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ORIGINAL ARTICLE

Cancer-Associated ThrOmboSIs – Patient-Reported OutcoMes With RivarOxaban (COSIMO) – Baseline characteristics and clinical outcomes

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Abstract

Background: Patients with cancer-associated thrombosis (CAT) have a high risk of recurrent venous thromboembolic events, which contribute to significant morbidity and mortality. Direct oral anticoagulants may provide a convenient treatment option for these patients.

Objectives: To assess clinical characteristics and outcomes of patients with active cancer changing to rivaroxaban after ≥4 weeks of standard therapy for the treatment of venous thromboembolism (VTE) in clinical practice. This analysis focused on secondary outcomes of Cancer-associated thrOmboSIs – Patient-reported outcoMes with rivarOxaban (COSIMO).

Patients: COSIMO was a multinational, prospective, noninterventional, single-arm cohort study. Overall, 505 patients received at least one dose of rivaroxaban; 96.6% changing from low-molecular-weight heparin, 1.6% from a vitamin K antagonist, and 1.8% from fondaparinux.

Results: Most patients had solid tumors (n = 449; 88.9%) and approximately half of these patients had metastases. The qualifying venous thromboembolic event was deep vein thrombosis (DVT) in 45.3% of patients, pulmonary embolism (PE) in 37.2% of patients, DVT with PE in 9.7% of patients, and catheter-associated DVT in 7.5% of patients. Approximately 75.1% of patients received rivaroxaban for at least 3 months; 150 (29.7%) patients received concomitant chemotherapy during the study. VTE recurrence, major bleeding, nonmajor bleeding, and major adverse cardiovascular events occurred in 18 (3.6%), 18 (3.6%), 81 (16.0%), and 12 (2.4%) patients, respectively.

Conclusions: In patients with CAT who changed to rivaroxaban treatment after ≥4 weeks of standard therapy, the observed incidence proportions of recurrent VTE

and bleeding events were in keeping with the recognized effectiveness and safety profile of rivaroxaban for the treatment of CAT.

KEYWORDS
active cancer, low-molecular-weight heparin, recurrent venous thromboembolism, rivaroxaban, vitamin K antagonist

Essentials

- Patients with active cancer are at risk of recurrent venous thromboembolism (VTE).
- Adherence with low-molecular-weight heparin therapy is low in these patients.
- Cancer-associated thrOmboSIs – Patient-Reported OutcoMes With RivarOxaban (COSIMO) enrolled patients with cancer changing to rivaroxaban from standard anticoagulation.
- Recurrent VTE and major bleeding occurred in 3.6% of patients after changing to rivaroxaban.

1 | INTRODUCTION

Cancer-associated thrombosis (CAT) is associated with significant morbidity and mortality.[1] Approximately 15% to 20% of all cases of venous thromboembolism (VTE) occur in patients with cancer, and the risk of VTE is higher in those with advanced cancer and in patients with certain solid cancers, such as lung, stomach, colon, ovarian, pancreatic, and brain cancer.[2,3] Six months after a venous thromboembolic event, the risk of a recurrent event in a patient treated for CAT is 4% to 17%, mortality risk ranges from ≈25% to ≈40%, and the risk of a major bleeding event is 3% to 7%.[1,4-6] Several anticancer and supportive therapies used to treat cancer have been demonstrated to be thrombogenic and increase the risk of VTE.[7]

Because of the high risk of VTE recurrence in patients with CAT, particularly in the first 6 months, guidelines often recommend extended anticoagulation therapy for the prevention of recurrent events if the risk of bleeding is not high.[8-13] Low-molecular-weight heparin (LMWH) had long been the guideline-preferred option over vitamin K antagonists (VKAs) for the initial and long-term treatment of CAT after superior efficacy was demonstrated in randomized controlled trials (RCTs).[9-11] VKAs are also associated with significant challenges, including frequent international normalized ratio monitoring and interactions with other drugs and food.[14] However, evidence demonstrates that patient persistence with LMWH therapy is lower than with oral anticoagulants, possibly because of injection-related side effects, the reluctance of patients to receive daily injections for long periods of time, and the high costs associated with LMWH therapy.[14,15]

Recent updates to international guidelines for the treatment of CAT have included recommendations for factor Xa inhibitors in appropriate patients with VTE and cancer.[8,9,11,12,16] Direct oral anticoagulants (DOACs) such as rivaroxaban may provide a more convenient treatment option for patients with CAT, because they can be given as a fixed oral dose (edoxaban requires at least 5 days of initial parenteral therapy) and without routine anticoagulation monitoring.[17] RCTs comparing the efficacy and safety of rivaroxaban, edoxaban, or apixaban versus LMWH (dalteparin) in patients with CAT were reported in the Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism (SELECT-D), Hokusai-VTE-Cancer, Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer (CARAVAGGIO), and Apixaban or Dalteparin in Reducing Blood Clots in Patients With Cancer Related Venous Thromboembolism (ADAM-VTE) studies, respectively.[5,6,18,19] A recent meta-analysis of these four RCTs, which included 2894 patients with any acute venous thromboembolic index event, showed that DOACs were associated with a 34% lower risk of recurrent VTE compared with LMWH (relative risk, 0.66; 95% confidence interval [CI], 0.39-1.13).[20] Although this was offset by a 32% higher risk of major bleeding compared with LMWH (relative risk, 1.32; 95% CI, 0.70-2.47).[20] However, CAT treatment also carries logistical, emotional, and psychological burdens for patients with cancer beyond efficacy and safety considerations that deserve attention and evaluation. The Cancer-associated thrOmboSIs – Patient-reported outcoMes with rivarOxaban (COSIMO) study builds upon the existing evidence for the use of DOACs for the treatment of CAT by providing insights into the patient-reported treatment satisfaction and clinical outcomes with rivaroxaban for the treatment of VTE in patients with active cancer. The analysis in this paper aimed to determine the clinical characteristics, including patterns of anticoagulation therapy, and outcomes of patients with CAT who switch to rivaroxaban after ≥4 weeks of standard anticoagulation. These are secondary outcomes of the COSIMO study.

2 | METHODS

2.1 | Study design and patient population

The COSIMO study was a prospective, noninterventional, single-arm cohort study performed across centers in Australia, Belgium, Canada, Denmark, France, Germany, Italy, the Netherlands, Spain,

and the United Kingdom (Table S1). The rationale and design of this study have been reported previously.[21]

Patients were invited to participate in the COSIMO study in a consecutive manner with a limited number of inclusion and exclusion criteria. Adult patients with active cancer other than basal cell or squamous cell carcinoma of the skin and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 were eligible (active cancer defined as the diagnosis or treatment of cancer within the previous 6 months or recurrent or metastatic cancer). Patients receiving standard anticoagulation therapy (LMWH or VKA) for ≥4 weeks who were changed to rivaroxaban at the discretion of the treating physician for the treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE), and/or prevention of recurrent DVT and PE, were invited to be included in the study. Patients were excluded if they had any contraindications to rivaroxaban according to the local marketing authorization; if they had developed an index venous thromboembolic event despite chronic anticoagulant therapy; or if they had received apixaban, edoxaban, or any investigational drug for the treatment of their index venous thromboembolic event. All patients provided written informed consent. Comprehensive inclusion and exclusion criteria are shown in Table S2.

2.2 | Treatment regimen and follow-up

Enrolled patients were treated with rivaroxaban and observed for up to 6 months or until withdrawal of consent, death, or loss to follow-up. Treatment duration with rivaroxaban and all treatment decisions were determined at the physician's discretion. The exclusion criteria specified situations where rivaroxaban use is contraindicated, including renal failure. Any need for subsequent dose reductions, for example, following a decrease in estimated glomerular filtration rate or creatinine clearance, would have been made according to routine clinical practice. Patient and treatment data were collected at baseline, approximately week 4, approximately month 3, and at the end of observation at month 6. The exact dates of the follow-up visits at approximately week 4 and month 3 were not specified by the protocol due to the observational nature of the study; instead, investigators were advised to schedule the follow-up visits to coincide with routine appointments. No additional diagnostic tests were performed outside of routine clinical practice.

2.3 | Outcome assessments

The primary outcome of the study was to assess patient-reported anticoagulation treatment satisfaction using the Anti-Clot Treatment Scale Burdens score at week 4[21] and will be reported separately. Here, the following prespecified secondary outcomes were evaluated:

- Clinical characteristics of cancer patients with VTE.
- Patterns of use of anticoagulant treatment and rivaroxaban specifically.
- Effectiveness and safety of rivaroxaban therapy, including rates of treatment-emergent thromboembolic and bleeding events.

Clinical outcomes were reported for the safety population, which included patients who received at least one dose of rivaroxaban. The clinical characteristics included demographics and details of cancer type and stage; details of the index venous thromboembolic event were also reported. The demographic data were captured in electronic case report forms from patient medical records as reported by the treating physician. "Patterns of use" included the type and duration of initial anticoagulation, the primary reason for the change to rivaroxaban, planned and actual duration of rivaroxaban use, dosage of rivaroxaban, reasons for any change from rivaroxaban during the study, persistence with rivaroxaban treatment, and reasons for permanent discontinuation. Bleeding events, thromboembolic events (recurrent VTE, major adverse cardiovascular events [MACEs], and other thromboembolic events), and causes of death were adjudicated by members of the external steering committee. Bleeding events were adjudicated and categorized as major or nonmajor in accordance with the ISTH criteria. Thromboembolic events (as defined by standardized Medical Dictionary for Regulatory Activities query "Embolic and thrombotic events") were adjudicated and categorized as symptomatic or incidental and as new or recurrent. Deaths were reported by the investigators, adjudicated, and classified as related to either cancer, thrombosis, bleeding, infectious diseases, or "other" causes. All-cause mortality included treatment-emergent (ie, occurring on or after the day of the first dose and up to 2 days after the last dose) adjudicated deaths. Premature discontinuation due to death included all deaths up to 30 days after the end of treatment.

2.4 | Study oversight

The COSIMO study was initiated and funded by Bayer AG, which was responsible for the overall study design, protocol, and oversight. An external steering committee supported development of the study protocol and provided guidance regarding the study conduct, adjudication of events, and the analysis, interpretation, and publication of results. Four expert physicians from the external steering committee formed the Central Adjudication Committee, which adjudicated all major bleeding and thromboembolic events and any events that resulted in death. The study was performed in accordance with the principles of the Declaration of Helsinki and with local regulations. Where required, the protocol was approved by an independent ethics committee or institutional review board at each study site.

3 | RESULTS

3.1 | Patient characteristics

The COSIMO study enrolled 509 patients from 10 countries. A total of 4 patients did not receive rivaroxaban and were excluded from

the safety analysis set. Overall, 117 (23.2%) patients from the safety analysis set discontinued the study prematurely; of these, 59 died, 21 withdrew consent, 17 were lost to follow-up, and 20 had other reasons for discontinuation. All patients who withdrew consent agreed to further use of data collected before discontinuation. The mean age (±standard deviation [SD]) was 64.0 (±11.7) years, and 44.6% were men. Their mean weight (±SD) was 76.7 (±17.0) kg. The ECOG performance status at baseline was 0 for 162 (32.1%) patients, 1 for 276 (54.7%) patients, and 2 for 63 (12.5%) patients (Table 1).

Most patients (n = 488; 96.6%) were changed to rivaroxaban from LMWH; 8 (1.6%) from a VKA, and 9 (1.8%) from fondaparinux. Median duration of all anticoagulant treatment before change to rivaroxaban was 100 days (interquartile range [IQR], 47-181 days). The most common reasons for changing to rivaroxaban were patient preference factors, including desire to cease parenteral administration (n = 136; 26.9%), improve quality of life (n = 94; 18.6%), patient decision (n = 76; 15.0%), and an undesirably long distance from their physician (n = 4; 0.8%), as well as physician decision (n = 174; 34.5%).

TABLE 1 Key baseline characteristics

Characteristic	Rivaroxaban (N = 505)
Country/region, n (%)	
Europe	370 (73.3)
Canada	128 (25.3)
Australia	7 (1.4)
Age, years, mean ± SD	64.0 ± 11.7
Male sex, n (%)	225 (44.6)
Weight, kg, mean ± SD	76.7 ± 17.0
<50.0 kg, n (%)	18 (3.6)
≥90.0 kg, n (%)	97 (19.2)
Missing, n (%)	57 (11.3)
First available creatinine clearance, n (%)	
<30 mL/min	4 (0.8)
30 to <50 mL/min	42 (8.3)
50 to <80 mL/min	148 (29.3)
≥80 mL/min	234 (46.3)
Missing	77 (15.2)
ECOG performance status, n (%)[a]	
0	162 (32.1)
1	276 (54.7)
2	63 (12.5)
Missing	4 (0.8)
Hypertension, n (%)	178 (35.2)
Diabetes, n (%)	56 (11.1)
Prior stroke, n (%)	15 (3.0)
Peripheral artery disease, n (%)	1 (2.9)
Acute coronary syndrome, n (%)	10 (2.0)
Dyslipidemia, n (%)	6 (1.2)
Obesity, n (%)	1 (2.9)
Index diagnosis, n (%)	
DVT only	229 (45.3)
Symptomatic	181 (35.8)
Incidental	48 (9.5)
PE only	188 (37.2)
Symptomatic	116 (23.0)
Incidental	72 (14.3)
DVT with PE	49 (9.7)
Symptomatic	34 (6.7)
Incidental	15 (3.0)
Catheter-associated DVT	38 (7.5)
Missing	1 (0.2)
VTE risk factors,[b] n (%)	
Known thrombophilia	6 (1.2)
Recent surgery/trauma (<3 mo before enrollment)	53 (10.5)
Prolonged immobilization with ≥2 days' bed rest	31 (6.1)
Use of estrogen-containing drugs	15 (3.0)
Recent long-haul travel (<4 wk before enrollment)	3 (0.6)
Venous insufficiency	10 (2.0)
Leg paresis	0 (0)
Puerperium	0 (0)
Other risk factors	35 (6.9)
No known risk factor for VTE,[c] n (%)	371 (73.5)

Abbreviations: DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

[a]The ECOG performance status scores: 0 = fully active, able to carry on all predisease performance without restriction, 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2 = ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours.

[b]Multiple responses were possible.

[c]Other than cancer.

A total of 449 (88.9%) patients had solid primary tumor types, the most common being gastrointestinal malignancy (n = 131; 25.9%); 56 (11.1%) patients had a hematological malignancy as their primary cancer type (Figure 1). At baseline, approximately half (245/449; 54.6%) of patients with solid tumors had a metastasis; the most common locations of metastases were in the liver (n = 94), lymph nodes (n = 87), lung (n = 82), and bone (n = 69). Status of cancer response at baseline was available for 320 (63.4%) patients in the safety analysis set; of these, 47 had complete remission, 38 had partial remission, 146 had stable disease, and 89 had relapsed or progressive disease.

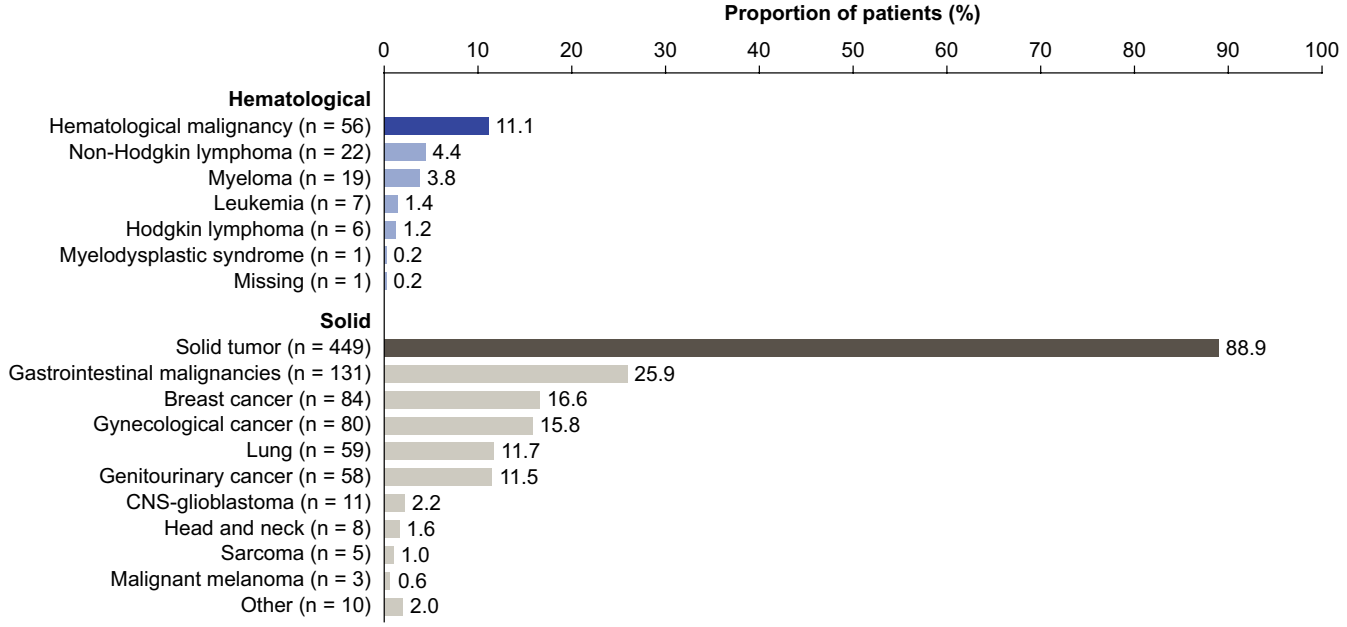


FIGURE 1 Patient cancer characteristics at baseline. Gastrointestinal malignancies included colon (n = 55), rectal (n = 33), pancreatic (n = 21), esophagogastric (n = 15), cholangiocarcinoma (n = 6), and hepatocellular carcinoma (n = 1). CNS, central nervous system

A total of 229 (45.3%) patients had an index venous thromboembolic event of DVT, 188 (37.2%) had PE, 49 (9.7%) had both DVT and PE, and 38 (7.5%) had a catheter-associated DVT (Table 1). Most patients (n = 371; 73.5%) had no known risk factors for VTE (other than cancer) at baseline (Table 1). A total of 44 patients (8.7%) reported at least one previous venous thromboembolic event (before the index event) within the past 5 years: 37 (7.3%) had one venous thromboembolic event, and 7 (1.4%) had more than one venous thromboembolic event. At baseline, the median time since the most recent previous venous thromboembolic event was 1.3 (IQR, 0.7-2.5) years.

3.2 | Anticoagulant and concomitant treatments during the study

A total of 405 (80.2%) patients were treated with rivaroxaban for at least 90 days and 223 (44.2%) patients for 180 days. The median duration of rivaroxaban treatment was 176 (IQR, 105-189) days (mean ± SD, 148.5 ± 65.4). The overall median duration of total anticoagulation treatment (ie, time on traditional anticoagulant plus rivaroxaban) was 272 (IQR, 213-361) days. At the end of the observation period, 302 (59.8%) patients had ongoing rivaroxaban treatment; 64 (12.7%) patients continued with another anticoagulant after permanently stopping rivaroxaban therapy. Treatment duration of rivaroxaban was similar across patients with DVT, PE, or catheter-associated thrombosis. Most patients (n = 397; 78.6%) received rivaroxaban 20 mg once daily on study entry; 28 (5.5%) patients were started on 15 mg twice daily and changed to 20 mg once daily after 21 days. Rivaroxaban dose was changed in 46 (9.1%) patients; 8 (1.6%) patients had more than one change to dose. The most common reasons for a dose change were an adverse event (AE) or decreased renal function (23 patients). A total of 32 (6.3%) patients had at least one interruption of rivaroxaban treatment; these were due to low platelet count in 3 (0.6%) patients, decreased renal function in 1 (0.2%), other AEs in 12 (2.4%), and other reasons in 17 (3.4%). Nine (1.8%) patients received concomitant local anticancer therapy (including cryotherapy ablation and radiofrequency ablation) and 79 (15.6%) patients received concomitant radiotherapy during the study. Of the 178 (35.2%) patients treated with concomitant systemic anticancer therapy, 150 (29.7%) patients received chemotherapy (Table 2).

TABLE 2 Concomitant procedures and anticancer therapy

Type of cancer therapy[c]	Number of patients (N = 505) n (%)
Systemic anticancer therapy	178 (35.2)
Chemotherapy	150 (29.7)
Hormonal therapy	18 (3.6)
Immunotherapy	15 (3.0)
Targeted therapy	15 (3.0)
Other systemic therapy	6 (1.2)
Local anticancer therapy	9 (1.8)
Radiotherapy	79 (15.6)

[a]Multiple responses were possible.

3.3 | Effectiveness and safety outcomes (treatment-emergent events)

Since 8.9% of patients discontinued the study prematurely due to death, the 6-month cumulative incidences of recurrent venous

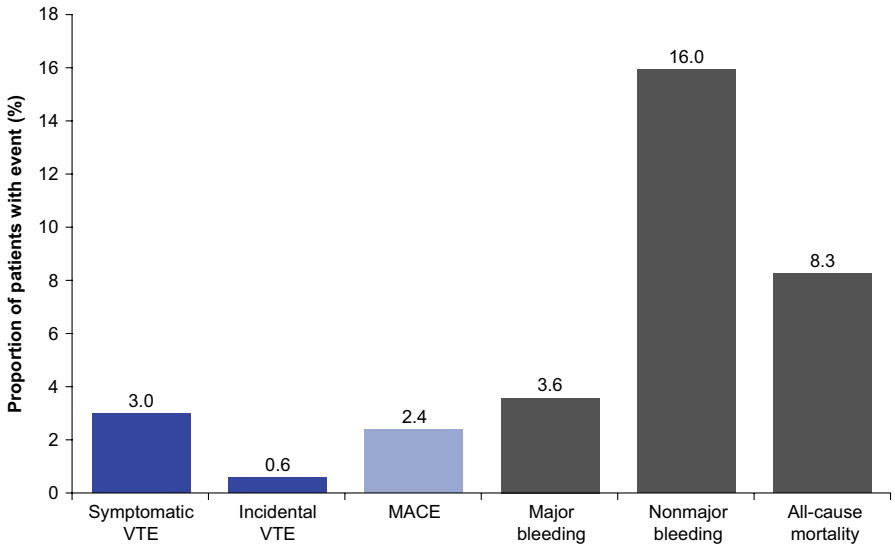


FIGURE 2 Proportions of patients with treatment-emergent thromboembolic and bleeding events with rivaroxaban. All events were adjudicated. Bleeding events were adjudicated in accordance with ISTH criteria. A fatal major bleeding event occurred in 2 patients (0.4%). MACE, major adverse cardiovascular event (stroke, myocardial infarction, or cardiovascular death); VTE, venous thromboembolism

thromboembolic events and bleeding events were estimated as post hoc analysis using the Aalen-Johansen estimator with premature discontinuation due to death as competing risk.

3.3.1 | Recurrent venous thromboembolic events

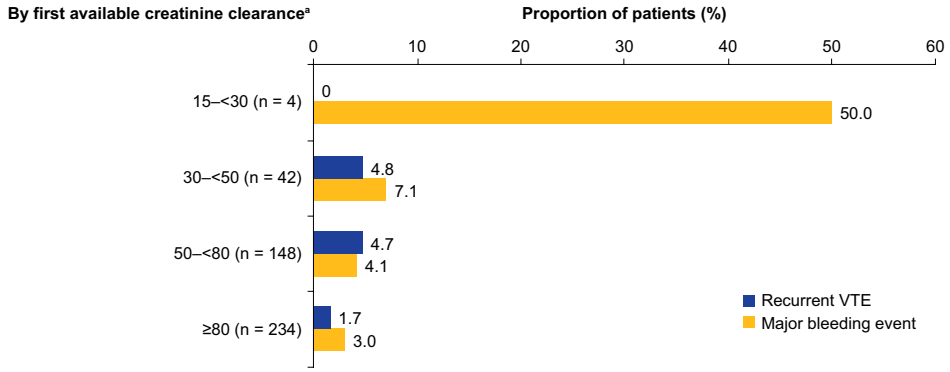
During the 6-month study period, symptomatic VTE recurrence occurred in 15 (3.0%) patients (incidence rate per 100 patient-years, 7.3; 95% CI, 4.1-12.1) and incidental VTE recurrence occurred in 3 (0.6%) patients (incidence rate per 100 patient-years, 1.47; 95% CI, 0.3-4.3; Figure 2). The 6-month cumulative incidence of recurrent VTE (symptomatic or incidental) is shown in Table S3 and Figure S1.

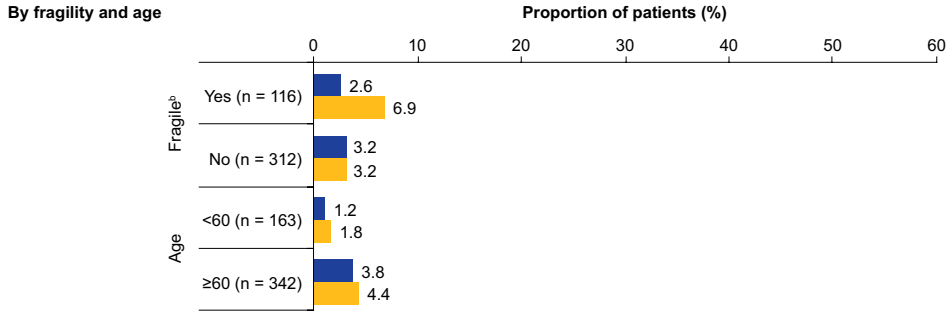
Of the 18 patients who experienced at least one event, 12 had symptomatic DVT, 2 had symptomatic PE, 1 had symptomatic catheter-associated thrombosis, and 3 had incidental PE. No patients experienced a fatal venous thromboembolic event. Relative to the 3.0% incidence in recurrent symptomatic VTE seen in the overall safety population, recurrent VTE occurred generally more frequently in patients ≥60 years old; patients with lymphoma, gynecological cancer, and genitourinary cancers; and patients with catheter-associated DVT (Figure 3).

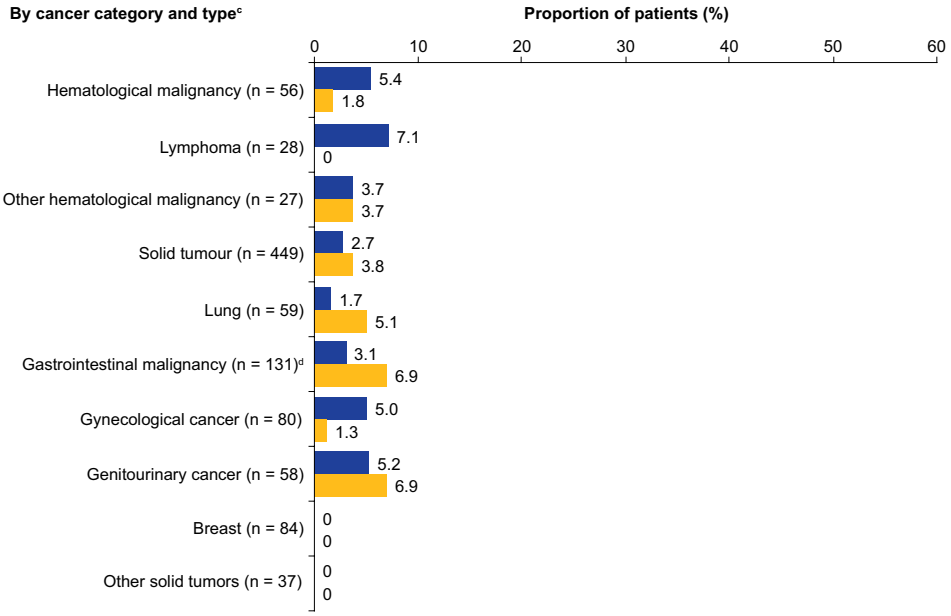
3.3.2 | Bleeding events

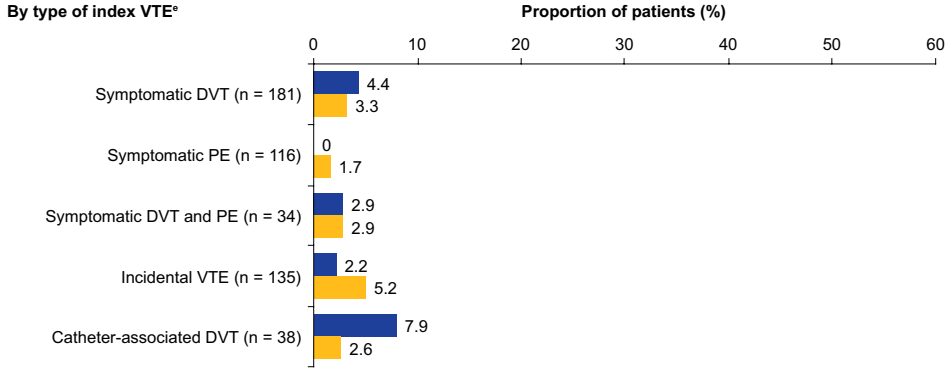
A total of 21 treatment-emergent adjudicated major bleeding events occurred in 18 (3.6%) patients (incidence rate per 100 patient-years, 8.84; 95% CI, 5.2-14.0; Figure 2). The cumulative incidence of major bleeding at 6 months was 3.7% (95% CI, 2.3-5.7). The 6-month cumulative incidence function estimates and plot are shown in Table S3 and Figure S1. Of these patients (and considering that a patient may have more than one criterion), 2 had a fatal event (1 event was adjudicated as intracranial hemorrhage in a patient with metastatic prostate cancer who experienced right-sided parietal subdural hemorrhage 9 days before death; and the other event was adjudicated as extracranial hemorrhage in a patient with non–small cell lung cancer who experienced hemoptysis and died the next day of spontaneous pulmonary hemorrhage), 1 had a nonfatal critical site bleeding event, 13 required transfusion, and 3 had a hemoglobin drop of ≥2 g/dL. Major bleeding events were "spontaneous" (ie, not caused by surgery, trauma, or an invasive procedure) in 14 (77.8%) of the patients experiencing major bleeding. Sites of the major bleeding events included gastrointestinal for 11 patients, genitourinary for 3 patients, central nervous system for 2 patients, head or neck for 1 patient, thorax for 1 patient, and other for 1 patient. Of the 18 patients with at least one major bleeding event, 9 had gastrointestinal cancer, 4 had genitourinary cancer, 3 had lung cancer, and 2 had "other" types of primary cancer. Nonmajor bleeding events occurred in 81 (16.0%) patients (incidence rate per 100 patient-years, 43.78; 95% CI, 34.8-54.4; Figure 2). Relative to the 3.6% incidence of major bleeding events seen in the overall safety population, the incidence of major bleeding events was more frequent in patients: with creatinine clearance (CrCl) 15 to <30 mL/min or CrCl 30 to <50 mL/min; categorized as fragile (patients who were >75 years

FIGURE 3 Proportions of patients with treatment-emergent symptomatic recurrent venous thromboembolic and major bleeding events. All events were adjudicated. [a]For 77 patients first available creatinine clearance (CrCl) was unknown; therefore, the event rates were not included in this analysis. [b]Fragile was defined as patients who were aged >75 years, weighed ≤50.0 kg, or had a first available CrCl <50 mL/min. For 77 patients the category of fragility was unknown; therefore, the event rates were not included in this analysis. [c]For 1 patient the category of hematological malignancy was unknown; therefore, the event rates were not included in this analysis. [d]Gastrointestinal malignancies included colon (n = 55), rectal (n = 33), pancreatic (n = 21), esophagogastric (n = 15), cholangiocarcinoma (n = 6), and hepatocellular carcinoma (n = 1). [e]For 1 patient the type of index VTE was unknown; therefore, the event rates were not included in this analysis. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism


By first available creatinine clearance[a]
Proportion of patients (%)
0
10
20
30
40
50
60
15–<30 (n = 4)
0
50.0
30–<50 (n = 42)
4.8
7.1
50–<80 (n = 148)
4.7
4.1
≥80 (n = 234)
1.7
3.0
Recurrent VTE
Major bleeding event


By fragility and age
Proportion of patients (%)
0
10
20
30
40
50
60
Fragile[b]
Yes (n = 116)
2.6
6.9
No (n = 312)
3.2
3.2
Age
<60 (n = 163)
1.2
1.8
≥60 (n = 342)
3.8
4.4


By cancer category and type[c]
Proportion of patients (%)
0
10
20
30
40
50
60
Hematological malignancy (n = 56)
5.4
1.8
Lymphoma (n = 28)
7.1
0
Other hematological malignancy (n = 27)
3.7
3.7
Solid tumour (n = 449)
2.7
3.8
Lung (n = 59)
1.7
5.1
Gastrointestinal malignancy (n = 131)[d]
3.1
6.9
Gynecological cancer (n = 80)
5.0
1.3
Genitourinary cancer (n = 58)
5.2
6.9
Breast (n = 84)
0
0
Other solid tumors (n = 37)
0
0


By type of index VTE[e]
Proportion of patients (%)
0
10
20
30
40
50
60
Symptomatic DVT (n = 181)
4.4
3.3
Symptomatic PE (n = 116)
0
1.7
Symptomatic DVT and PE (n = 34)
2.9
2.9
Incidental VTE (n = 135)
2.2
5.2
Catheter-associated DVT (n = 38)
7.9
2.6

old, weighed ≤50.0 kg, or had a first available CrCl <50 mL/min); or aged ≥60 years, and varied according to type of index VTE. Major bleeding was more frequent in patients with gastrointestinal or genitourinary cancer than in patients with other types of cancer (Figure 3).

3.3.3 | Major adverse cardiovascular events and "other thromboembolic" events

A total of 13 MACEs occurred in 12 (2.4%) patients (Figure 2). Of these, 9 (1.8%) had a stroke (5 of which were fatal; 1 patient had more than one type of stroke), 2 reported a nonfatal myocardial infarction, and 1 suffered cardiovascular death. Of the 12 patients who experienced a MACE, 5 patients had lung cancer, 4 had genitourinary cancer, and 3 had gastrointestinal cancer. For other thromboembolic events, incidental portal vein thrombosis occurred in 1 (0.2%) patient and symptomatic thrombophlebitis in 1 (0.2%) patient.

3.3.4 | Adverse events

AEs were reported in 312 (61.8%) patients: 181 (35.8%) reported cancer-related AEs, 135 (26.7%) reported cancer therapy-related AEs; rivaroxaban-related AEs, excluding bleeding events, were reported by the investigator in 38 (7.5%) patients. AEs leading to discontinuation occurred in 62 (12.3%) patients. Of the 148 (29.3%) patients who reported serious AEs (SAEs), 110 (21.8%) reported cancer-related SAEs, 36 (7.1%) serious cancer therapy-related AEs, and 8 (1.6%) rivaroxaban-related SAEs, excluding bleeding events reported by the investigator. Rivaroxaban-related SAEs, excluding bleeding events, included nervous system disorders (2 patients; 0.4%); respiratory, thoracic, and mediastinal disorders (2 patients; 0.4%); vascular disorders (2 patients; 0.4%); infections and infestations (1 patient; 0.2%); and gastrointestinal disorders (1 patient; 0.2%). SAEs leading to prolonged hospitalization occurred in 111 (22.0%) patients and rivaroxaban-related SAEs leading to death were reported in 2 patients.

3.3.5 | All-cause mortality

Death during the observational period occurred in 42 (8.3%) patients in the safety analysis set (Figure 2, Figure S1; incidence rate per 100 patient-years (20.58; 95% CI, 14.8-27.8); 6-month cumulative incidences are shown in Table S3 and Figure S1), of whom 25 (5.0%) died due to cancer, 6 (1.2%) due to infectious disease, 5 (1.0%) due to ischemic stroke, 2 (0.4%) from a bleeding event, 2 (0.4%) from unexplained death (reported to be respiratory failure and cardiac arrest by the investigators and adjudicated as unexplained death), 1 (0.2%) from myocardial infarction, and 1 (0.2%) from other cause(s).

4 | DISCUSSION

The COSIMO study previously demonstrated that patients with CAT who change their VTE treatment from LMWH, fondaparinux, or a VKA to rivaroxaban in everyday clinical practice experience an improvement in treatment satisfaction.[22] In the current analysis, this study also provided insights into the types of patients selected for and who chose rivaroxaban treatment in routine clinical practice, and associated clinical outcomes. Patients were recruited sequentially, and inclusion and exclusion criteria were minimal; this allowed for insights into the benefit-risk profile of rivaroxaban across a range of patients with active cancer who have been considered suitable for rivaroxaban by treating physicians, including patients differing from those enrolled in previous RCTs. Because patients were only enrolled after a median of 100 days (IQR, 47-181) of anticoagulant therapy and most recurrent VTE events occur early after the index VTE (as observed in the Evaluation of Dalteparin for Long-Term [One Year] Treatment of Blood Clots in Subjects With Cancer [DALTECAN] study), it is likely that patients at lower risk of VTE recurrence and bleeding were enrolled than in other studies. Therefore, lower rates of VTE recurrence may be expected in COSIMO.[23] Furthermore, the results of COSIMO apply only to patients who have already received acute and short-term anticoagulation.[24] For the same reason, the study is limited by the immortal time bias and the results cannot be compared directly with those of other studies. The results are also limited to patients with ECOG scores ≤2. Regardless, the key baseline cancer characteristics of patients in COSIMO were not dissimilar to the RCT SELECT-D, which used the same DOAC rivaroxaban.[6] Furthermore, the COSIMO study demonstrated that the types of patients considered for rivaroxaban in clinical practice include those with metastases and those receiving cancer treatment (≈50% and ≈70% of the COSIMO study population, respectively). The proportion of patients in the COSIMO study with any gastrointestinal malignancies (26%) reflects the expected prevalence of gastrointestinal malignancies in the overall population of patients with CAT.[25]

The present study provides further evidence to support the long-term use of rivaroxaban treatment to prevent the recurrence of VTE in patients with active cancer, with a median duration of rivaroxaban treatment of ≈6 months and overall median duration of total anticoagulation treatment of ≈9 months. During the COSIMO study, only 32 (6.3%) patients had an interruption to treatment and only 58 (11.5%) patients discontinued the study prematurely for reasons other than death, suggesting a high level of persistence with rivaroxaban. Low rates of premature discontinuation (for reasons other than death or being transferred to another institution) were also reported in other observational studies of patients with CAT.[26,27]

This study builds on the clinical efficacy and safety of rivaroxaban for the treatment of VTE in patients with active cancer, and supports the use of anticoagulants beyond 6 months for the long-term treatment of CAT previously reported in single-arm studies.[23,28] The RCTs Hokusai-VTE-Cancer, SELECT-D, CARAVAGGIO, and ADAM-VTE examined the acute treatment setting and enrolled

patients with cancer and an acute venous thromboembolic index event, and excluded those who received anticoagulant therapy for >3 to 7 days before randomization,[5,6,18,19] whereas the COSIMO study examined the long-term treatment of CAT and enrolled patients who had completed a median duration of 100 (IQR, 47-181) days of anticoagulant treatment.

The clinical outcomes from this study were consistent with other prospective observational studies of rivaroxaban treatment for patients with CAT, which reported VTE recurrence in 3.4% to 4.3% of patients, and major bleeding events in 1.1% to 7.4% of patients at 6 months.[26,27,29] Similarly, overall all-cause mortality in COSIMO (11.7%) is close to the range reported from these real-world studies (12.8% to 18.5% at 6 months).[27,29] Although the COSIMO study was not specifically designed to assess associations between patient characteristics and major bleeding, the most common site of major bleeding was gastrointestinal, and an exploratory analysis suggested an association between gastrointestinal cancer and major bleeding. Similar observations were reported in other studies such as SELECT-D and Hokusai-VTE-Cancer.[5,6] Due to differences in study design, however, these observational studies cannot be compared directly.

Data from prospective studies on optimal anticoagulation therapy in patients with catheter-related DVT are limited and the COSIMO study contributes to this important topic. In the small subgroup of patients with catheter-related DVT, the duration of rivaroxaban therapy was comparable with that of the overall population, although rates of recurrent VTE were higher and rates of major bleeding were lower. These results are interesting, and further investigation is warranted to determine optimal approaches to anticoagulation therapy in these patients.

Of the 12 (2.4%) patients in the COSIMO study who had MACEs, ≈60% were fatal. Previous studies have shown that patients with VTE and cancer have an increased risk of MACEs, which appears to be a major cause of mortality in patients with CAT.[30-32] These findings suggest that the influence of arterial ischemic events on clinical outcomes in patients with CAT needs to be elucidated. AEs reported in the COSIMO study were mostly cancer- or cancer therapy–associated events and were similar to those observed in the RCTs of DOACs in patients with CAT.[5] These data suggest that investigators were able to include appropriate patients with CAT to change to rivaroxaban therapy.

Limitations of the COSIMO study have been previously described.[21,22] COSIMO was a single-arm study, and although a comparator intervention might have provided further clinical perspective, a two-armed noninterventional study would have required propensity score adjustment to address the high levels of heterogeneity in populations of patients with CAT; the larger sample size required for this may have been complicated by recruitment and retention challenges.[33] Because the study was limited to patients switching to rivaroxaban, the possibility of bias according to DOAC selection cannot be excluded. Because of the limited geographic distribution, the patterns of anticoagulant use observed may be less applicable to countries where differences in medical care apply. As with all observational studies, bias by indication was possible in COSIMO. Although only a small number of enrollment criteria were applied, the population was limited to patients with ECOG scores ≤2 and anticoagulation therapy for a median of 100 days before initiation of rivaroxaban. There was also potential for selection bias for lower-risk patients as in other studies in this setting where patients with short life expectancy and low ECOG scores are also frequently excluded. This means that the results of COSIMO do not apply to all patients in clinical practice, including those initiating DOAC therapy shortly after VTE.

5 | CONCLUSIONS

The COSIMO study provides unique insights into patient management and outcomes associated with rivaroxaban use for the prevention of recurrent VTE after an initial period of standard-of-care therapy for CAT. Patients chosen to be treated with rivaroxaban had advanced stages of cancer and demonstrated similar cancer characteristics to previous studies investigating the use of DOACs for the treatment of CAT. The incidence of recurrent VTE, rivaroxaban-related AEs, and bleeding events during the study was relatively low in this population of patients with previous anticoagulation therapy, suggesting that with appropriate patient selection, clinical benefit can be achieved with DOAC treatment in patients with CAT.

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RELATIONSHIP DISCLOSURE

ATC reports personal fees from Bayer AG and Janssen during the conduct of the study; grants and personal fees from Bristol Myers Squibb, Daiichi Sankyo Europe, and Pfizer; and personal fees from Boehringer Ingelheim, Portola, AbbVie, Exxom group, and ONO Pharmaceuticals outside the submitted work. AM reports personal fees and grants from Bayer AG during the conduct of the study; personal fees and grants from Bristol Myers Squibb; and personal fees from LEO Pharma outside the submitted work. JB-W reports grants and personal fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Bristol Myers Squibb, and Pfizer, and personal fees from CSL Behring and LEO Pharma outside the submitted work. AYL reports personal fees from Bayer during the conduct of the study; grants from Bristol Myers Squibb; and personal fees from LEO Pharma and Pfizer outside the submitted work. LGM reports personal fees from Bayer AG and nonfinancial support and other from the Italian Ministry of Health Ricerca Corrente – IRCCS MultiMedica during the conduct of the study; personal fees from

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AUTHOR CONTRIBUTIONS

The authors are solely responsible for the design and conduct of this study; all study analyses, interpretation of data, the drafting and editing of the manuscript, and its final contents.

DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations/Pharmaceutical Research and Manufacturers of America Principles for Responsible Clinical Trial Data Sharing. This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical study data, study-level clinical study data, and protocols from clinical studies in patients for medicines and indications approved in the United States and European Union as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study Sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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