Post Authorization Safety Study (PASS)

Acronym/Title	Observational Studies in Cancer Associated Thrombosis for Rivaroxaban - United Kingdom Cohort (OSCAR-UK)
Report version and date	v1.0, 26 August 2022
IMPACT study number	22020
Study type / Study phase	Observational PASS: Yes Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS43329
Active substance	Direct factor Xa inhibitor, Rivaroxaban (B01AF01) Direct acting oral anticoagulants (DOACs): Factor Xa inhibitors: apixaban, edoxaban, rivaroxaban Factor IIa inhibitor: dabigatran
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	Not applicable
Procedure number	Not applicable
Comparator / Reference therapy	Low molecular weight heparin (LMWH): Dalteparin, Enoxaparin, Tinzaparin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen
Research question and objectives	The objective of this study was to evaluate the effectiveness (recurrent venous thromboembolism) and safety (significant bleeds and all-cause mortality) of DOAC/rivaroxaban treatment compared to LMWH treatment in patients with active cancer-associated venous thromboembolism (CAT)
Country(-ies) of study	England
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
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Confidentiality statement:

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1. Abstract

Acronym/Title	Observational Studies in Cancer Associated Thrombosis for Rivaroxaban - United Kingdom Cohort (OSCAR-UK)
Report version and date **Author**	V1.0, 26 August 2022 PPD and PPD Institute for Epidemiology, Statistics and Informatics GmbH PPD Department of Haematological Medicine, Guy's and St Thomas' NHS Foundation Trust, King's College London, London, United Kingdom
IMPACT study number	22020
Keywords	Rivaroxaban, DOAC, direct oral anticoagulants, CAT, active cancer, VTE, venous thromboembolism, PE, pulmonary embolism
Rationale and background	Patients with active cancer are ~5-fold more likely to develop VTE. When cancer-associated thrombosis (CAT) occurs, cancer patients carry an up to a 3-fold higher rate of VTE recurrence. Guidelines list direct oral anticoagulants (DOACs) and low molecular weight heparins (LMWHs) as options for the treatment of CAT and the prophylaxis of VTE recurrences. The strength of recommendation for DOACs is based on efficacy and safety data from randomized controlled trials (RCTs) for secondary prevention of CAT comparing DOAC to LMWH or vitamin K antagonists. Observational studies have also investigated the bleeding risk in patients treated with DOACs for CAT. Some studies lack a comparison with LMWHs, lack information on cancer type, or include cancer cohorts not recommended for DOAC treatment.
Research question and objectives	Evaluate the effectiveness (recurrent VTE) and safety (clinically relevant bleeding-related hospitalization and all-cause mortality) of rivaroxaban versus LMWH for CAT treatment in active cancer patients. Evaluate the effectiveness (recurrent VTE) and safety (clinically relevant bleeding-related hospitalization and all-

	cause mortality) of all DOACs (as a group) vs. LMWH for CAT treatment in active cancer patients. Estimate duration of anticoagulation treatment and rivaroxaban (or DOAC) and LMWH discontinuation rates at 3-, 6- and 12-months.
Study design	Retrospective observational cohort study of patients with incident CAT subsequently treated with either DOACs or LMWHs.
Setting	UK primary care database (CPRD) with additional linkage to inpatient and outpatient data (HES), mortality data (ONS) and socio-economic information (IMD).
Subjects and study size, including dropouts	Study cohort of 2259 patients, 314 treated with rivaroxaban and 1945 with LMWH within 30 days following the CAT. To compare all DOACs vs LMWH, 656 patients initially treated with DOACs.
Variables and data sources	Exposure of interest was use of DOACs and LMWHs in therapeutic doses. Outcomes of interest were VTE recurrences, significant bleeds defined as major bleeds or clinically-relevant non-major bleeding requiring hospitalisation (CRNMB-H) and all-cause mortality. Covariates included variables intended for description of the study cohort, variables potentially related with choice of AC type in CAT patients and known or suspected risk factors for VTE recurrences, significant bleeding events and death from any cause.
Results	Treatment with DOACs and rivaroxaban compared with LMWH was associated with consistent but not statistically significant slightly smaller point estimates for VTE recurrences at 3, 6 and 12 months in all analyses. Treatment with DOACs and rivaroxaban compared with LMWH was associated with consistent smaller point estimates for major bleeds in all analyses. Treatment with DOACs and rivaroxaban compared with LMWH was associated with a non-statistically significant increased risk of CRNMB-H which appeared more pronounced in those treated with rivaroxaban.

	Treatment with DOACs and rivaroxaban was associated with consistent decreased point estimates for all-cause mortality in all analyses, but only statistically significant in the all DOACs on-treatment analysis at 3 months. Duration of anticoagulation treatment with DOACs and with rivaroxaban was about 2-fold and significantly greater at one year after CAT compared to LMWH.
Discussion	In this cohort study of patients with cancer-associated thrombosis treated with either DOACs or LMWHs, DOACs and rivaroxaban were as effective as LMWH at preventing VTE recurrence and without an impact on the significant bleeds (composite outcome), major bleeds (including critical organ bleeds) or clinically-relevant non-major bleeding requiring hospitalization, or all-cause mortality. Patients with cancer-associated thrombosis treated with either rivaroxaban/DOACs or LMWHs have a comparable benefit-risk balance. This finding supports the recommendation that DOACs and rivaroxaban are reasonable alternatives to LMWH for the treatment of CAT when used in accordance with guidelines.
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen

2. List of abbreviations

AC	Anticoagulant
BMI	Body mass index
CAT	Active cancer-associated venous thromboembolism
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CRNMB-H	Clinically-relevant non-major bleeding requiring hospitalisation
CYP3A4	Cytochrome P450 3A4
DM+D	Dictionary of Medicines and Devices
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
GP	General practitioner
HES	Hospital Episodes Statistics
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
ISTH	International Society of Thrombosis and Haemostasis
ITT	Intention-to-treat
LMWH	Low molecular weight heparin
NHS	National Health Service
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys
OS	Observational study
OSCAR	Observational Studies in Cancer Associated Thrombosis for Rivaroxaban
PASS	Post-authorization safety study
PE	Pulmonary embolism
SD	Standard deviation
SHR	Sub-distribution hazard ratio
SNOMED CT	Systematized Nomenclature of Medicine - Clinical Terms
UK	United Kingdom
VKA	Vitamin K antagonists
VTE	Venous thromboembolism

3. Investigators

Role:	Principal Investigator
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4. Other responsible parties

4.1 Study Team (internal or external)

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5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	September 2021	September 2021	Preparation of code sets for data queries
End of data collection	December 2021	1 December 2021	Receipt of last linkage dataset
Registration in the EU PAS register	October 2021	29 October 2021	
Delivery of preliminary result tables	December 2021	9 December 2021	Preliminary data for ICTHIC abstract
Delivery of result tables	May 2022	19 May 2022	Results of main analysis
First draft of final study report	July 2022	3 August 2022	
Second draft of final study report		18 August 2022	

Final report of study results	August 2022	26 August 2022	

6. Rationale and background

Venous thromboembolism (VTE) which consists of deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common cause of morbidity and mortality, particularly in patients with cancer. Patients with active cancer are ~5-fold more likely to develop a VTE than those without. When cancer-associated thrombosis (CAT) occurs, cancer patients carry an up to a 3-fold higher rate of thrombosis recurrence. Guidelines list direct oral anticoagulants (DOACs) and low molecular weight heparins (LMWHs) as options for the treatment of CAT and the prophylaxis of VTE recurrences.(1, 2) The strength of recommendation for DOACs is based on efficacy and safety data from randomized controlled trials (RCTs) for secondary prevention of CAT (3-8) comparing DOAC to LMWH or vitamin K antagonists. Results indicate that DOAC therapy compared to standard care, i.e. LMWH therapy, is associated with a reduction of recurrent VTE, comparable rates of major bleeds but also with an increased risk of non-major bleeding (9-11), the latter more likely in patients with thrombocytopenia, end-stage kidney disease, and with gastrointestinal and genitourinary tract malignancies.(3, 5, 8, 12-16)

Observational studies have also investigated the bleeding risk in patients treated with DOACs for CAT. (17-19) Some studies lack a comparison with LMWHs, lack information on cancer type, or include cancer cohorts not recommended for DOAC treatment. Overall, there is a lack of study power resulting in a small number of recurrent VTE and bleeding events, and therefore preventing from studying time-dependencies among recurrent VTE and bleeding events at any given time of DOACs and LMWH therapy respectively.

This study is also part of the Observational Studies in Cancer Associated Thrombosis for Rivaroxaban (OSCAR study program) with independent studies in the US, (20) UK (21) and Sweden (22). The study design, the definitions of the exposures of interest, covariates and data analyses have been harmonized in the three countries accordingly, taking differences of database structures and included information of the different databases that were used in the 3 countries into account. Therefore, another aim of this study is provide an analytic dataset for the conduct of a meta-analysis.

7. Research question and objectives

7.1 Research question

What is the comparative effectiveness and safety of rivaroxaban vs LMWH and of all DOACs vs LMWH for CAT treatment in active cancer patients?

7.2 Objectives

The study objective was to evaluate the effectiveness and safety of rivaroxaban versus LMWH and of DOACs (as a group) versus LMWH for CAT treatment in active cancer patients using the CPRD dataset, specifically:

- Evaluate the effectiveness (VTE recurrences) and safety (significant bleeds and all-cause mortality) of rivaroxaban treatment compared to LMWH treatment for acute VTE in active

cancer patients without a malignant neoplasm associated with a high risk of bleeding at 3, 6 and 12 months of treatment using the CPRD and linked databases.

- Evaluate the effectiveness (VTE recurrences) and safety (significant bleeds and all-cause mortality) of all DOACs (as a group) treatment compared to LMWH treatment for acute VTE in active cancer patients without a malignant neoplasm associated with a high risk of bleeding at 3, 6 and 12 months of treatment using the CPRD and linked databases.
- Estimate incidence rates of recurrent VTE, significant bleeds and all-cause mortality in patients with active CAT with rivaroxaban, DOAC and LMWH treatment.
- Estimate duration of anticoagulation treatment and rivaroxaban, DOAC and LMWH discontinuation rates at 3-, 6- and 12-months of treatment.
- Exploratory objective: Investigate the risk of critical organ bleeds (a subgroup of major bleeds including intracranial bleeds and other critical organ bleeds) as a separate study outcome for rivaroxaban or DOACs compared with LMWH.

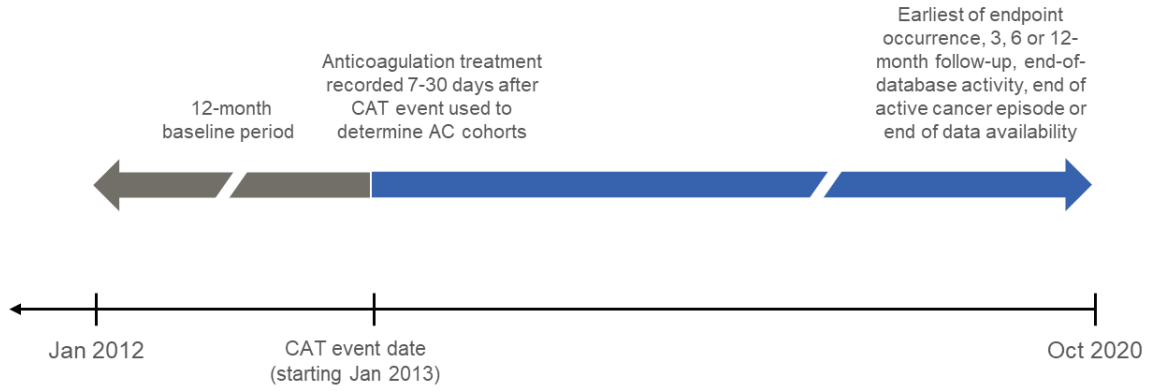
8. Amendments and updates

None

9. Research methods

9.1 Study design

This was a retrospective observational cohort study of patients with incident CAT subsequently treated with either DOACs or LMWHs.



Retrospective cohort analysis using CPRD GOLD and Aurum data from Jan 2012 to Oct 2020

9.2 Setting

Data were extracted from the subset of patients in the UK primary care Clinical Practice Research Datalink (CPRD) GOLD and Aurum database with additional linkage to inpatient and outpatient

data from the English Hospital Episodes Statistics (HES), Office for National Statistics (ONS) mortality data and socio-economic information from the Index of Multiple Deprivation (IMD) data.

CPRD is an anonymised electronic health record database from primary care practices and includes patient demographics, lifestyle factors, medical diagnoses and symptoms recorded with Read medical (GOLD) and SNOMED CT (Aurum) codes, referrals to secondary care, test results, and general practitioner (GP) prescriptions.

HES inpatient and outpatient hospital data include hospital admission and discharge dates, discharge diagnoses recorded with ICD-10 codes and surgical operations and procedures performed during hospital stay recorded with OPCS-4 codes.

ONS mortality data consist of date and cause of death recorded with ICD-10 codes.

IMD data include the official measure of relative material deprivation for small areas across England recorded as quintiles of deprivation.

9.3 Subjects

The study population consisted of all patients from English practices in the CPRD that were eligible for linkage to HES and ONS data, that were 18 years or older and that were at risk for an incident VTE during the study period, i.e. between 1 January 2013 and 31 October 2020.

The study cohort was formed from all individuals in the study population with a CAT during the study period consisting of a first episode of VTE and an active cancer at the time of first VTE. Patients with a CAT were required to have evidence of therapeutic DOAC or LMWH use within 30 days following the VTE.

Patients with less than 1-year contribution to the CPRD-HES-ONS link before the CAT were excluded as were patients with a 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 (atrial fibrillation or artificial heart valves), thrombocytopenia, end-stage kidney disease, recent hip or knee preplacement (35 days), active pregnancy (women only) or a recording indicative of palliative care initiation before the CAT. Patients with Vitamin K antagonists (VKA) use, a significant bleeding event or a VTE recurrence between the initial CAT and the initiation of DOAC/LMWH were also excluded. Cancer types for which use of DOACs is endorsed by interpretation of the International Society of Thrombosis and Haemostasis (ISTH) guidelines were considered, thus patients with the following cancer types were excluded from the study cohort: non-brain central nervous system, unresected colorectal/lower gastrointestinal tract, hematologic (except lymphoma and myeloma), oesophagus, stomach and bladder.(2)

9.3.1 Venous thromboembolism

VTE was identified according to our previously developed, validated and published algorithm.(23) In brief, VTE events were identified from any of the following: (a) primary care encounters in combination with subsequent anticoagulation, and (b) hospital discharge diagnoses and procedures with or without a record of subsequent anticoagulation. VTE comprised pulmonary embolisms and deep vein thromboses. 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.

9.3.2 Active cancer

Active cancer was defined as cancer being actively treated, diagnosed within 6-months prior to the index CAT or associated with metastatic disease (regardless of time from initial cancer diagnosis). We considered individuals to have an active cancer for 180 days following a first-ever cancer diagnosis identified from hospital and GP-based diagnoses. Cancer-specific procedures or therapies, including chemotherapy, immunotherapy, radiotherapy and hormonal therapy, were also credited with 180 days of active cancer after the treatment. In the presence of a subsequent recording of cancer therapy within the active cancer period, e.g. a diagnosis followed by a cancer-specific therapy within 180 days, then the active cancer episode was extended for another 180 days from the day of the subsequent cancer-therapy recording. Cancer therapies outside a preceding active cancer period constituted a new active cancer episode.

9.3.3 Observational period

The day of the incident CAT was designated the cohort entry day and the day of the first recording of therapeutic DOAC or LMWH initiation within 30 days after the acute CAT was designated the index day. When the DOAC/LMWH initiation was recorded during the initial CAT hospitalisation, the index day was shifted to the first day after hospital discharge. As in-hospital pharmacy data, including group and type of anticoagulant, are not systematically recorded in the linked HES database, we used the first post-discharge prescription of an anticoagulant to determine the patient's initial type of anticoagulant use. The 30-day gap after hospital discharge was used to account for any supply of anticoagulant at discharge 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 (31/10/2020), 1 year after CAT, patient transferred out of GP practice, end of data collection of GP practice, initiation of palliative care, patient died, 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 VTE recurrence or a significant bleeding event.

9.3.4 Selection of comparison groups

DOAC and LMWH users in the study cohort were compared using overlap weighting based on Propensity Scores for rivaroxaban/DOAC initiation, see section data analysis for details.

9.4 Variables

9.4.1 Exposures

Exposure of interest was AC use including DOACs and LMWHs in therapeutic dose.

DOACs included prescriptions for apixaban, dabigatran, edoxaban and rivaroxaban. The duration of a single DOAC prescription was calculated as the number of prescribed tablets/capsules divided by the GP-recorded dosage instructions. When the dosage instruction was missing or implausible, we imputed the duration from the recommended daily dose as follows: two tablets or capsules per day for apixaban and dabigatran and one per day for rivaroxaban and edoxaban.

LMWHs included prescriptions for bemiparin, dalteparin, enoxaparin and tinzaparin. The duration of a patient's single LMWH prescription was derived from the median number of days between consecutive LMWH prescriptions over all patients.

Repeat prescriptions of either DOAC or LMWH were concatenated when the subsequent prescription of the same oral AC class was issued within the calculated supply of the previous prescription, adding a grace period of 30 days to each DOAC and LMWH prescription to account for any remaining medication, lack of patient compliance or residual drug effect. AC users were considered to have discontinued AC treatment when there was no subsequent prescription of AC within the calculated end of AC use or when there was a medical code indicating discontinuation of AC use.

Patients were allocated to either the rivaroxaban, DOAC or LMWH treatment arm of the study based on the first recorded AC prescription after CAT, with the following exception: patients with a LMWH prescription as their first AC recording and a subsequent DOAC prescription within 7 days after the LMWH were allocated to the DOAC group with the day of first DOAC recording being their index day.

The base analysis was an-intention-to treat (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 his initial AC treatment or switched the AC type (i.e. from LMWH to DOAC, VKA or other parenteral AC, or from DOAC to LMWH, VKA or other parenteral AC). In the analyses for comparison of rivaroxaban with LMWH, switching of AC type also included switching to a DOAC other than rivaroxaban.

9.4.2 Outcomes

The outcomes of interest were VTE recurrences, significant bleeds defined as major bleeds or clinically-relevant non-major bleeding requiring hospitalisation (CRNMB-H) and all-cause mortality.

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.[6,7] All identified potential VTE recurrences and significant bleeds were manually reviewed by utilizing patient summaries/profiles including recorded symptoms, signs, laboratory tests, diagnostic and therapeutic procedures, medication use, discharge diagnoses, and causes of death to confirm that outcomes had been appropriately identified.

9.4.2.1 Effectiveness outcomes

9.4.2.1.1 Recurrent VTE

Recurrent VTE was identified from (i) ONS if PE was recorded as primary or second cause of death, (ii) from HES if patients were hospitalised with an emergency type of admission and a primary diagnostic code for VTE and a change of VTE type, specific symptoms, specific investigations or subsequent AC initiation, and (iii) from CPRD if a VTE was recorded by the GP with at least two additional criteria, e.g. a change of VTE type, specific symptoms, specific investigations, subsequent AC initiation or a subsequent emergency hospitalisation.

9.4.2.2 Safety outcomes

9.4.2.2.1 Significant bleeds

Consistent with the definition of the ISTH, major bleeds were required to be: (i) a fatal bleeding (recorded as primary, secondary or tertiary cause of death), (ii) bleeding at a critical site (i.e. intraocular bleeding in non-diabetics, intracranial, intraspinal, pericardial, intra-articular,

retroperitoneal or intramuscular bleeding), or a hematoma and a compartment syndrome recorded within 7 days, or (iii) record of post-haemorrhagic anaemia or a bleeding event followed by a blood transfusion or a record for anaemia within 7 days. Critical organ bleeds, a subset of major bleeds, were defined as intracranial bleeds and other critical organ bleeds.

CRNMB-H consisted of bleeding events that resulted in hospitalisation but did not satisfy the criteria of major bleeds. CRNMB-H were identified from hospital diagnosis codes (recorded as first, second or third discharge diagnosis), hospital procedure codes (recorded in the first hospital episode) or GP recorded diagnoses with a hospital admission on the same day.

9.4.2.2.2 All-cause mortality

Mortality was identified from ONS data that includes information from death certificates.

9.4.2.2.3 Duration of anticoagulation treatment

Duration of anticoagulation treatment with rivaroxaban/DOAC and LMWH use was defined as continuous treatment with the respective medication from initiation to discontinuation. Duration of anticoagulation treatment estimates (presented as proportion of patients still on treatment) were accounted for overlap weights, for outcome events (death, significant bleeds and VTE recurrence) as competing events and for switching of anticoagulant as censoring events.

9.4.3 Covariates/Potential Confounders

Covariates included variables intended for description of the study cohort (including cancer type and treatment), variables potentially related with choice of AC type in CAT 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).

These 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.

Comorbidities included bleeding history, anaemia, asthma, bronchiectasis, acute bronchitis, cellulitis or skin infection, cerebrovascular disease (ischemic stroke, haemorrhagic stroke, unspecific stroke, transient ischemic attack, other), chronic inflammatory disease, chronic obstructive pulmonary disease, dementia, depression, diabetes mellitus, congestive heart failure, hiatus hernia, hyperlipidaemia, hypertension, inflammatory bowel disease, influenza, liver disease, peripheral artery disease, venous insufficiency, pneumonitis or bronchiolitis, kidney disease (moderate or severe), rheumatoid arthritis, osteoarthritis, upper urinary tract infection, lower urinary tract infection, central venous catheter, trauma, gastro-oesophageal reflux disease, sleep apnoea, diverticulitis, hypothyroidism, angina pectoris, ischemic heart disease, osteoporosis, alcohol misuse, gastritis, myocardial infarction, acute respiratory distress syndrome, coagulation disorders, coronary procedures, osteomyelitis, paroxysmal nocturnal hemoglobinuria, polycythaemia, sickle cell disease, systemic embolism, thrombophilia and thrombotic microangiopathy, and IV drug misuse.

Comedications included antiplatelets, serotonin and norepinephrine reuptake inhibitor, selective serotonin reuptake inhibitor, other antidepressants, corticosteroids, testosterone, statins, macrolides, non-steroidal anti-inflammatory drugs (excluding antiplatelets), antidiabetic medications, angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, benzodiazepines, beta

blocker, calcium channel blocker, moderate inducers of Cytochrome P450 3A (including 3A4) (CYP3A4), moderate inhibitors of CYP3A4, strong inhibitors of CYP3A4, thiazide diuretics, loop diuretics, histamine-2 receptor antagonists, proton pump inhibitors, hormone replacement therapy, other antiarrhythmic drugs, antivirals, cancer immunotherapies, digoxin, misoprostol, and oral contraceptives.

Other factors included age, gender, race, weeks hospitalized in year before CAT, calendar year of CAT, body mass index (BMI), smoking status, socio-economic status, haemoglobin level, serum creatinine, glomerular filtration rate, type of first VTE, cancer type, metastases, and type of cancer therapy.

9.5 Data sources and measurement

CPRD holds anonymised patient data securely shared by GP practices across the UK. To provide a more complete and accurate picture of a patient's healthcare, CPRD also receives anonymised patient data from other sources such as hospital data from NHS Digital data from Public Health England. It is not possible to identify individual patients in any dataset that CPRD holds because CPRD never receives patient identifiable information such as name, address, NHS number or date of birth from any data source. The patient health data that CPRD holds has been processed in accordance with the Information Commissioner's Office (ICO) Anonymisation Code of Practice. In England, NHS Digital, the statutory body legally permitted to receive identifiable patient data, collects and processes identifiable data on CPRD's behalf to allow different datasets to be linked together. The data CPRD receives from NHS Digital is anonymised, see "https://cprd.com/safeguarding-patient-data" and section 9.2 ("Setting") for more information.

9.6 Bias

One-year duration of anticoagulation treatment with DOACs or to rivaroxaban was about 2-fold and significantly greater compared to LMWH. Different factors could have contributed to this finding: (1) better compliance to DOACs compared with parenteral anticoagulants, (2) differential changes of covariate exposure during the at-risk period in the treatment groups of interest which may have altered the use of parenteral anticoagulants. However, despite the differences in the duration of anticoagulation treatment with DOACs and LMWH, results of the on-treatment analyses were consistent with the results of the intention-to-treat analysis.

Although a vast set of covariates were used for adjustment (see section 9.4.3 ("Covariates/Potential Confounders"), unmeasured confounding cannot be ruled out as certain covariates were not available in the database (such as cancer staging). 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/DOACs with LMWH during the at-risk period and may have affected both the ITT and the on-treatment analyses.

By definition, the study cohort consisted of patients with cancer-associated VTE and DOAC or LMWH use. Patients with a missing record of active cancer, VTE or AC therapy did not form part of our study cohort. Exact onset and end of cancer is unclear. Therefore some patients in the study cohort may have not had cancer during part of the observational period (if cancer remitted) and some patients may be missing from our cohort. We think it is unlikely that this may have influenced the results substantially.

Small event numbers, such as critical organ bleeds in rivaroxaban/DOACs, resulted in unstable risk estimates leading to wide confidence intervals.

Medical diagnoses including venous thromboembolism or bleeding events are recorded as hospital discharge diagnoses but the day of occurrence during the hospitalisation is either 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 the misclassification of exposure and of outcomes, we excluded outcome events that occurred during the same hospitalization as the initial VTE event.

9.7 Study size

For the objective to compare rivaroxaban with LMWH the cohort included 2259 patients, 314 treated with rivaroxaban and 1945 with LMWH within 30 days following the CAT. For the objective to compare all DOACs vs LMWH 656 patients initially treated with DOACs within 30 days following the CAT were included.

9.8 Data transformation

Not applicable.

9.9 Statistical methods

All statistical procedures were performed using Stata MP Version 14.2 (StataCorp LLC).

9.9.1 Main summary measures

Effectiveness and safety outcomes were measured using sub-distribution hazard ratios (SHRs) at 3, 6 and 12 months following CAT separately in the rivaroxaban/DOAC group compared to the LMWH group (reference).

9.9.2 Main statistical methods

Baseline characteristics at cohort entry were described separately for rivaroxaban/DOAC 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/DOAC and LMWH cohort, probabilities for rivaroxaban/DOAC initiation in CAT were estimated from multivariate logistic regression models based on covariates identified at cohort entry. Covariates were only included in the model when ≥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/DOAC and LMWH groups using the overlap weighting method, i.e. patients were weighted with the probability of belonging to the opposite treatment group.(24, 25) By design, overlap weighting resulted in the exact balance of all variables included in the logistic regression model in the 2 exposure groups rivaroxaban/DOAC and LMWH.

Crude incidence rates of recurrent VTE, significant bleeds and death within 3, 6 and 12 months following CAT were calculated in the rivaroxaban/DOAC and LMWH group separately before and after weighting.

Univariate Fine and Gray regression models accounting for competing risks using AC exposure (i.e. DOAC or 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 CAT separately. Models were performed with and without overlap weighting. Competing risks for each study outcome were the other 2 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.(26)

All analyses including the determination of probability weights were performed for comparison of rivaroxaban with LMWH and for comparison of all DOACs with LMWH separately.

9.9.3 Missing values

Missing data were allocated to a category "unknown", e.g. when BMI or smoking status was missing. See Section 9.4.1 ("Exposures") for addressing missing dosage instructions.

9.9.4 Sensitivity analyses

In a sensitivity analysis, an on treatment approach instead of an ITT approach was used. I.e. patients that discontinued AC treatment or switched to a different AC type, e.g. from DOAC to VKA were censored. In addition to the analyses mentioned above the duration of anticoagulation use following initial CAT was described for rivaroxaban/DOAC and LMWH separately using a competing risk approach and the overlap weighting.

In an exploratory analysis, critical organ bleeds (a subgroup of major bleeds) were investigated as a separate study outcome.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

All coding (Read medical codes, SNOMED codes, OPCS, ICD-codes and product codes) were prepared and reviewed by at least two clinical experts and trained investigators to assure its accuracy.

IfESI and LIRN have developed standard definitions of recurrent venous thromboembolism, {Martinez, 2014 #1822} many variables and disease states and developed programs/coding to apply these standards as needed on projects. These standards help ensure consistency, repeatability, and accuracy for each project.

Potential VTE recurrences and significant bleeds were manually assessed by reviewing patient summaries/profiles including HES APC, HES Outpatient, ONS DRD and GP recorded symptoms, signs, laboratory tests, diagnostic and therapeutic procedures, medication use, discharge diagnoses, and cause of death to confirm that both exposure (anticoagulant) and outcomes have been appropriately identified.

The external partners IfESI and LIRN followed the next implemented quality assurance steps to assure a low risk of errors:

- Appropriate working conditions
    - Execution of workflow by adequately qualified personnel
    - Foresighted planning of timelines to reduce time pressure

- Provision of a convenient working environment

- Standardization of processes
  - Adherence to standard operating procedure descriptions
  - Usage of validated software and document templates
  - Automatization of processes whenever feasible
- Application of control mechanisms
  - Review of all source code files and other documents by a 2nd individual (four-eyes principle)
  - Run of analyses on 2 different personal computers and subsequent automated comparison of result files to assure reproducibility and system-independency of study results
- Extensive documentation
  - Usage of a version control system for source code files and other documents
  - Bookkeeping of study progress and changes via log files
  - Successive backups of study relevant files during study conduct

In addition, all key study documents, such as the statistical analysis plan and study reports, underwent quality control and senior scientific review. The study was executed in line with all applicable regulations and guidelines, such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology.

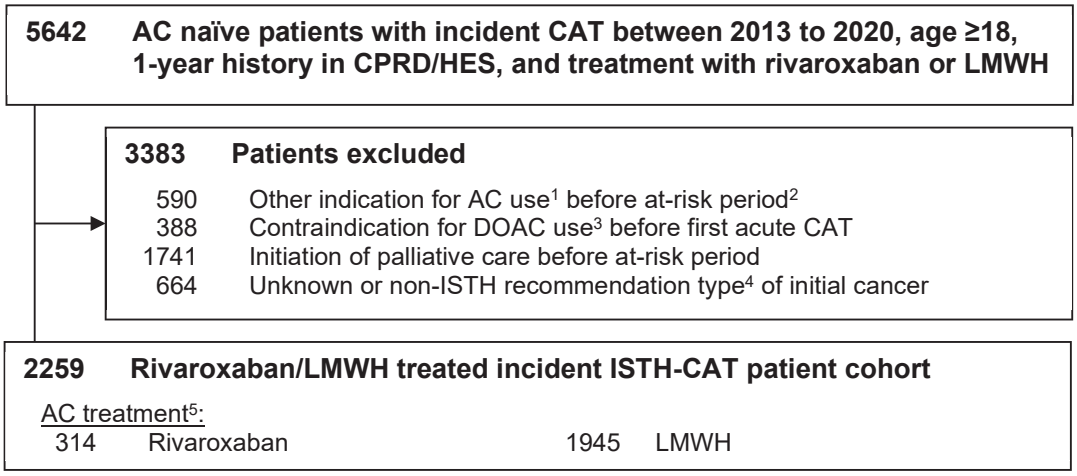
The study protocol was approved by the Independent Scientific Advisory Committee for CPRD research (Protocol 21_000514).

10. Results

10.1 Participants

A total of 6288 anticoagulation naïve adult patients with active cancer and CAT, with at least one year of history in CPRD/HES and treated with either DOAC or LMWH, were identified between 2013 and 2020. Of those, 3687 patients were excluded due to indications for anticoagulation use other than VTE, contraindications for DOAC use, initiation of palliative care before the start of the at-risk period or an unknown or non-ISTH recommendation type of initial cancer. From the remaining 2601 patients 314 were treated with rivaroxaban (Figure 1), 656 were initially treated with DOACs (Figure 2) and 1945 with LMWH (Figures 1 and 2) within 30 days following the CAT.

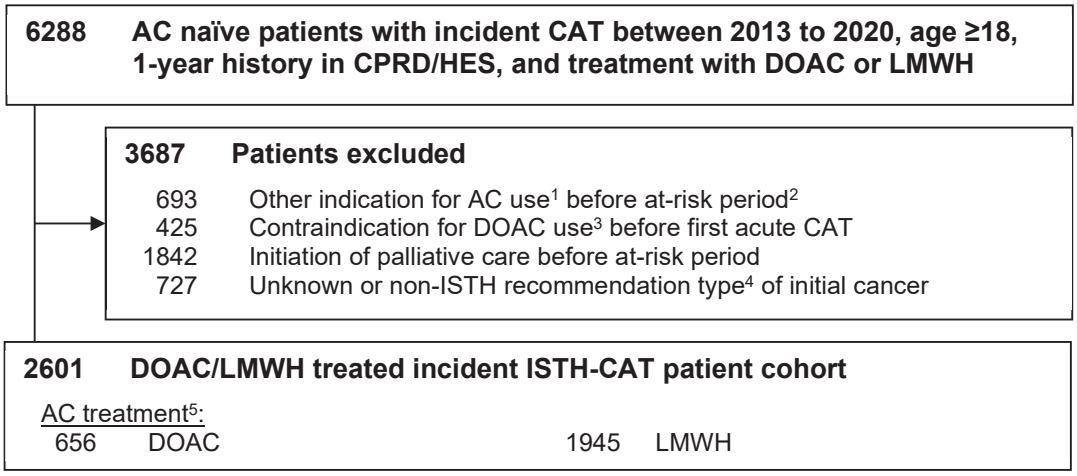
Figure 2: Ascertainment of Rivaroxaban vs. LMWH-treated CAT cohort



AC: Anticoagulant; CAT: 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.

[1]: Atrial fibrillation, cardiac valve replacement, unusual site DVT (cerebral and abdominal vein thrombi), or hip or knee replacement in last month.
[2]: At risk period: starts on day of first Rivaroxaban/LMWH recording after CAT but not earlier than 1 day after VTE hospital discharge or 1 day after day of general practitioner recording of VTE.
[3]: Thrombocytopenia, active pregnancy or end-stage kidney disease.
[4]: Including the following cancer types: non-brain central nervous system, unresected colorectal, leukaemia, other hematologic, oesophagus, stomach and bladder.
[5]: 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.

Figure 2: Ascertainment of DOACs vs LMWH-treated CAT cohort



AC: Anticoagulant; CAT: 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.

[1]: Atrial fibrillation, cardiac valve replacement, unusual site DVT (cerebral and abdominal vein thrombi), or hip or knee replacement in last month.

[2]: At risk period: starts on day of first DOAC/LMWH recording after CAT but not earlier than 1 day after VTE hospital discharge or 1 day after day of general practitioner recording of VTE.
[3]: Thrombocytopenia, active pregnancy or end-stage kidney disease.
[4]: Including the following cancer types: non-brain central nervous system, unresected colorectal, leukaemia, other hematologic, oesophagus, stomach and bladder.
[5]: Patients switching from LMWH to DOAC within the first 7 days after initial LMWH treatment were allocated to the DOAC group with the day of DOAC as start of at-risk period.

10.2 Descriptive data

Rivaroxaban users were older, were more likely to be males, less likely to be smokers and least deprived. Cancer types varied in the two anticoagulant exposure cohorts with breast and prostate cancer more likely in rivaroxaban users, while cancers of the gastrointestinal tract, lung and of other than the 12 prespecified sites were more prevalent in the LMWH exposure cohort, Table 1.

At one year of observation only 16 of 314 initial rivaroxaban users were still at-risk for study outcomes and cumulated a total of 184 person-years of observation, Table 2a and Figure 2a.

10.3 Outcome data

10.3.1 Effectiveness outcomes

10.3.1.1 Recurrent VTE

A total of 66 and 10 incident recurrent VTE events were identified in temporal relationship with LMWH and rivaroxaban use in the first year after the initial CAT, Table 2a.

10.3.2 Safety outcomes

10.3.2.1 Significant bleeds

Significant bleeds comprise the first major bleed or CRNMB-H during the defined observational period. There were 102 and 20 significant bleeds in LMWH and rivaroxaban treated patients in the first year after CAT.

There were 39 and 3 major bleeds in LMWH and rivaroxaban at one year of observation. Of the major bleeds, 24 and 2 bleeds in LMWH and rivaroxaban users were intracranial bleeds or bleeds in another critical organ.

There were 63 and 17 CRNMB-H in LMWH and rivaroxaban at one year of observation, Table 2b.

10.3.2.2 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 CAT, Table 2c.

10.4 Main results

10.4.1 Effectiveness outcomes

10.4.1.1 Recurrent VTE

Crude incidence rates of recurrent VTE in the first year after the initial CAT were 6.2 (0.95-CI: 4.8-8.0) and 5.4 (2.6-10.0) per 100 person-years in LMWH and rivaroxaban use respectively. The weighted SHR for VTE recurrences in rivaroxaban compared with LMWH at 12 months was 0.80 (0.37-1.73). Restricting the observational period to 3 and 6 months after the CAT, the weighted SHRs were 0.96 (0.25-3.74) and 1.31 (0.47-3.67) respectively, Table 2a and Figure 2a.

10.4.2 Safety outcomes

10.4.2.1 Significant bleeds

Crude incidence rates of significant bleeds in the first year after the initial CAT were 9.7 (7.8-11.8) and 10.9 (6.6-16.8) per 100 person-years of LMWH and rivaroxaban use respectively. The weighted SHR for significant bleeds in rivaroxaban compared to LMWH at 12 months was 1.01 (0.57-1.81). Restricting the observational period to 3 and 6 months after CAT resulted in weighted SHRs of 1.03 (0.44-2.40) and 0.85 (0.43-1.71) respectively.

Major bleeds

The weighted SHRs at 3, 6 and 12 months after CAT were decreased for rivaroxaban compared with LMWH but not statistically significant, 0.37 (0.08-1.76), 0.40 (0.11-1.44) and 0.35 (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.

CRNMB-H

The weighted SHRs at 3, 6 and 12 months after CAT in rivaroxaban compared to LMWH were increased but not statistically significant, 2.02 (0.72-5.62), 1.30 (0.57-2.98) and 1.57 (0.80-3.05) respectively, Table 2b and Figure 2b.

10.4.2.2 All-cause mortality

Cumulative crude mortality rates in the first year after the initial CAT were 12.6 (10.5-15.0) and 5.4 (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 to LMWH at 12 months was 0.49 (0.23-1.06). At 3 and 6 months after CAT, the weighted SHRs were 0.63 (0.25-1.60) and 0.59 (0.26-1.33) respectively, Table 2c and Figure 2c.

10.5 Other analyses

10.5.1 Sensitivity Analysis - Rivaroxaban compared with LMWH, on-treatment analysis

10.5.1.1 Study cohort

The at-risk period (observational period) in the intention-to-treat analysis comprised the time from the initial anticoagulant recording until the occurrence of a study outcome, the end-of-database activity, end of data availability or end of designated follow-up time (3-, 6- or 12-months), whichever came first. In contrast, the study cohort for the on-treatment analysis excluded 86 patients that switched AC type before the start of the at-risk period. Patients were censored when anticoagulation was discontinued or when patients switched AC type after the start of the at-risk period, see section 9.4.1 ("Exposure") for details.

The study cohort for the on-treatment analysis consisted of a subset of 2173 patients, 1867 initially treated with LMWH (96% of the ITT cohort) and 306 with rivaroxaban (97% of the respective ITT cohort), Figure 3. Thus, the characteristics of the LMWH and rivaroxaban users in the on-treatment cohort were similar to the characteristics of the ITT cohort, Table 3.

At one 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), Table 4a.

The duration of anticoagulation treatment with LMWH and rivaroxaban in the first year of observation is illustrated in Figure 4. Duration of anticoagulation treatment with LMWH use was lower than the duration of anticoagulation treatment with rivaroxaban throughout the complete year of observation following the CAT. While the duration of anticoagulation treatment of LMWH use was 25.8% at one year, the respective duration of anticoagulation treatment for rivaroxaban was 49.5%, $p<0.05$.

10.5.1.2 Effectiveness outcomes

10.5.1.2.1 Recurrent VTE

A total of 26 and 6 incident recurrent VTE events were identified in temporal relationship with LMWH and rivaroxaban use in the year after the initial CAT yielding crude incidence rates of 4.9 (3.2-7.3) and 4.5 (1.6-9.8) per 100 person-years in LMWH and rivaroxaban use respectively. The weighted SHR for VTE recurrences in rivaroxaban compared with LMWH at 12 months was 0.82 (0.31-2.17). Restricting the observational period to 3 and 6 months after the CAT, the weighted SHRs were 0.56 (0.11-2.79) and 0.86 (0.28-2.63) respectively, Table 4a and Figure 5a.

10.5.1.3 Safety outcomes

10.5.1.3.1 Significant bleeds

There were 64 and 17 significant bleeds in LMWH and rivaroxaban treated patients in the first year after CAT yielding crude incidence rates of 12.1 (9.3-15.5) and 12.7 (7.4-20.4) per 100 person-years of LMWH and rivaroxaban treatment respectively. The weighted SHR for significant bleeds in rivaroxaban compared to LMWH at 12 months was 1.08 (0.55-2.14). Restricting the observational period to 3 and 6 months after CAT resulted in weighted SHRs of 1.23 (0.51-2.96) and 1.04 (0.47-2.29) respectively.

Major bleeds

There were 29 and 2 major bleeds in LMWH and rivaroxaban at one year of observation. Weighted SHRs at 3, 6 and 12 months after CAT were not calculated due to the small number of major bleeds in association with rivaroxaban exposure. Of the major bleeds, 17 and 1 bleeds in LMWH and rivaroxaban users were intracranial bleeds or bleeds in another critical organ.

CRNMB-H

There were 35 and 15 CRNMB-H in LMWH and rivaroxaban at one year of observation. The increased weighted SHRs at 3, 6 and 12 months after CAT in rivaroxaban compared to LMWH of 1.85 (0.61-5.58), 1.60 (0.62-4.12) and 1.80 (0.81-4.03) respectively were not statistically significant, Table 4b and Figure 5b.

10.5.1.3.2 All-cause mortality

There were 87 and 10 deaths due to any cause in the LMWH and rivaroxaban treated patients within the first year after CAT yielding cumulative crude mortality rates of 16.5 (13.1-20.3) and 7.5 (3.5-13.8) per 100 person-years in LMWH and rivaroxaban use respectively. The weighted SHRs for death from any cause in rivaroxaban compared with LMWH at 3, 6 and 12 months were decreased but showed no statistical significance, 0.66 (0.25-1.74), 0.71 (0.31-1.61) and 0.67 (0.30-1.49) respectively, Table 4c and Figure 5c.

10.5.2 DOACs compared with LMWH, intention-to-treat analysis

10.5.2.1 Study cohort

DOAC users were older, were more likely to have a PE as initial CAT, to be ex-smoker and least deprived. Cancer types varied in the two anticoagulant exposure cohorts with breast and prostate cancer more likely in DOAC users, while cancers of the gastrointestinal tract, lung and of other than the 12 prespecified sites were more prevalent in the LMWH exposure cohort, Table 5.

At one year of observation only 99 of 1945 initial LMWH and 30 of 656 initial DOAC users were at-risk for study outcomes and cumulated a total of 1057 (LMWH) and 361 (DOAC) person-years of observation, Table 6a and Figure 7a.

10.5.2.2 Effectiveness outcomes

10.5.2.2.1 Recurrent VTE

A total of 16 incident recurrent VTE events were identified in temporal relationship with DOAC use in the first year after the initial CAT yielding a crude incidence rate of 4.4 (2.5-7.2) per 100 person-years in DOAC use. The weighted SHR for VTE recurrences in DOACs compared with LMWH at 12 months was 0.73 (0.38-1.39). Restricting the observational period to 3 and 6 months after the CAT, the weighted SHRs were 0.88 (0.30-2.59) and 1.07 (0.46-2.52) respectively, Table 6a and Figure 7a.

10.5.2.3 Safety outcomes

10.5.2.3.1 Significant bleeds

There were 30 significant bleeds in DOAC- treated patients in the first year after CAT yielding a crude incidence rate of 8.3 (5.6-11.9) per 100 person-years of DOAC treatment. The weighted SHR for significant bleeds in DOACs compared to LMWH at 12 months was 0.79 (0.49-1.30). Restricting the observational period to 3 and 6 months after CAT resulted in weighted SHRs of 0.88 (0.46-1.70) and 0.68 (0.39-1.20) respectively.

Major bleeds

There were 6 major bleeds in DOAC at one year of observation. The weighted SHRs at 3 and 6 months after CAT were 0.40 (0.12-1.38) and 0.35 (0.12-1.04) respectively. The lower weighted SHR for DOACs compared to LMWH at 12 months was statistically significant with an SHR of 0.32 (0.12-0.91). Of the 6 major bleeds, 3 bleeds in DOAC users were intracranial bleeds or bleeds in another critical organ.

CRNMB-H

There were 24 CRNMB-H in DOAC at one year of observation. The weighted SHRs at 3, 6 and 12 months after CAT in DOACs compared to LMWH were 1.52 (0.67-3.48), 1.00 (0.50-2.00) and 1.21 (0.68-2.16), Table 6b and Figure 7b.

10.5.2.3.2 All-cause mortality

There were 19 deaths due to any cause in the DOAC treated patients within the first year after CAT yielding a cumulative crude mortality rate of 5.3 (3.1-8.3) per 100 person-years of DOAC use. The weighted SHR for death from any cause in DOACs compared to LMWH at 12 months was 0.59 (0.34-1.05). At 3 and 6 months after CAT, the weighted SHRs were 0.45 (0.20-1.03) and 0.57 (0.30-1.08) respectively, Table 6c and Figure 7c.

10.5.3 Sensitivity analysis - DOACs compared with LMWH, on-treatment analysis

10.5.3.1 Study cohort

The at-risk period (observational period) in the intention-to-treat analysis comprised the time from the initial anticoagulant recording until the occurrence of a study outcome, the end-of-database activity, end of data availability or end of designated follow-up time (3-, 6- or 12-months), whichever came first. In contrast, the study cohort for the on-treatment analysis excluded 91 patients that switched AC type before the start of the at-risk period. Patients were censored when anticoagulation was discontinued or when patients switched AC type after the start of the at-risk period, see "Exposure" section for details.

The study cohort for the on-treatment analysis consisted of a subset of 2510 patients, 1867 initially treated with LMWH (96% of the ITT cohort) and 643 with DOACs (98% of the respective ITT cohort), Figure 8. Thus, the characteristics of the LMWH and DOAC users in the on-treatment cohort were similar to the characteristics of the ITT cohort, Table 7.

At one year of observation DOAC users cumulated a total of 275 person-years (76.2%) of the respective person-years in the ITT analysis, Table 8a.

The duration of anticoagulation treatment with LMWH and DOACs in the first year of observation is illustrated in Figure 9. Duration of anticoagulation treatment with LMWH use was lower than the duration of anticoagulation treatment with DOACs throughout the complete year of observation following the CAT. While the duration of anticoagulation treatment of LMWH use was 25.8% at one year, the respective duration of anticoagulation treatment for DOACs was 50.9%, $p<0.05$. Of 1867 LMWH users 17.5% switched to oral anticoagulants, while of 643 DOAC users 2.5% switched to LMWH and further 3.3% to VKA at some point during the 12-month observational period.

10.5.3.2 Effectiveness outcomes

10.5.3.2.1 Recurrent VTE

A total of 8 incident recurrent VTE events were identified in temporal relationship with DOAC use in the year after the initial CAT yielding a crude incidence rate of 2.9 (1.2-5.8) per 100 person-years in DOAC use. The weighted SHR for VTE recurrences in DOACs compared with LMWH at 12 months was 0.64 (0.27-1.52). Restricting the observational period to 3 and 6 months after the CAT, the weighted SHRs were 0.62 (0.18-2.08) and 0.70 (0.26-1.86) respectively, Table 8a and Figure 10a.

10.5.3.3 Safety outcomes

10.5.3.3.1 Significant bleeds

There were 25 significant bleeds in DOAC treated patients in the first year after CAT yielding a crude incidence rate of 9.1 (5.8-13.5) per 100 person-years of DOAC treatment. The weighted SHR for significant bleeds in DOACs compared to LMWH at 12 months was 0.78 (0.44-1.38). Restricting the observational period to 3 and 6 months after CAT resulted in weighted SHRs of 0.93 (0.46-1.85) and 0.76 (0.40-1.45) respectively.

Major bleeds

There were 4 major bleeds in DOAC at one year of observation. The weighted SHRs at 3 and 6 months after CAT were 0.53 (0.15-1.86) and 0.40 (0.12-1.41) respectively. There was a further but

not statistically significant decrease of the weighted SHR at 12 months of 0.32 (0.09-1.16). Of the major bleeds, 2 bleeds in DOAC users were intracranial bleeds or bleeds in another critical organ.

CRNMB-H

There were 21 CRNMB-H in DOAC at one year of observation. The weighted SHRs at 3, 6 and 12 months after CAT in DOACs compared to LMWH were 1.34 (0.56-3.23), 1.11 (0.50-2.42) and 1.22 (0.62-2.41), Table 8b and Figure 10b.

10.5.3.3.2 All-cause mortality

There were 16 deaths due to any cause in the DOAC treated patients within the first year after CAT yielding a cumulative crude mortality rate of 5.8 (3.3-9.5) per 100 person-years in DOAC use. The weighted SHR for death from any cause in DOACs compared with LMWH yielded a statistically significant decrease at 3 months, 0.40 (0.16-0.98), but not at 6 and 12 months of observation, 0.62 (0.32-1.22) and 0.63 (0.34-1.17) respectively, Table 8c and Figure 10c.

10.6 Safety data (Adverse events/adverse reactions)

As per the EMA Guideline on Good Pharmacovigilance Practices, non-interventional study designs that are based on secondary use of data do not require individual reporting of adverse reactions. Reports of the following a priori specified adverse events, i.e. CRNMB-H, major bleeds, and all-cause mortality are study outcomes and summarized in the study report, where applicable.

11. Discussion

11.1 Key results

We generated a cohort of patients with active cancer and incident venous thromboembolism, defined as cancer-associated thromboembolism to evaluate the effectiveness and safety at 3, 6 and 12 months of rivaroxaban/DOAC therapy compared with LMWH. The effectiveness consisted of recurrent VTE, whereas safety was defined by significant bleeds which included major bleeds and clinically-relevant non-major bleeding requiring hospitalization and by all-cause mortality. An intention-to-treat analysis was a priori defined as the main analysis. On-treatment analyses for rivaroxaban compared with LMWH and for all DOACs (as a group) compared with LMWH were conducted as sensitivity analyses. The following findings are to be pointed out:

(i) treatment with DOACs and rivaroxaban compared with LMWH was associated with consistent but not statistically significant slightly smaller point estimates for VTE recurrences at 3, 6 and 12 months in all analyses. This decrease was more pronounced in the on treatment analysis of all DOACs .

(ii) treatment with DOACs and rivaroxaban compared with LMWH was associated with consistent smaller point estimates for major bleeds in all analyses. This decrease was only statistically significant for DOACs in the ITT analysis at 12 months.

(iii) treatment with DOACs and rivaroxaban compared with LMWH was associated with a non-statistically significant increased risk of CRNMB-H which appeared more pronounced in those treated with rivaroxaban.

(iv) treatment with DOACs and rivaroxaban was associated with consistent smaller point estimates for all-cause mortality in all analyses, but only statistically significant in the all DOACs on-treatment analysis at 3 months.

(v) duration of anticoagulation treatment with DOACs and with rivaroxaban was about 2-fold and significantly greater at one year after CAT compared to LMWH.

11.2 Limitations

One-year duration of anticoagulation treatment with DOACs or to rivaroxaban was about 2-fold and significantly greater compared to LMWH. Different factors could have contributed to this finding: (1) better compliance to DOACs compared with parenteral anticoagulants, (2) some factors (covariates) that have an influence in the choice of DOACs or LMWH might have changed after treatment initiation, resulting in switching/discontinuation. Despite the differences in duration of anticoagulation treatment with DOACs and LMWH, results of the on-treatment analyses were consistent with the results of the intention-to-treat analysis.

Although a vast set of covariates were used for adjustment (see section 9.4.3 ("Covariates/Potential Confounders"), 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). 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/DOACs with LMWH during the at-risk period and may have affected both the ITT and the on-treatment analyses.

By definition, the study cohort consisted of patients with cancer-associated VTE and DOAC or LMWH use. Patients with a missing record of active cancer, VTE or AC therapy did not form part of our study cohort. However, those potential cases should have a similar distribution in the rivaroxaban/DOAC and LMWH groups, thus it is unlikely that this may have influenced the results.

Subdistribution hazard ratio estimates for outcomes with small event numbers, such as critical organ bleeds in rivaroxaban/DOACs, had low precision as reflected by wide confidence intervals.

Medical diagnoses including venous thromboembolism or bleeding events are recorded as hospital discharge diagnoses but the day of occurrence during the hospitalisation is either 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 CAT.

11.3 Interpretation

In this cohort study of patients with cancer-associated thrombosis treated with either DOACs or LMWHs, DOACs and rivaroxaban were as effective as LMWH at preventing VTE recurrence and without an impact on the significant bleeds (composite outcome), major bleeds, critical organ bleeds, clinically-relevant non-major bleeding requiring hospitalization, or on all-cause mortality.

Patients treated with DOACs or rivaroxaban remained on therapy for a longer period of time compared with LMWH.

Our study findings support the recommendation that DOACs and rivaroxaban are reasonable alternatives to LMWH for the treatment of CAT when used in accordance with guidelines.

We used the overlap weighting adjustment method based on Propensity Scores to make the two anticoagulant exposure groups comparable. The overlap weighting led to exact balance of all measured baseline characteristics in the two anticoagulant exposure groups.

Outcome events were captured only if 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 anticoagulant 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 underestimation of absolute risk estimates.

11.4 Generalizability

This study is also part of the Observational Studies in Cancer Associated Thrombosis for Rivaroxaban (OSCAR study program) with independent studies in the US, (20) UK (21) and Sweden (22), and using consistent definitions of design, exposures of interest, covariates and data analyses. While the study in Sweden is being conducted, the comparison of the UK and US arm of the OSCAR program indicate that the study findings are generalizable to patients with active cancer excluding non-brain central nervous system, unresected colorectal/lower gastrointestinal tract, hematologic (except lymphoma and myeloma), oesophagus, stomach and bladder.

12. Other information

None.

13. Conclusion

Patients with cancer-associated thrombosis treated with either rivaroxaban/DOACs or LMWHs have a comparable benefit-risk balance. This finding support the recommendation that DOACs and rivaroxaban are reasonable alternatives to LMWH for the treatment of CAT when used in accordance with guidelines.

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Appendices

Annex 1: List of stand-alone documents

Table 3: List of stand-alone documents

Document Name	Final version and date (if available)*
"BACAT01 - Report - Figures and Tables - 26 Aug 2022.docx"	26 August 2022
“BACAT01 - OSCAR UK SAP - 23 Aug 2022.docx”	23 August 2022

Annex 2 Additional information

Not applicable

Annex 3 Signature Pages

Signature page- PPD

Title	**OSCAR-UK: O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban – **U**nited **K**ingdom Cohort
Report version and date	V1.0, 26 August 2022
IMPACT study number	22020
Study type / Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS43329
Medicinal product / Active substance / Medical Device / Combination Product	Direct factor Xa inhibitor, Rivaroxaban (B01AF01) Direct acting oral anticoagulants (DOACs): Factor Xa inhibitors: apixaban, edoxaban, rivaroxaban Factor IIa inhibitor: dabigatran
Comparator / Reference therapy	Low molecular weight heparin (LMWH): Dalteparin, Enoxaparin, Tinzaparin
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

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