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Comparison of Clinical Outcomes in Patients with Active Cancer Receiving Rivaroxaban or Low-Molecular-Weight Heparin: The OSCAR-UK Study

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Abstract

Background In most patients with cancer-associated venous thromboembolism (CT), essentially those not at high risk of bleeding, guidelines recommend treatment with direct oral anticoagulants as an alternative to low-molecular-weight heparins (LMWHs). Population-based studies comparing these therapies are scarce.

Objectives To compare the risk of venous thromboembolism (VTE) recurrences, significant bleeding, and all-cause mortality in patients with CT receiving rivaroxaban or LMWHs.

Patients/Methods Using UK Clinical Practice Research Datalink data from 2013 to 2020, we generated a cohort of patients with first CT treated initially with either rivaroxaban or LMWH. Patients were observed 12 months for VTE recurrences, significant bleeds (major bleeds or clinically relevant nonmajor bleeding requiring hospitalization), and all-cause mortality. Overlap weighted sub-distribution hazard ratios (SHRs) compared rivaroxaban with LMWH in an intention-to-treat analysis.

Results The cohort consisted of 2,259 patients with first CT, 314 receiving rivaroxaban, and 1,945 LMWH, mean age 72.4 and 66.9 years, respectively. In the 12-month observational period, 184 person-years following rivaroxaban and 1,057 following LMWH, 10 and 66 incident recurrent VTE events, 20 and 102 significant bleeds, and 10 and 133 deaths were

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- venous thromboembolism
- anticoagulants
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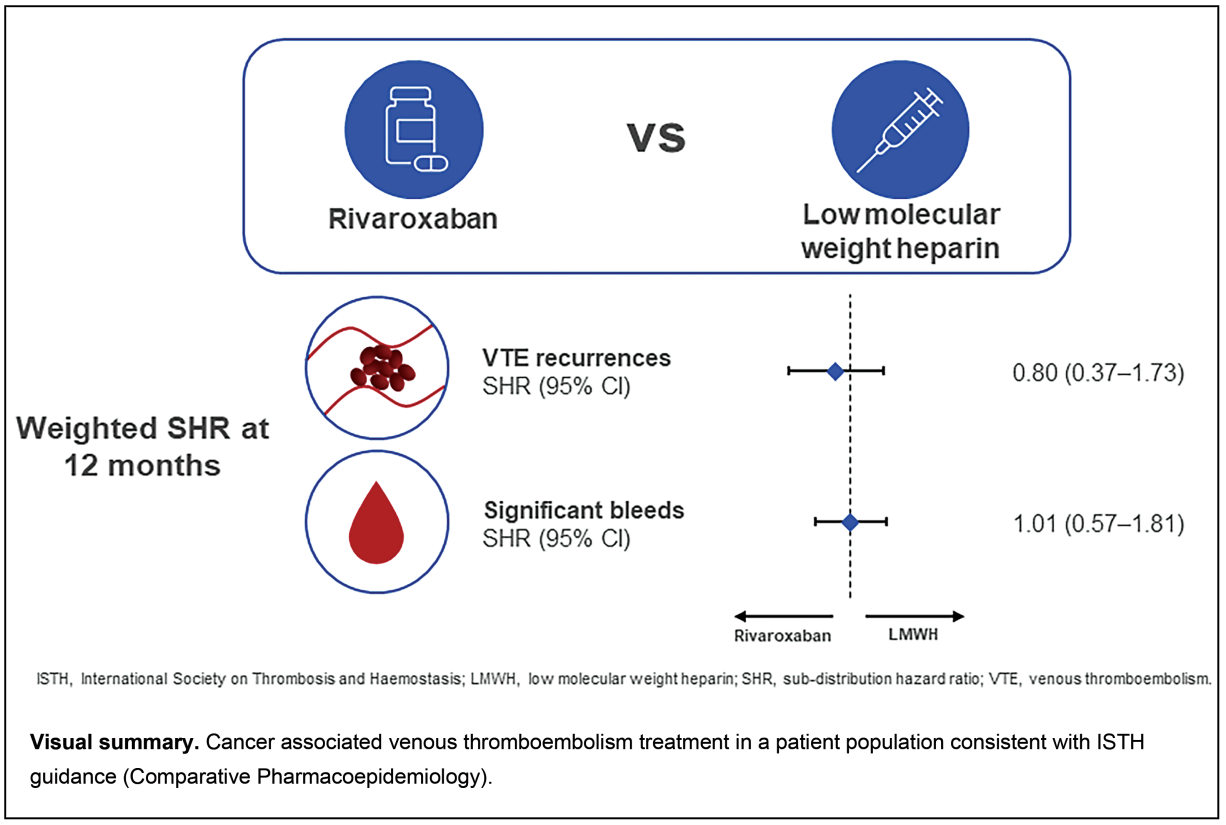

Visual summary. Cancer associated venous thromboembolism treatment in a patient population consistent with ISTH guidance (Comparative Pharmacoepidemiology).

observed in rivaroxaban and LMWH users, respectively. The weighted SHR at 12 months for VTE recurrences in rivaroxaban compared with LMWH were 0.80 (0.37–1.73); for significant bleeds 1.01 (0.57–1.81); and for all-cause mortality 0.49 (0.23–1.06).

Conclusion Patients with CT, not at high risk of bleeding, treated with either rivaroxaban or LMWH have comparable effectiveness and safety outcomes. This supports the recommendation that rivaroxaban is a reasonable alternative to LMWH for the treatment of CT.

Introduction

Patients with cancer-associated venous thromboembolism (CT) have a higher risk of bleeding, venous thromboembolism (VTE) recurrences, and all-cause mortality compared with those without cancer.[1–3] Guidelines list direct oral anticoagulants (DOACs) and low-molecular-weight heparins (LMWHs) as options for the treatment of CT and the secondary prevention of VTE recurrences.[4–6] The strength of recommendation for DOACs is based on efficacy and safety data from randomized controlled trials comparing DOAC to LMWH or vitamin K antagonists (VKAs).[7] Observational studies have also investigated the bleeding risk in patients treated with DOACs for CT. Some of these studies lack a comparison with LMWHs, lack information on cancer type, or include cancer types not recommended for DOAC treatment.[8,9] Overall, many studies had a lack of study power because of a small number of recurrent VTE and bleeding events, affecting, amongst other things, the analysis of recurrent VTE and bleeding events over time.

Our primary objective was to evaluate with an intention-to-treat (ITT) analysis the effectiveness (recurrent VTE) and safety (significant bleeds and all-cause mortality) of rivaroxaban versus LMWH for CT treatment in patients with active cancer excluding those with a malignant neoplasm associated with a high risk of bleeding. The recognition of patients with CT at high risk of bleeding was guided by expert interpretation of the International Society on Thrombosis and Haemostasis (ISTH) guidance.[6] The Observational Studies in Cancer Associated Thrombosis for Rivaroxaban in the United Kingdom Cohort (OSCAR-UK) is part of the OSCAR program with independent studies in the United States,[10] United Kingdom,[11] and Sweden.[12]

Methods

Study Design and Data Source

This was a retrospective, observational cohort study of patients with active cancer and incident CT subsequently treated with anticoagulants (AC).

Data were obtained from the UK Clinical Practice Research Datalink (CPRD) GOLD and Aurum databases with linkage to inpatient and outpatient data from the Hospital Episodes

Statistics (HES) and the Office for National Statistics (ONS) mortality data. CPRD includes patient demographics, lifestyle factors, medical diagnoses, and symptoms recorded with primary care Read medical and Systematized Nomenclature of Medicine–Clinical Terms (SNOMED CT) codes, referrals to secondary care, test results, and general practitioner (GP) prescriptions. HES data include hospital admission and discharge dates, discharge diagnoses recorded with ICD-10 codes (International Classification of Diseases, Tenth Revision), and surgical operations and procedures (OPCS-4 codes). ONS mortality data consist of date and cause of death (ICD-10 codes).

Selection of Participants

The study population consisted of all patients 18 years or older from English practices in the CPRD that were eligible for linkage to HES and ONS data in the study period, between January 1, 2013 and October 31, 2020. The study cohort included all eligible patients in CPRD with an incident VTE and active cancer, and with evidence of therapeutic rivaroxaban or LMWH use within 30 days following the VTE. VTE was identified according to our previously developed, validated, and published algorithm.[11] VTE comprised pulmonary embolisms and deep vein thromboses (DVTs). DVT included thromboses of the deep veins of the legs, calf vein thromboses, thromboses of pelvic veins and vena cava as well as thromboses of the upper limb. Cerebral and abdominal vein thrombi were not included.

Active cancer was defined as a cancer being diagnosed within 180 days prior to the index CT, or associated with metastatic disease (regardless of time from initial cancer diagnosis), or 180 days following the patient receiving anticancer therapy. To generate a cohort of patients with incident CT and new users of ACs, we excluded patients with: less than 1-year contribution to the CPRD-HES-ONS link before CT, and those with a prior history of VTE (including cerebral and abdominal vein thrombi), insertion of an inferior vena cava filter, prior therapeutic AC use, other indications for long-term AC use (e.g., atrial fibrillation or artificial heart valves), thrombocytopenia, end-stage kidney disease, recent hip or knee preplacement (35 days), active pregnancy, or a recording indicative of palliative care initiation before the CT. Patients with VKA use, a significant bleeding event, or a VTE recurrence between the initial CT and the initiation of rivaroxaban/LMWH were also excluded. Cancer types for which use of DOACs is endorsed by interpretation of the ISTH guidance were considered, thus patients with the following cancer types were excluded from the study cohort: non-brain central nervous system (i.e., spinal cord tumors), unresected colorectal/lower gastrointestinal tract, hematologic (except lymphoma and myeloma), esophagus, stomach, and bladder.[6]

Observational Period

The day of the incident CT was designated as the cohort entry day and the day of the first recording of therapeutic rivaroxaban or LMWH initiation within 30 days after the acute CT was designated as the index day. When the rivaroxaban/LMWH initiation was recorded during the initial CT hospitalization, the index day was shifted to the first day after hospital discharge. As in-hospital pharmacy data, including group and type of AC, are not systematically recorded in the linked HES database, we used the first postdischarge prescription of an AC to determine the patient's initial type of AC use. The 30-day period after hospital discharge was used to allow for any supply of AC supplied by the hospital but not recorded by the GP.

The observational period started on the index day and ended on the first of the following events: end of the study period (October 31, 2020), 1 year after CT, patient transferred out of GP practice, end of data collection of GP practice, initiation of palliative care, end of active cancer episode, cerebral or abdominal vein thrombus, first atrial fibrillation recording or artificial heart valve insertion, patient became pregnant, patient developed a study outcome.

Exposure

Exposure of interest was AC use with rivaroxaban or LMWH in a therapeutic dose. The primary analysis was an ITT approach. In this approach switching and discontinuation of AC treatment during the observational period was ignored. In a sensitivity analysis, an on-treatment approach was performed whereby the observational period ended when a patient discontinued the initial AC treatment or switched the AC. Patients switching AC type before the start of the at-risk period from LMWH to VKA/other parenteral AC/a DOAC other than rivaroxaban, or from rivaroxaban to LMWH/VKA/other parenteral AC/other DOAC were excluded. Patients switching from LMWH to rivaroxaban within the first 7 days after initial LMWH treatment were allocated to the rivaroxaban group with the day of rivaroxaban as start of at-risk period. Patients switching from LMWH to DOAC other than rivaroxaban within 7 days after first LMWH record were removed from the cohort.

Outcome

The outcomes of interest were VTE recurrences, significant bleeds defined as major bleeds, or clinically relevant nonmajor bleeding requiring hospitalization (CRNMB-H), and all-cause mortality.[12,13] Algorithms for the definition of recurrent VTE and of the bleeding events have previously been developed and refined using all information available in CPRD, HES, and ONS.[2,11,14] All identified potential VTE recurrences and significant bleeds were manually reviewed by three physicians (A.T.C., S.C., and C.M.). During the outcome reviews, the physicians were blinded to AC treatment type. All-cause mortality was identified from ONS death certificates. Duration of anticoagulation treatment (a secondary outcome) with rivaroxaban and LMWH use was defined as time on continuous treatment with the respective medication from initiation to discontinuation.

Covariates

Covariates included variables intended for description of the study cohort (including cancer type and treatment), variables potentially related with choice of AC type in CT patients (required for the determination of probability weights), and known or suspected risk factors for VTE recurrences, significant bleeds, and death from any cause (potential confounders).

Covariate groups were not mutually exclusive and consisted of demographics, comorbidities, comedications, laboratory values, and vital signs. Clinical conditions were defined from medical codes entered by GPs (Read and SNOMED CT codes), hospital discharge diagnoses and procedures (ICD and OPCS codes), medication use derived from GP-issued prescriptions (Gemscript and DM + D codes), and test results recorded by the GP. A full list of baseline characteristics and covariates is included in the ►**Supplementary Material** (available in the online version).

Data Analysis

Baseline characteristics at cohort entry were described separately for rivaroxaban- and LMWH-treated patients using numbers (proportions) for categorical variables and mean (standard deviation) for continuous variables.

To adjust for potential confounding between the rivaroxaban and LMWH cohort, probabilities for rivaroxaban initiation were estimated from multivariate logistic regression models based on covariates identified at cohort entry (baseline). Covariates were only included in the model when $\geq$3 patients were exposed to the covariate in each exposure group. These probabilities were then used to assign weights to all individual patients in the rivaroxaban and LMWH groups using the overlap weighting method, i.e., patients were weighted with the probability of belonging to the opposite treatment group.[15,16] By design, overlap weighting resulted in the exact balance of all variables included in the logistic regression model in the two exposure groups rivaroxaban and LMWH.

Crude incidence rates of recurrent VTE, significant bleeds, and death within 3, 6, and 12 months following CT were calculated in the rivaroxaban and LMWH groups separately before and after weighting. Univariate Fine and Gray regression models, accounting for competing risks using AC exposure (i.e., LMWH) as the independent variable, were used to estimate sub-distribution hazard ratios (SHRs) for VTE recurrence, significant bleeds, and all-cause mortality at 3, 6, and 12 months following CT separately. Models were performed with and separately without (unadjusted) overlap weighting. Competing risks for each study outcome were the other two study outcomes, e.g., significant bleeds and all-cause mortality for the analysis of VTE recurrences. The proportional hazards assumption was investigated using Schoenfeld residuals.[17] Missing data were allocated to a category "unknown."

In a sensitivity analysis, an on-treatment approach instead of an ITT approach was used, i.e., patients who discontinued AC treatment or switched to a different AC type, (e.g., from rivaroxaban to VKA) were censored. In addition, the duration of anticoagulation use following initial CT was described for rivaroxaban and LMWH groups separately using a competing risk approach and overlap weighting. In an exploratory analysis, critical organ bleeds (a subgroup of major bleeds) were investigated as a separate study outcome.

All statistical procedures were performed using Stata MP Version 14.2 (StataCorp LLC). The study protocol was approved by CPRD's Research Data Governance process (Protocol ID 21_000514). This study was registered at the European Union electronic Register of Post-Authorisation Studies (EU PAS Register; EUPAS43329).

Results

Population Characteristics

A total of 5,642 anticoagulation-naïve adult patients with active cancer and CT, with at least 1 year of history in CPRD/HES and treated with either rivaroxaban or LMWH, were identified between 2013 and 2020. Of those, 3,383 patients were excluded due to indications for anticoagulation use other than VTE, contraindications for rivaroxaban use, initiation of palliative care before the start of the at-risk period, or an unknown or non-ISTH-guided type of initial cancer. From the remaining 2,259 patients, 314 were treated with rivaroxaban, and 1,945 with LMWH (►**Fig. 1**) within 30 days following the CT diagnosis.

Rivaroxaban users were older, more likely to be males, less likely to be smokers, and socioeconomically deprived. Cancer types varied in the two AC exposure cohorts. Breast and prostate cancers were more prevalent in rivaroxaban users, while gastrointestinal tract, lung, and cancers in "other" sites (other than the 12 specified sites) were more prevalent in the LMWH users (►**Table 1**).

Main Outcomes

Recurrent VTE

A total of 66 and 10 incident recurrent VTE events were identified with LMWH and rivaroxaban use respectively in the first year after the initial CT (►**Table 2**). Crude incidence rates of recurrent VTE in the first year after the initial CT were 6.2 (95% confidence interval [CI]: 4.8–8.0) and 5.4 (95% CI: 2.6–10.0) per 100 person-years for LMWH and rivaroxaban use, respectively. The weighted SHR for VTE recurrences in rivaroxaban compared with LMWH at 12 months was 0.80 (95% CI: 0.37–1.73). At 3, 6, and 12 months after the CT, the incidence rates and SHRs are shown in ►**Table 2** and weighted survival probabilities in the first 12 months after CT are shown in ►**Supplementary Fig. S1** (available in the online version).

Significant Bleeds

There were 102 and 20 significant bleeds in LMWH and rivaroxaban-treated patients, respectively, in the first year after CT. There were 39 and 3 major bleeds in the LMWH and rivaroxaban cohorts respectively, at 1 year. Of the major bleeds, 24 and 2 bleeds in LMWH and rivaroxaban users respectively were intracranial bleeds or bleeds in another critical organ. There were 63 and 17 CRNMB-H in LMWH and rivaroxaban cohorts, respectively, at 1 year of observation (►**Table 2**). Crude incidence rates of significant bleeds in the first year after the initial CT were 9.7 (95% CI: 7.8–11.8) and 10.9 (95% CI: 6.6–16.8) per 100 person-years of LMWH and rivaroxaban use, respectively. The weighted SHR for significant bleeds in rivaroxaban compared with LMWH at 12 months was 1.01 (95% CI: 0.57–1.81). Incidence rates and weighted SHRs at 3, 6, and 12 months are shown in ►**Table 2** and weighted survival probabilities in the first

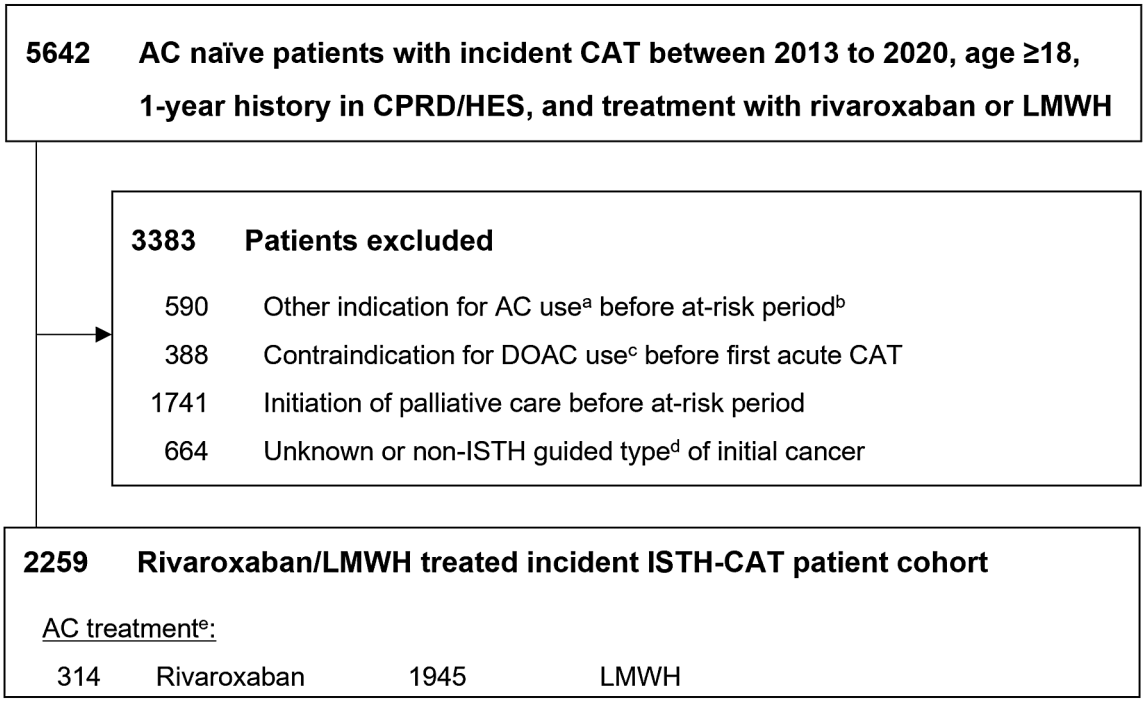

Fig. 1 Ascertainment of rivaroxaban versus LMWH-treated CT cohort. AC, anticoagulant; CT, cancer-associated VTE; CPRD, Clinical Practice Research Datalink; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HES, Hospital Episode Statistics; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism. [a]Atrial fibrillation, cardiac valve replacement, unusual site DVT (cerebral and abdominal vein thrombi), or hip or knee replacement in the last month. [b]At risk period: starts on day of first rivaroxaban/LMWH recording after CT but not earlier than 1 day after VTE hospital discharge or 1 day after day of general practitioner recording of VTE. [c]Thrombocytopenia, active pregnancy, or end-stage kidney disease. [d]Including the following cancer types: non-brain central nervous system, unresected colorectal, leukemia, other hematologic, esophagus, stomach, and bladder. [e]Patients switching from LMWH to rivaroxaban within the first 7 days after initial LMWH treatment were allocated to the rivaroxaban group with the day of rivaroxaban as start of at-risk period. Patients switching from LMWH to DOAC other than rivaroxaban within 7 days after first LMWH record were removed from the cohort.

12 months after CT are shown in ►**Supplementary Fig. S2** (available in the online version).

For major bleeds, the weighted SHRs at 3, 6, and 12 months after CT were decreased for rivaroxaban compared with LMWH but were not statistically significant, 0.37 (95% CI: 0.08–1.76), 0.40 (95% CI: 0.11–1.44), and 0.35 (95% CI: 0.10–1.24), respectively. Due to the low number of events in rivaroxaban users, no further analyses for intracranial bleeds or bleeds in another critical organ were performed.

For CRNMB-H the weighted SHRs at 3, 6, and 12 months after CT in rivaroxaban compared with LMWH were increased but not statistically significant, 2.02 (95% CI: 0.72–5.62), 1.30 (95% CI: 0.57–2.98), and 1.57 (95% CI: 0.80–3.05), respectively (►**Table 2** and ►**Supplementary Fig. S2** [available in the online version]).

All-Cause mortality

There were 133 and 10 deaths due to any cause in the LMWH and rivaroxaban-treated patients within the first year after CT (►**Table 2**). Cumulative crude mortality rates in the first year after the initial CT were 12.6 (95% CI: 10.5–15.0) and 5.4 (95% CI: 2.6–10.0) per 100 person-years of LMWH and rivaroxaban use, respectively. The weighted SHR for death from any cause in rivaroxaban compared with LMWH at 12 months was 0.49 (95% CI: 0.23–1.06). The weighted SHRs at 3 and 6 months after CT are shown in ►**Table 2** and weighted survival probabilities in the first 12 months after CT are shown in ►**Supplementary Fig. S3** (available in the online version).

Sensitivity Analysis—Rivaroxaban Compared with LMWH, On-Treatment Analysis

The study cohort for the on-treatment analysis excluded 86 patients that switched AC type before the start of the at-risk period. The definition of switching in these 86 patients is delineated in the Methods, in the exposure sub-section. These were patients switching from LMWH and rivaroxaban to other ACs. The on-treatment analysis consisted of a subset of 2,173 patients, 1,867 initially treated with LMWH (96% of the ITT cohort), and 306 with rivaroxaban (97% of the respective ITT cohort; ►**Supplementary Fig. S4** [available in the online version]). At 1 year of observation, LMWH users cumulated a total of 529 person-years (50.0% of the person-years in the ITT analysis) and rivaroxaban users cumulated a total of 134 person-years (72.8% of the person-years in the ITT analysis) of follow-up.

The duration of anticoagulation treatment in the first year of observation, as shown by discontinuations of therapy over time, is illustrated in ►**Fig. 2**. Duration of anticoagulation treatment with LMWH use was less than the duration of anticoagulation treatment with rivaroxaban throughout the complete year of observation following the CT. The proportion of patients on anticoagulation treatment at 1 year was

Table 1 Baseline characteristics (prior to weighting) of study cohort by type of anticoagulant

	Rivaroxaban, *n* (%)	LMWH, *n* (%)
Total	314	1,945
Age[a] [years]		
Mean (SD)	72.4 (12.1)	66.9 (11.7)
Median (p25–p75)	73 (65–81)	68 (59–75)
<18	0 (0.0)	0 (0.0)
≥18 to <65	64 (20.4)	716 (36.8)
≥65 to <75	106 (33.8)	703 (36.1)
≥75 to <85	92 (29.3)	436 (22.4)
≥85	52 (16.6)	90 (4.6)
Gender		
Male	148 (47.1)	802 (41.2)
Female	166 (52.9)	1,143 (58.8)
BMI[b] [kg/m^2]		
Known BMI	305 (97.1)	1,856 (95.4)
Mean (SD)	27.8 (5.4)	28.1 (5.7)
Median (p25–p75)	27 (24–31)	27 (24–31)
<18.5	7 (2.3)	40 (2.2)
≥18.5 to <25	83 (27.2)	545 (29.4)
≥25 to <30	123 (40.3)	690 (37.2)
≥30 to <35	67 (22.0)	376 (20.3)
≥35	25 (8.2)	205 (11.0)
Unknown BMI	9 (2.9)	89 (4.6)
Smoking status[b]		
Known smoking status	313 (99.7)	1,929 (99.2)
Never	130 (41.5)	776 (40.2)
Ex	162 (51.8)	939 (48.7)
Current	21 (6.7)	214 (11.1)
Unknown smoking status	1 (0.3)	16 (0.8)
Socioeconomic status[c] [quintile]		
1st (least deprived)	87 (27.7)	480 (24.7)
2nd	72 (22.9)	421 (21.6)
3rd	71 (22.6)	383 (19.7)
4th	47 (15.0)	330 (17.0)
5th	37 (11.8)	331 (17.0)
Type of first VTE		
DVT only	99 (31.5)	612 (31.5)
PE only	200 (63.7)	1,235 (63.5)
PE and DVT	15 (4.8)	98 (5.0)
Cancer type		
Breast	104 (33.1)	437 (22.5)
Brain	7 (2.2)	94 (4.8)
Gastrointestinal tract[d]	16 (5.1)	258 (13.3)
Lymphoma	13 (4.1)	91 (4.7)
Myeloma	5 (1.6)	37 (1.9)
Head or neck	3 (1.0)	32 (1.6)
Lung	29 (9.2)	301 (15.5)
Malignant melanoma	13 (4.1)	34 (1.7)
Ovarian	6 (1.9)	102 (5.2)
Prostate	88 (28.0)	197 (10.1)
Kidney/other urinary	5 (1.6)	53 (2.7)
Cervix/uterus	10 (3.2)	90 (4.6)
Other[e]	15 (4.8)	219 (11.3)

Abbreviations: BMI, body mass index; CT, cancer-associated VTE; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; p, percentile; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.
[a]At the day of CT.
[b]Latest information available before the day of CT.
[c]Defined by index for multiple deprivation 2015 data.
[d]Resected colorectal, other lower gastrointestinal tract, or small intestine.
[e]Including, e.g., hepatobiliary, pancreas, and testicular.

25.8% for LMWH users and 49.5% for rivaroxaban users. The main outcomes for the on-treatment analysis are shown in ►**Table 3**.

Discussion

In this large cohort of patients with VTE and active cancer, not at high risk for bleeding, we evaluated the effectiveness and safety at 3, 6, and 12 months of rivaroxaban therapy compared with LMWH therapy. Treatment with rivaroxaban compared with LMWH was associated with similar weighted (adjusted) SHR estimates for VTE recurrences at 3, 6, and 12 months in all analyses. Treatment with rivaroxaban compared with LMWH was associated with similar risk of all significant bleeds, the principal safety outcome. In the bleeding subgroups, the results demonstrated that rivaroxaban had a consistently lower but not statistically different risk of major bleeds and critical site bleeds at each of the time points, and a higher but not statistically significant risk of CRNMB-H. No significant differences were seen in all-cause mortality in the two treatment cohorts, but in the rivaroxaban cohort all-cause mortality was consistently lower in all analyses. Lower mortality in the rivaroxaban cohort may indicate unmeasured prognostic differences in the cohorts.

These findings are consistent with the OSCAR-US study that demonstrated a reduced risk of recurrent VTE and no differences in bleeding or mortality outcomes.[18] The outcomes for VTE recurrences, bleeding, and mortality are similar with the on-treatment analyses to the ITT (main) analyses. Furthermore, these results comparing a DOAC (rivaroxaban) with LMWH were consistent with the findings of other smaller observational studies, clinical trials, and meta-analyses.[7,19–23]

Table 2 VTE recurrences, bleeding, and mortality at 3, 6, and 12 months after CT (sub-distribution hazard ratios) in the intention-to-treat population

Time since CT	Events	Person-years	Incidence rate[a] (0.95 CI)	Unweighted SHR[b] (0.95 CI)	Overlap weighted[c] SHR[b] (0.95 CI)
VTE recurrences					
3 months					
LMWH	19	341	5.6 (3.3–8.8)	1	1
Rivaroxaban	3	57	5.3 (1.0–15.4)	0.95 (0.28–3.19)	0.96 (0.25–3.74)
6 months					
LMWH	34	655	5.2 (3.5–7.3)	1	1
Rivaroxaban	6	111	5.4 (1.9–11.8)	1.04 (0.44–2.47)	1.31 (0.47–3.67)
12 months					
LMWH	66	1,057	6.2 (4.8–8.0)	1	1
Rivaroxaban	10	184	5.4 (2.6–10.0)	0.90 (0.46–1.75)	0.80 (0.37–1.73)
All significant bleeds					
3 months					
LMWH	46	341	13.5 (9.8–18.1)	1	1
Rivaroxaban	10	57	17.5 (8.4–32.3)	1.30 (0.65–2.59)	1.03 (0.44–2.40)
6 months					
LMWH	74	655	11.3 (8.8–14.2)	1	1
Rivaroxaban	14	111	12.6 (6.8–21.1)	1.13 (0.64–2.01)	0.85 (0.43–1.71)
12 months					
LMWH	102	1,057	9.7 (7.8–11.8)	1	1
Rivaroxaban	20	184	10.9 (6.6–16.8)	1.17 (0.73–1.89)	1.01 (0.57–1.81)
Major bleeds					
3 months					
LMWH	23	341	6.8 (4.2–10.2)	1	1
Rivaroxaban	2	57	3.5 (0.4–12.7)	0.52 (0.12–2.20)	0.37 (0.08–1.76)
6 months					
LMWH	31	655	4.7 (3.2–6.8)	1	1
Rivaroxaban	3	111	2.7 (0.5–7.9)	0.58 (0.18–1.90)	0.40 (0.11–1.44)
12 months					
LMWH	39	1,057	3.7 (2.6–5.1)	1	1
Rivaroxaban	3	184	1.6 (0.3–4.8)	0.46 (0.14–1.50)	0.35 (0.10–1.24)
Critical organ bleeds[d]					
3 months					
LMWH	12	341	3.5 (1.8–6.2)	1	1
Rivaroxaban	1	57	1.8 (0.0–9.8)	0.50 (0.06–3.87)	0.49 (0.05–4.39)
6 months					
LMWH	17	655	2.6 (1.5–4.2)	1	1
Rivaroxaban	2	111	1.8 (0.2–6.5)	0.71 (0.16–3.09)	0.52 (0.10–2.60)
12 months					
LMWH	24	1,057	2.3 (1.4–3.4)	1	1
Rivaroxaban	2	184	1.1 (0.1–4.0)	0.50 (0.12–2.13)	0.42 (0.09–2.01)
CRNMB-H					
3 months					
LMWH	23	341	6.8 (4.2–10.2)	1	1
Rivaroxaban	8	57	14.0 (6.0–27.7)	2.09 (0.93–4.69)	2.02 (0.72–5.62)

(*Continued*)

Table 2 (*Continued*)

Time since CT	Events	Person-years	Incidence rate[a] (0.95 CI)	Unweighted SHR[b] (0.95 CI)	Overlap weighted[c] SHR[b] (0.95 CI)
6 months					
LMWH	43	655	6.6 (4.7–8.9)	1	1
Rivaroxaban	11	111	9.9 (4.9–17.7)	1.53 (0.79–2.98)	1.30 (0.57–2.98)
12 months					
LMWH	63	1,057	6.0 (4.5–7.7)	1	1
Rivaroxaban	17	184	9.2 (5.3–14.8)	1.61 (0.94–2.75)	1.57 (0.80–3.05)
All-cause mortality					
3 months					
LMWH	73	341	21.4 (16.7–27.0)	1	1
Rivaroxaban	7	57	12.3 (4.9–25.4)	0.57 (0.26–1.24)	0.63 (0.25–1.60)
6 months					
LMWH	102	655	15.6 (12.7–19.0)	1	1
Rivaroxaban	9	111	8.1 (3.6–15.4)	0.51 (0.26–1.02)	0.59 (0.26–1.33)
12 months					
LMWH	133	1,057	12.6 (10.5–15.0)	1	1
Rivaroxaban	10	184	5.4 (2.6–10.0)	0.44 (0.23–0.83)	0.49 (0.23–1.06)

Abbreviations: CT, cancer-associated venous thromboembolism; CI, confidence interval; CRNMB-H, clinically relevant nonmajor bleeding requiring hospitalization; LMWH, low-molecular-weight heparin; SHR, sub-distribution hazard ratio; VTE, venous thromboembolism.
[a]Incidence rate per 100 person-years.
[b]Sub-distribution hazard ratio estimated from univariate Fine & Gray regression accounting for competing risks.
[c]Applying overlap weighting based on predicted rivaroxaban initiation probabilities.
[d]Critical organ bleeds are a subset of major bleeds including intracranial bleeds and other critical organ bleeds.

The 1-year duration of anticoagulation treatment for patients receiving rivaroxaban was approximately twofold greater compared with those receiving LMWH, a significant difference. Different factors could have contributed to this finding including: (1) better adherence/tolerability with rivaroxaban compared with parenteral ACs, (2) some factors (covariates) that have an influence in the choice of rivaroxaban or LMWH might have changed after treatment initiation, resulting in switching/discontinuation, and (3) other burdens such as drug cost that favor persistent use of rivaroxaban compared with LMWH. Despite the differences in duration of anticoagulation treatment with rivaroxaban and LMWH, results of the on-treatment analyses were consistent with the results of the ITT analyses.

Strengths and Weaknesses of the Study

The study cohort comprised a large heterogeneous cohort of 2,259 patients treated with ACs for CT and followed up for 12 months, the period during which most patients with CT are anticoagulated and which is associated with a high risk of recurrences, bleeding events, and mortality.[2] The effectiveness and safety were assessed by validated outcomes that were verified by clinicians who were blind to the therapy. These outcomes were recurrent VTE, significant bleeds (major bleeds and CRNMB-H), and all-cause mortality. We used standard definitions consistent with those used in clinical trials.[12,21–23] However, patients with a missing record of active cancer, VTE, or AC therapy did not form part of our study cohort. Patients who had a recording of anticoagulation later in the 30-day period post-CT diagnosis or anticoagulation treatment started in hospital may have had early outcomes prior to the index day. Those potential cases should have a similar distribution in the rivaroxaban and LMWH groups based on the SELECT-D data, thus it is unlikely that this may have influenced the results.[23]

Although a vast set of covariates were used for adjustment, unmeasured confounding cannot be ruled out as some covariates associated with a study outcome of interest were not available in the database (such as cancer staging) and this may affect outcomes such as mortality. Furthermore, covariate changes over time during the at-risk period were not considered in the analyses of the different effectiveness and safety outcomes. This could have resulted in differential/unbalanced risk sets for the comparison of rivaroxaban with LMWH during the at-risk period and may have affected both the ITT and the on-treatment analyses.

VTE and bleeding events were defined based on coded information rather than complete clinical data. However, our VTE algorithm has previously been validated and showed a sensitivity of 92.6% and a specificity of 98.8%.[11] Bleeding events were defined according to ISTH criteria and were validated by manual review of all available patient records by three physicians who assessed all potential bleeding events.[12] In-hospital pharmacy data including anticoagulation use are not available in the CPRD-HES datalink. Medical diagnoses are recorded as hospital discharge diagnoses but the day of occurrence during the hospitalization is either

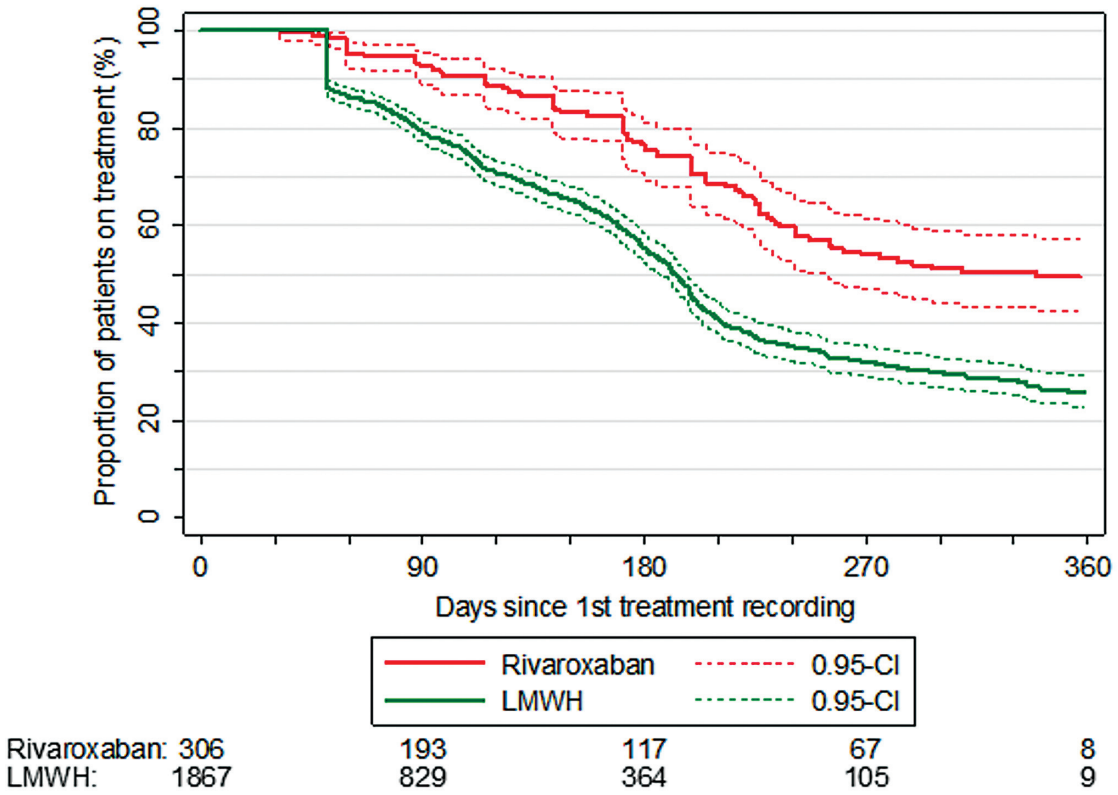

Fig. 2 Discontinuation[a,b] of anticoagulant treatment by anticoagulant and time since first treatment recording. DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism. [a]Persistence estimate accounting for death, significant bleeds, and VTE recurrence as competing events and switching of anticoagulant (rivaroxaban, other DOAC, LMWH, VKA, other parenteral) as censoring event. [b]Applying overlap weighting based on predicted rivaroxaban initiation probabilities.

Table 3 VTE recurrences, bleeding, and mortality at 3, 6, and 12 months after CT (sub-distribution hazard ratios) in the on-treatment population

Time since CT	Events	Person-years	Incidence rate[a] (0.95 CI)	Unweighted SHR[b] (0.95 CI)	Overlap weighted[c] SHR[b] (0.95 CI)
VTE recurrences					
3 months					
LMWH	17	290	5.9 (3.4–9.5)	1	1
Rivaroxaban	2	53	3.8 (0.4–13.8)	0.63 (0.15–2.73)	0.56 (0.11–2.79)
6 months					
LMWH	22	452	4.9 (3.0–7.4)	1	1
Rivaroxaban	4	96	4.2 (1.1–10.7)	0.89 (0.31–2.53)	0.86 (0.28–2.63)
12 months					
LMWH	26	529	4.9 (3.2–7.3)	1	1
Rivaroxaban	6	134	4.5 (1.6–9.8)	1.00 (0.42–2.37)	0.82 (0.31–2.17)
All significant bleeds					
3 months					
LMWH	39	290	13.5 (9.5–18.5)	1	1
Rivaroxaban	9	53	17.1 (7.8–32.5)	1.31 (0.63–2.72)	1.23 (0.51–2.96)

(*Continued*)

Table 3 (*Continued*)

Time since CT	Events	Person-years	Incidence rate[a] (0.95 CI)	Unweighted SHR[b] (0.95 CI)	Overlap weighted[c] SHR[b] (0.95 CI)
6 months					
LMWH	54	452	11.9 (8.9–15.6)	1	1
Rivaroxaban	11	96	11.4 (5.7–20.5)	1.06 (0.55–2.04)	1.04 (0.47–2.29)
12 months					
LMWH	64	529	12.1 (9.3–15.5)	1	1
Rivaroxaban	17	134	12.7 (7.4–20.4)	1.10 (0.64–1.87)	1.08 (0.55–2.14)
Major bleeds					
3 months					
LMWH	19	290	6.6 (3.9–10.3)	1	1
Rivaroxaban	2	53	3.8 (0.4–13.8)	0.60 (0.14–2.55)	0.60 (0.13–2.84)
6 months					
LMWH	24	452	5.3 (3.3–7.9)	1	1
Rivaroxaban	2	96	2.1 (0.2–7.6)	0.44 (0.10–1.88)	0.43 (0.09–2.05)
12 months					
LMWH	29	529	5.5 (3.6–7.9)	1	1
Rivaroxaban	2	134	1.5 (0.1–5.5)	0.31 (0.07–1.34)	0.33 (0.07–1.67)
Critical organ bleeds[d]					
3 months					
LMWH	10	290	3.5 (1.6–6.4)	1	1
Rivaroxaban	1	53	1.9 (0.0–10.6)	0.57 (0.07–4.51)	0.62 (0.06–6.08)
6 months					
LMWH	13	452	2.9 (1.5–5.0)	1	1
Rivaroxaban	1	96	1.0 (0.0–5.8)	0.41 (0.05–3.23)	0.40 (0.04–3.90)
12 months					
LMWH	17	529	3.2 (1.8–5.2)	1	1
Rivaroxaban	1	134	0.7 (0.0–4.2)	0.24 (0.03–1.97)	0.27 (0.03–2.82)
CRNMB-H					
3 months					
LMWH	20	290	6.9 (4.2–10.7)	1	1
Rivaroxaban	7	53	13.3 (5.3–27.4)	2.00 (0.84–4.76)	1.85 (0.61–5.58)
6 months					
LMWH	30	452	6.6 (4.4–9.5)	1	1
Rivaroxaban	9	96	9.4 (4.2–17.8)	1.54 (0.72–3.29)	1.60 (0.62–4.12)
12 months					
LMWH	35	529	6.6 (4.6–9.3)	1	1
Rivaroxaban	15	134	11.2 (6.2–18.6)	1.71 (0.93–3.12)	1.80 (0.81–4.03)
All-cause mortality					
3 months					
LMWH	66	290	22.8 (17.6–29.1)	1	1
Rivaroxaban	7	53	13.3 (5.3–27.4)	0.59 (0.27–1.30)	0.66 (0.25–1.74)
6 months					
LMWH	81	452	17.9 (14.2–22.3)	1	1
Rivaroxaban	9	96	9.4 (4.2–17.8)	0.57 (0.29–1.14)	0.71 (0.31–1.61)

Table 3 (*Continued*)

Time since CT	Events	Person-years	Incidence rate[a] (0.95 CI)	Unweighted SHR[b] (0.95 CI)	Overlap weighted[c] SHR[b] (0.95 CI)
12 months					
LMWH	87	529	16.5 (13.1–20.3)	1	1
Rivaroxaban	10	134	7.5 (3.5–13.8)	0.55 (0.28–1.07)	0.67 (0.30–1.49)

Abbreviations: CT, cancer-associated venous thromboembolism; CI, confidence interval; CRNMB-H, clinically relevant nonmajor bleeding requiring hospitalization; LMWH, low-molecular-weight heparin; SHR, sub-distribution hazard ratio; VTE, venous thromboembolism.
[a]Incidence rate per 100 person-years.
[b]Sub-distribution hazard ratio estimated from univariate Fine & Gray regression accounting for competing risks.
[c]Applying overlap weighting based on predicted rivaroxaban initiation probabilities.
[d]Critical organ bleeds are a subset of major bleeds including intracranial bleeds and other critical organ bleeds.

unknown or uncertain. Consequently, in-hospital data were insufficient to establish the temporal relationship between the status of anticoagulation treatment and the onset of an outcome event. To avoid misclassification of anticoagulation exposure and of outcomes, we did not consider outcome events that occurred during the same hospitalization as the initial CT. To study an inception cohort, we excluded patients with a history of VTE or anticoagulation, however, that meant we could not assess the risks in patients presenting with recurrent VTE events. We also excluded patients with other indications for anticoagulation (10%), and palliative care patients (as this affects management and data recording) (31%) as well as cancer types that are associated with a high risk of bleeding or unknown cancer type (12%). These exclusions were important for cohort definition, data quality, and to be consistent with the guidelines; however, they impact the generalizability of the findings.

We used the overlap weighting adjustment method based on propensity scores to make the two AC exposure groups comparable with respect to baseline cohort differences such as age, sex, and cancer site. The overlap weighting led to exact balance of all measured baseline characteristics that were included in the regression model in the two AC exposure groups. Outcome events were captured only if they were recorded according to our outcome definitions based on previously developed and validated algorithms, and manual review of all potential cases with reviewers blinded to the AC exposure of interest. Missed outcome events were likely to be at random and independent of the exposure of interest resulting in unaffected relative risk estimates but may lead to underestimation of the absolute risk estimates. SHR estimates for outcomes with small event numbers, such as critical organ bleeds in rivaroxaban, had low precision as reflected by wide CIs.

In this cohort study of patients with CT treated with either rivaroxaban or LMWHs, rivaroxaban was as effective as LMWH at preventing VTE recurrence and without differences in the rates of significant bleeding (composite outcome), major bleeds, critical organ bleeds, CRNMB-H, or all-cause mortality. Patients treated with rivaroxaban remained on therapy for a longer period of time compared with LMWH. Our study findings support the recommendation that rivaroxaban is a reasonable alternative to LMWH for the treatment of CT when used in accordance with guidelines.

This study is part of the OSCAR program with independent studies in the United States,[10,20] United Kingdom,[13] and Sweden[24] that use consistent definitions of design, exposures of interest, covariates, and data analyses. While the study in Sweden is being reported, the comparison of the UK and U.S.[20] cohorts of the OSCAR program indicates that the study findings are generalizable to patients with active cancer not including non-brain central nervous system, unresected colorectal/lower gastrointestinal tract, hematologic (except lymphoma and myeloma), esophagus, stomach, and bladder cancer and patients with conditions such as thrombocytopenia, end-stage kidney disease, and current pregnancy.

Conclusion

Patients who are not at high risk of bleeding with cancer-associated thrombosis treated with either rivaroxaban or LMWHs have comparable effectiveness and safety outcomes. This finding supports the recommendation that rivaroxaban is a reasonable alternative to LMWH for the treatment of CT when used in accordance with guidelines.

What is known about this topic?

- Guidelines recommend the use of direct oral anticoagulants such as rivaroxaban, and low-molecular-weight heparins (LMWHs), in treating patients with cancer-associated venous thromboembolism (CT) based on clinical trials.
- There is a paucity of population-based data allowing treatment outcome comparisons in clinical practice.

What does this paper add?

- Patients who are not at high risk of bleeding with CT treated with either rivaroxaban or LMWH have comparable risk of recurrent venous thromboembolism.
- The patients also have similar risk of significant bleeding and all-cause mortality.
- These data support the use of rivaroxaban as an alternative to LMWH for the treatment of CT.

Note
Trial registration number: NCT05112666

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Conflict of Interest
A.T.C. reports grants, consulting fees, and honoraria from Alexion/AstraZeneca, grants, consulting fees, and honoraria from Bristol Myers Squibb/Pfizer, and consulting fees and honoraria from Bayer AG. C.W. and C.M. are employees of the Institute for Epidemiology, Statistics and Informatics GmbH. The Institute for Epidemiology, Statistics and Informatics GmbH has received support from Bayer for the conduct of the submitted work and has received grants from Astra Zeneca, Bayer, Bristol-Myers Squibb, and CSL Behring outside the submitted work. M.R. was an employee of Bayer AG at the time of study conduct and is currently an employee of Janssen Research and Development. C.A. reports honoraria from Bayer AG, BMS/Pfizer, Daiichi-Sankyo, and Sanofi. B.S. was an employee of Bayer AG at the time of study conduct and is currently a consultant for Bayer AG. K.A. and G.P. are employees of Bayer AG. G.B. is a consultant for Bayer AG. A.E. reports no conflicts of interest. A.Y.Y.L. reports consulting fees and honoraria from Bayer AG, consulting fees and honoraria from LEO Pharma, consulting fees and honoraria from Pfizer, consulting fees from Servier, and honoraria from Bristol Myers Squibb. A.A.K. reports consulting fees, honoraria, and travel support from Bayer AG, consulting fees, honoraria, and travel support from Janssen, consulting fees and honoraria from Bristol Myers Squibb, consulting fees and honoraria from Anthos, consulting fees and honoraria from Pfizer, consulting fees and honoraria from Sanofi, and honoraria from WebMD. C.B. reports consulting fees and honoraria from Bayer AG, consulting fees and honoraria from Bristol Myers Squibb, consulting fees and honoraria from Daiichi Sankyo, and consulting fees from Pfizer. M.C. reports grants and consulting fees from Pfizer, grants and consulting fees from LEO Pharma, grants and consulting fees from Bristol Myers Squibb, consulting fees from Bayer AG, consulting fees from Sanofi, and consulting fees from Servier. C.I.C. reports grants, consulting fees, and travel support from Bayer AG, grants and consulting fees from Janssen Pharmaceuticals, grants and consulting fees from Alexion Pharmaceutical, and honoraria from Medscape.

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References

1 Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100(10):3484–3488
2 Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. Thromb Haemost 2017;117(01):57–65
3 Weitz JI, Haas S, Ageno W, et al; GARFIELD-VTE investigators. Cancer associated thrombosis in everyday practice: perspectives from GARFIELD-VTE. J Thromb Thrombolysis 2020;50(02):267–277
4 Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021;5(04):927–974
5 Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021;5(03):872–888
6 Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16(09):1891–1894
7 Giustozzi M, Agnelli G, Del Toro-Cervera J, et al. Direct oral anticoagulants for the treatment of acute venous thromboembolism associated with cancer: a systematic review and meta-analysis. Thromb Haemost 2020;120(07):1128–1136
8 Mahé I, Plaisance L, Chapelle C, et al. Long-term treatment of cancer-associated thrombosis (CAT) beyond 6 months in the medical practice: USCAT, a 432-patient retrospective non-interventional study. Cancers (Basel) 2020;12(08):12
9 Sakamoto J, Yamashita Y, Morimoto T, et al; COMMAND VTE Registry Investigators. Cancer-associated venous thromboembolism in the real world - From the COMMAND VTE registry. Circ J 2019;83(11):2271–2281
10 Coleman C, Caroti KS, Abdelgawwad K, et al. Patient characteristics and temporal changes in anticoagulation treatment patterns in patients diagnosed with cancer-associated thrombosis: an Oscar-US Analysis. Blood 2021;138(01):2132
11 Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost 2014;112(02):255–263
12 Schulman S, Kearon CSubcommittee on Control of Anticoagulation of the Scientific and 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(04):692–694
13 Bayer AG. A study to gather information about rivaroxaban in patients in the United Kingdom who have cancer and thrombosis (OSCAR-UK). 2021. Accessed February 9, 2024 at: https://clinicaltrials.gov/ct2/show/NCT05112666
14 Martinez C, Katholing A, Wallenhorst C, Cohen AT. Prediction of significant bleeding during vitamin K antagonist treatment for venous thromboembolism in outpatients. Br J Haematol 2020;189(03):524–533
15 Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol 2019;188(01):250–257
16 Thomas LE, Li F, Pencina MJ. Overlap weighting: a propensity score method that mimics attributes of a randomized clinical trial. JAMA 2020;323(23):2417–2418
17 Schoenfeld D. Partial residuals for the proportional hazards model. Biometrika 1982;69:51–55
18 Coleman CI, Caroti KS, Abdelgawwad K, et al. Effectiveness and safety of rivaroxban and low molecular-weight heparin in cancer-assocaited venous thromboembolism. JACC Cardiooncol 2023;5(02):189–200
19 Cominacini M, Suardi S, Ferrari G, et al. DOAC in the treatment of cancer-associated venous thromboembolism: a retrospective

cohort study beyond the guidelines. J Cancer Res Clin Oncol 2023; 149(09):5773–5779
20 Michalopoulou H, Polyzos D, Thomopoulos C, et al. Net clinical benefit of DOACs vs. usual anticoagulation treatment in venous thromboembolism and active cancer: systematic review and meta-analysis. J Thromb Thrombolysis 2023;55(01):92–101
21 Agnelli G, Becattini C, Meyer G, et al; Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382(17):1599–1607
22 Raskob GE, van Es N, Verhamme P, et al; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378(07): 615–624
23 Young AM, Marshall A, Thirlwall J, 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(20):2017–2023
24 Bayer AG. A study to gather information about rivaroxaban in patients in Sweden with cancer who also have thrombosis (OSCAR-SE). Accessed December 17, 2021; available at: https://clinicaltrials.gov/ct2/show/NCT05150938?term=oscar-se&draw=2&rank=1

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