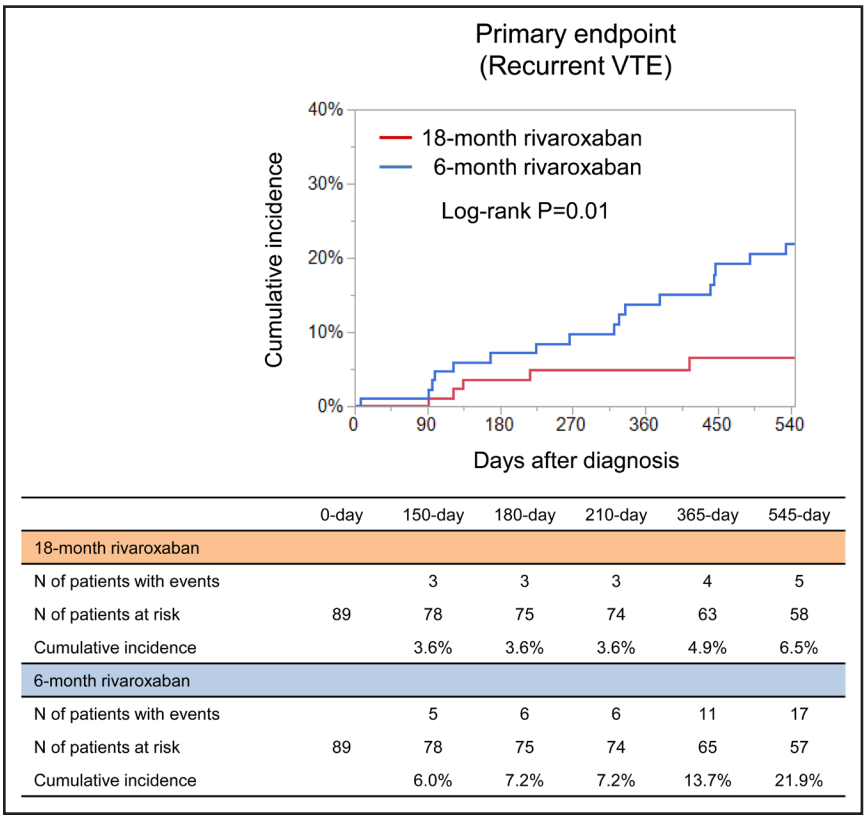
OR indicates odds ratio; PE, pulmonary embolism; and VTE, venous thromboembolism.

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 the exclusion of patients who withdrew consent. For patients who did not experience an event, the time to the first event was to be censored at day 545 or the last day the patient had a complete assessment for study outcomes, whichever occurred first.

We calculated the odds ratios, computed using the logistic regression model, along with the corresponding 95% CIs for all clinical end points, which have not been adjusted for multiple comparisons.

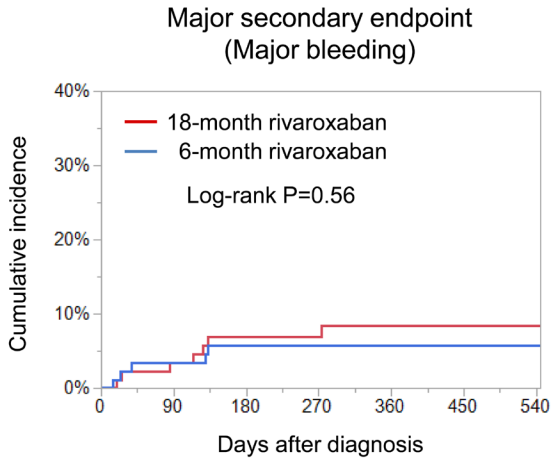
relevant VTE. On the other hand, a minority of the recurrent VTE presented as symptomatic recurrent VTE. In addition to the risk of the occurrence of thrombotic events, clinicians should consider the clinical weight of thrombotic events.

For the decision-making of anticoagulation strategies, the risk of bleeding associated with anticoagulation therapy should be taken into account.[25] In particular, patients with cancer-associated VTE were reported to be at a higher risk of bleeding, even in the direct oral anticoagulant era, compared with those without active cancer, leading to difficulty in achieving a good risk-benefit balance with anticoagulation therapy.[26,27] The SELECT-D trial (Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism) showed that the 6-month cumulative rate



	0-day	150-day	180-day	210-day	365-day	545-day
18-month rivaroxaban						
N of patients with events		3	3	3	4	5
N of patients at risk	89	78	75	74	63	58
Cumulative incidence		3.6%	3.6%	3.6%	4.9%	6.5%
6-month rivaroxaban						
N of patients with events		5	6	6	11	17
N of patients at risk	89	78	75	74	65	57
Cumulative incidence		6.0%	7.2%	7.2%	13.7%	21.9%

Figure 3. Kaplan-Meier curves for the primary end point.
The time-to-event curves of the primary end point (recurrent venous thromboembolism [VTE]) over 18 months after the diagnosis. Number of patients with events indicates the number of cumulative events.



	0-day	150-day	180-day	210-day	365-day	545-day
18-month rivaroxaban						
N of patients with events		6	6	6	7	7
N of patients at risk	89	76	73	71	61	56
Cumulative incidence		7.0%	7.0%	7.0%	8.4%	8.4%
6-month rivaroxaban						
N of patients with events		5	5	5	5	5
N of patients at risk	89	79	77	76	70	68
Cumulative incidence		5.8%	5.8%	5.8%	5.8%	5.8%

Figure 4. Kaplan-Meier curves for the major secondary end point.
The time-to-event curves of the major secondary end point (major bleeding) over 18 months after the diagnosis. Number of patients with events indicates the number of cumulative events. 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 ≥2 g/dL or leading to a transfusion of ≥2 units of whole blood or red cells.

of major bleeding was 6% in the rivaroxaban treatment group of patients with cancer-associated VTE.[15] The current trial showed that the cumulative 18-month incidence of major bleeding was 7.8% in the 18-month rivaroxaban group, and there was no statistically significant difference compared with the 6-month rivaroxaban group (5.6%). The time-to-event curves for major bleeding events demonstrated that major bleeding seemed to be more common in the first 6 months in both groups and that the risk of major bleeding did not significantly differ beyond 6 months, suggesting that the major bleeding risk associated with rivaroxaban might be more remarkable in the early period after the initiation of rivaroxaban, and continuation of rivaroxaban beyond that phase might not necessarily be associated with an increased risk of major bleeding. However, considering a potentially higher risk of bleeding with prolonged anticoagulation therapy, especially among patients at a high risk of bleeding, clinicians should still be cautious about the risk of bleeding and base the decision of anticoagulation strategies for these patients on a risk-benefit balance with anticoagulation therapy in individual patients.

Some limitations should be noted. First, the open-label design had the potential to introduce the treatment and ascertainment bias. All the clinical end points were adjudicated by the members of an independent committee who were unaware of the study group assignments; however, the diagnostic testing strategies could have been influenced by the open-label design, which might have led to a certain ascertainment bias on the primary end point. However, the study protocol did not recommend follow-up imaging examinations other than those for cancer, and the absolute numbers and incidences of contrast CT scans were comparable between the 2 groups, indicating that there was no apparent influence of the 2 different anticoagulation managements on the diagnostic testing strategies during the follow-up period. Furthermore, to mitigate the influence of the diagnostic testing strategies on the primary end point, we also evaluated symptomatic recurrent VTE and confirmed a similar trend with the primary end point. Second, the trial was prematurely terminated before the enrollment of the estimated sample size. In addition, the number reaching the primary end point was lower than expected in both the 18-month and 6-month rivaroxaban groups. Despite that limitation, superiority was established. The reason could be in part that the estimated event rates were calculated in different study populations from the current study population[15,18] and that the event rate in the 18-month rivaroxaban group was much lower than expected. Therefore, the possibility of chance should be considered. Third, adherence to the rivaroxaban treatment was relatively low according to the study protocol. In particular, some of the patients in the 18-month rivaroxaban group discontinued rivaroxaban prematurely because of bleeding events or cancer progression. This issue could have underestimated the risk of major bleeding in the 18-month rivaroxaban group by the intention-to-treat analysis. Although

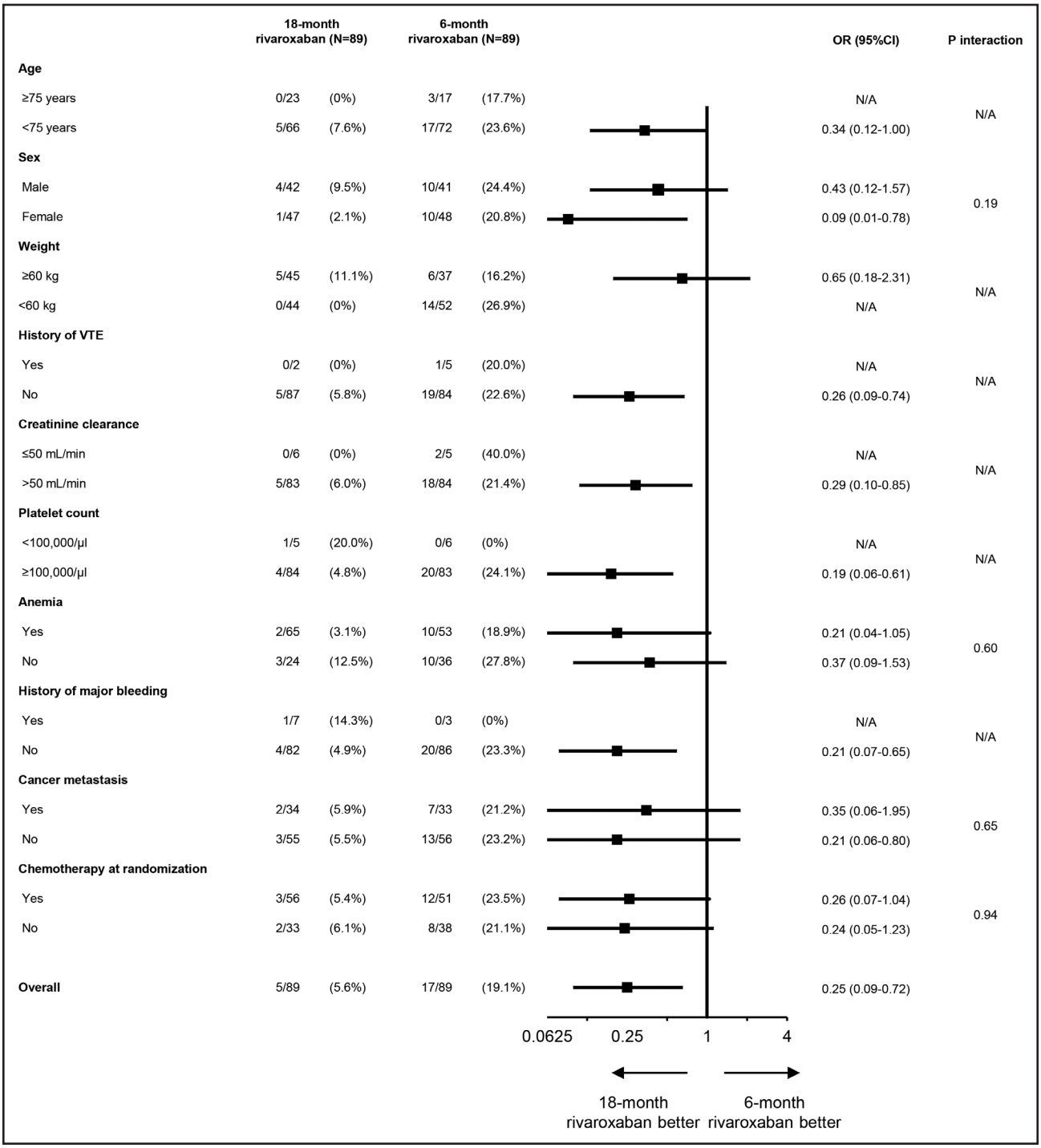


Figure 5. Subgroup analyses for the primary end point.
The odds ratios (ORs) for the primary end point in the 2 groups are described according to the predefined subgroups. The 95% CIs have not been adjusted for multiple comparisons. N/A indicates not applicable; and VTE, venous thromboembolism.

the sensitivity analysis of the per-protocol population and as-treated population confirmed the results of the primary analysis including major bleeding, physicians should be still cautious about the balance between thrombotic and bleeding risk when interpreting the current trial. Fourth, we evaluated the parameter of imaging examinations at each institution using the predetermined criteria in the study protocol, not at a core laboratory. Thus, we could not evaluate the detailed parameters such as right ventricular/left ventricular ratios. In addition, we did not evaluate all patients by echocardiography. Finally, there could be racial differences and practice differences, depending on the region. The current results should be generalized carefully.

Conclusions

In patients with cancer and acute low-risk PE of sPESI score=1, the 18-month rivaroxaban treatment was superior to the 6-month rivaroxaban treatment with respect to recurrent VTE events.

ARTICLE INFORMATION

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Supplemental Material

Appendices 1–8
Tables S1–S6
Figures S1–S8
Final statistical analysis plan

REFERENCES

1. Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, Boriani G, Cardinale D, Cordoba R, Cosyns B, et al; ESC Scientific Document Group. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J.* 2022;43:4229–4361. doi: 10.1093/eurheartj/ehac244
2. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293:715–722. doi: 10.1001/jama.293.6.715
3. Di Nisio M, Lee AY, Carrier M, Liebman HA, Khorana AA; Subcommittee on Haemostasis and Malignancy. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2015;13:880–883. doi: 10.1111/jth.12883
4. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *Lancet.* 2010;376:2032–2039. doi: 10.1016/S0140-6736(10)60962-2
5. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, et al; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J.* 2020;41:543–603. doi: 10.1093/eurheartj/ehz405
6. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, et al. Antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel Report. *Chest.* 2021;160:e545–e608. doi: 10.1016/j.chest.2021.07.055
7. Witt DM, Nieuwlaat R, Clark NP, Ansell J, Holbrook A, Skov J, Shehab N, Mock J, Myers T, Dentali F, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv.* 2018;2:3257–3291. doi: 10.1182/bloodadvances.2018024893
8. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Gates LE, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update. *J Clin Oncol.* 2023;41:3063–3071. doi: 10.1200/JCO.23.00294
9. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. *J Clin Oncol.* 2011;29:2405–2409. doi: 10.1200/JCO.2010.34.0984
10. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, et al; EINSTEIN CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med.* 2017;376:1211–1222. doi: 10.1056/NEJMoa1700518
11. Chatani R, Yamashita Y, Morimoto T, Muraoka N, Shioyama W, Shibata T, Nishimoto Y, Ogihara Y, Doi K, Oi M, et al; ONCO PE Trial Investigators. Home treatment for active cancer patients with low-risk pulmonary embolism: a predetermined companion report From the ONCO PE trial [published online March 8, 2024]. *Circ J.* doi: 10.1253/circj.CJ-24-0004. https://jstage.jst.go.jp/article/circj/advpub/0/advpub_CJ-24-0004/_article
12. Jimenez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, Otero R, Monreal M, Muriel A, Yusen RD; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med.* 2010;170:1383–1389. doi: 10.1001/archinternmed.2010.199
13. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018;378:615–624. doi: 10.1056/NEJMoa1711948

14. Yamashita Y, Morimoto T, Muraoka N, Oyakawa T, Umetsu M, Akamatsu D, Nishimoto Y, Sato Y, Takada T, Jujo K, et al; ONCO DVT Study Investigators. Edoxaban for 12 months versus 3 months in patients with cancer with isolated distal deep vein thrombosis (ONCO DVT study): an open-label, multicenter, randomized clinical trial. *Circulation*. 2023;148:1665–1676. doi: 10.1161/CIRCULATIONAHA.123.066360
15. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36:2017–2023. doi: 10.1200/JCO.2018.78.8034
16. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694. doi: 10.1111/j.1538-7836.2005.01204.x
17. Bleker SM, Brekelmans MPA, Eerenberg ES, Cohen AT, Middeldorp S, Raskob G, Buller HR. Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists. an individual patient data meta-analysis. *Thromb Haemost*. 2017;117:1944–1951. doi: 10.1160/TH16-12-0946
18. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, Konishi T, Akao M, Kobayashi Y, Inoue T, et al; COMMAND VTE Registry Investigators. Anticoagulation therapy for venous thromboembolism in the real world: from the COMMAND VTE Registry. *Circ J*. 2018;82:1262–1270. doi: 10.1253/circj.CJ-17-1128
19. Carrier M, Righini M, Wells PS, Perrier A, Anderson DR, Rodger MA, Pleasance S, Le Gal G. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications: a systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost*. 2010;8:1716–1722. doi: 10.1111/j.1538-7836.2010.03938.x
20. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med*. 2011;171:831–837. doi: 10.1001/archinternmed.2011.178
21. Font C, Farrus B, Vidal L, Caralt TM, Visa L, Mellado B, Tassies D, Monteagudo J, Reverter JC, Gascon P. Incidental versus symptomatic venous thrombosis in cancer: a prospective observational study of 340 consecutive patients. *Ann Oncol*. 2011;22:2101–2106. doi: 10.1093/annonc/mdq720
22. Kraaijpoel N, Bleker SM, Meyer G, Mahe I, Munoz A, Bertoletti L, Bartels-Rutten A, Beyer-Westendorf J, Porreca E, Boulon C, et al; UPE Investigators. Treatment and long-term clinical outcomes of incidental pulmonary embolism in patients with cancer: an international prospective cohort study. *J Clin Oncol*. 2019;37:1713–1720. doi: 10.1200/JCO.18.01977
23. Farge D, Bounameaux H, Brenner B, Cajfinger F, Debourdeau P, Khorana AA, Pabinger I, Solymoss S, Douketis J, Kakkar A. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2016;17:e452–e466. doi: 10.1016/S1470-2045(16)30369-2
24. van der Hulle T, den Exter PL, Planquette B, Meyer G, Soler S, Monreal M, Jimenez D, Portillo AK, O'Connell C, Liebman HA, et al. Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. *J Thromb Haemost*. 2016;14:105–113. doi: 10.1111/jth.13172
25. Klok FA, Huisman MV. How I assess and manage the risk of bleeding in patients treated for venous thromboembolism. *Blood*. 2020;135:724–734. doi: 10.1182/blood.2019001605
26. Chatani R, Yamashita Y, Morimoto T, Mushiake K, Kadota K, Kaneda K, Nishimoto Y, Ikeda N, Kobayashi Y, Ikeda S, et al; COMMAND VTE Registry-2 Investigators. Cancer-associated venous thromboembolism in the direct oral anticoagulants era: insight from the COMMAND VTE Registry-2. *Thromb Res*. 2024;234:86–93. doi: 10.1016/j.thromres.2023.12.016
27. Chatani R, Yamashita Y, Morimoto T, Kaneda K, Mushiake K, Kadota K, Nishimoto Y, Ikeda N, Kobayashi Y, Ikeda S, et al; COMMAND VTE Registry-2 Investigators. Transition of management strategies and long-term outcomes in cancer-associated venous thromboembolism from the warfarin era to the direct oral anticoagulant era. *Eur J Intern Med*. 2024;123:72–80. doi: 10.1016/j.ejim.2024.01.012