Observational Study Information

Acronym/Title	**Observational Studies in Cancer Associated Thrombosis for Rivaroxaban – United Kingdom Cohort (OSCAR—UK)**
Protocol version and date	V1, 23 Aug 2021
IMPACT study number	22020
Study type / Study phase	Observational, Phase IV PASS: Yes Joint PASS: ☐ YES ☒ NO
EU PASS register number	Study not yet registered
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01) Direct acting Oral Anticoagulants (DOACs): factor Xa inhibitors: rivaroxaban, apixaban, edoxaban; factor IIa inhibitor: dabigatran
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto® Direct acting Oral Anticoagulants (DOACs): factor Xa inhibitors: rivaroxaban, apixaban, edoxaban; factor IIa inhibitor: dabigatran
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 will be to evaluate the effectiveness (recurrent VTE) and safety (major bleeding and bleeding-related hospitalization) of rivaroxaban and other DOACs vs. LMWH for treatment of CAT in the UK CPRD dataset
Country(-ies) of study	UK
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	PPD PPD Bayer AG

The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2. List of abbreviations

APC	Admitted Patient Care
CAT	Cancer-associated thrombosis
CFR	Code of Federal Regulations
CI	Confidence interval
CPT	Current Procedural Terminology
CPRD	Clinical Practice Research Datalink
CrCl	Creatinine clearance
DOAC	Direct-acting oral anticoagulant
DVT	Deep vein thrombosis
EHR	Electronic health record
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GI	Gastrointestinal
HES	Hospital Episode Statistics
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard ratio
ICD-CM	International Classification of Diseases – Clinical Modification
ICD-PCS	International Classification of Diseases – Procedure Coding System
ICH	Intracranial hemorrhage
IRB	Institutional Review Board
LMWH	Low molecular weight heparin
N/A	Not Applicable
NOAC	Non-vitamin K antagonist oral anticoagulant
OAC	Oral anticoagulation
OD	Once daily
ONS	Office of National Statistics
OS	Observational study
OSCAR—UK	Observational Studies in Cancer Associated Thrombosis for Rivaroxaban – United Kingdom
PASS	Post-authorization safety study
PCP	Primary care practitioner
PE	Pulmonary embolism
PY	Person-year
RCT	Randomized controlled trial
RDG	Research data governance process
RECORD-PE	Observational routinely collected health data statement for pharmacoepidemiology
VTE	Venous thromboembolism

3. Responsible parties

3.1 Study initiator and funder

Role: OS Conduct Responsible, OS Epidemiologist
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E-mail: PPD

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
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Name: PPD

Role: External OS Epidemiologist
Name: PPD

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborator(s)/External partner(s)/Committee(s)

Role: External Physician and Clinical Epidemiologist
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Role: External Physician and Clinical Epidemiologist

Name: PPD

Institute for Epidemiology, Statistics and Informatics (IfESI), Im Dinkelfeld 32, 60388 Frankfurt, Germany

4. Abstract

Acronym/Title	**Observational Studies in Cancer Associated Thrombosis for Rivaroxaban – United Kingdom Cohort (OSCAR—UK)**
Protocol version and date	V1, 23 Aug 2021
IMPACT study number	22020
Study type / Study phase	Observational / Phase 4
Author	PPD
Rationale and background	Patients with active cancer are ~5-fold more likely to develop a venous thromboembolism (VTE) than those without. When VTE occurs, cancer patients carry an up to a 3-fold higher rate of thrombosis recurrence and ~twice the risk of bleeding during anticoagulation. Therefore, it is critical to utilize anticoagulants that optimize efficacy while minimizing bleeding risk when treating cancer-associated thrombosis (CAT). The strength-of-recommendation for DOACs is based on data from multiple randomized controlled trials (RCTs) comparing them to LMWHs to treat CAT, with results suggesting DOACs may reduce thrombosis risk but with potentially more frequent bleeding (particularly in those with gastrointestinal and genitourinary cancers). Observational studies evaluating DOACs for CAT treatment have been published, but these studies have been either single-arm, evaluated cancer subtypes not recommended for DOAC treatment (e.g., gastrointestinal, genitourinary), were of limited sample size and/or employed heterogeneous definitions of active cancer.
Research question and objectives	The objective of this study will be to evaluate the effectiveness (recurrent VTE) and safety (major bleeding and bleeding-related

	hospitalization) of rivaroxaban and other DOACs vs. LMWH for treatment of CAT in the UK CPRD dataset.
Study design	Retrospective cohort study.
Population	Adults diagnosed with active (primary or metastatic) cancer experiencing a hospitalization or emergency department admission or a primary care visit with an incident VTE, being administered rivaroxaban or other DOACs or a LMWH on or after January 1, 2013. We will identify the first record of anticoagulant therapy between day 7 and day 30 following CAT diagnosis. Subjects will need to be registered with their primary care practitioner (PCP) for at least 12-months prior to the acute CAT event.
Variables	Baseline demographics, comorbidities and concomitant prescribed medications.
Data sources	UK (CPRD GOLD and Aurum HES-linked dataset)
Study size	We anticipate having at least 1000 rivaroxaban new users eligible for analysis. Corresponding number of LMWH new users will be at least 3 times the number of rivaroxaban new users.
Data analysis	Overlap weighting will be used to adjust for potential confounding between treatment cohorts (exposures of interest). Patients receiving rivaroxaban will also be *1:1* matched to LMWH patients based on propensity scores. Analysis of the primary effectiveness and safety endpoints by key subgroups will be performed as well.
Milestones	This study will be conducted between October 2021 and May 2022.

5. Amendments

None.

6. Milestones

Table 1: Milestones

Milestone	**Planned date**
Kick-off meeting	March 2021
Concept document approval	June 2021
Protocol document approval	September 2021

Start of analysis	November 2021
End of analysis	February 2021
Final study results	May 2021
Manuscript (first draft)	June 2022
Final report	July 2022

7. Rationale and background

Patients with active cancer are ~5-fold more likely to develop a venous thromboembolism (VTE) than those without. When VTE occurs, cancer patients carry an up to a 3-fold higher rate of thrombosis recurrence and ~twice the risk of bleeding during anticoagulation [1, 2]. Therefore, it is critical to utilize anticoagulants that optimize efficacy while minimizing bleeding risk when treating cancer-associated thrombosis (CAT).

Guidelines list direct-acting oral anticoagulants (DOACs) as an alternative to low molecular-weight heparin (LMWH) for treatment of CAT. The strength-of-recommendation for DOACs is based on data from multiple randomized controlled trials (RCTs) comparing them to LMWHs to treat CAT, with results suggesting DOACs may reduce thrombosis risk but with potentially more frequent bleeding (particularly in those with certain gastrointestinal and genitourinary cancers).

Observational studies evaluating DOACs for CAT treatment have been published, but these studies have been either single-arm, evaluated cancer subtypes not recommended for DOAC treatment, were of limited sample size and/or employed heterogeneous definitions of active cancer. We sought to evaluate the effectiveness and safety of rivaroxaban versus LMWH for CAT treatment in active cancer patients using a large de-identified electronic health record database.

This study is part of the OSCAR study program with independent studies in the US, UK and Sweden. One aim of the program is to conduct a meta-analysis of the results of the three studies to increase the study size and power. Harmonization of the studies design and definitions was intended, and thus this protocol is based on the protocol developed by the study team for the OSCAR-US Study (impact number 21982).

8. Research questions and objectives

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

8.1 Objectives

The objective of this study will be 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:

- Compare effectiveness and safety (primary and secondary outcomes) of rivaroxaban versus LMWH prescribed for treatment of VTE, at 3, 6 and 12-months of treatment in patients with acute VTE and active cancer without a malignant neoplasm associated with a high risk of bleeding, defined per:
    - Section 6.1 of the Xarelto® SmPC (i.e. gastrointestinal and genitourinary cancers).
    - The International Society on Thrombosis and Haemostasis (ISTH) guidelines (i.e. gastric, esophageal, unresected colorectal, bladder, central nervous system, and hematological cancers (except for myeloma)) [3].

  Primary outcomes:
    - Risk of recurrent VTE (fatal and non-fatal).
    - Any major bleeding or clinically relevant bleeding-related hospitalization.
    - All-cause mortality.

  Secondary outcomes:
    - Intracranial hemorrhage (ICH), other critical organ bleeding and extracranial bleeding-related hospitalizations as separate outcomes.
    - Please refer to section 9.3.2 for detailed definitions of all secondary outcomes.

- Compare effectiveness and safety (primary outcomes) of all DOACs (as a group) vs LMWH in active CAT patients without a malignant neoplasm associated with a high risk of bleeding.
- Estimate incidence rates of recurrent VTE, any clinically relevant bleeding-related hospitalization and all-cause mortality in patients with active CAT with DOAC and LMWH treatment in the overall CAT cohort, i.e. regardless of the bleeding risk associated with cancer type.

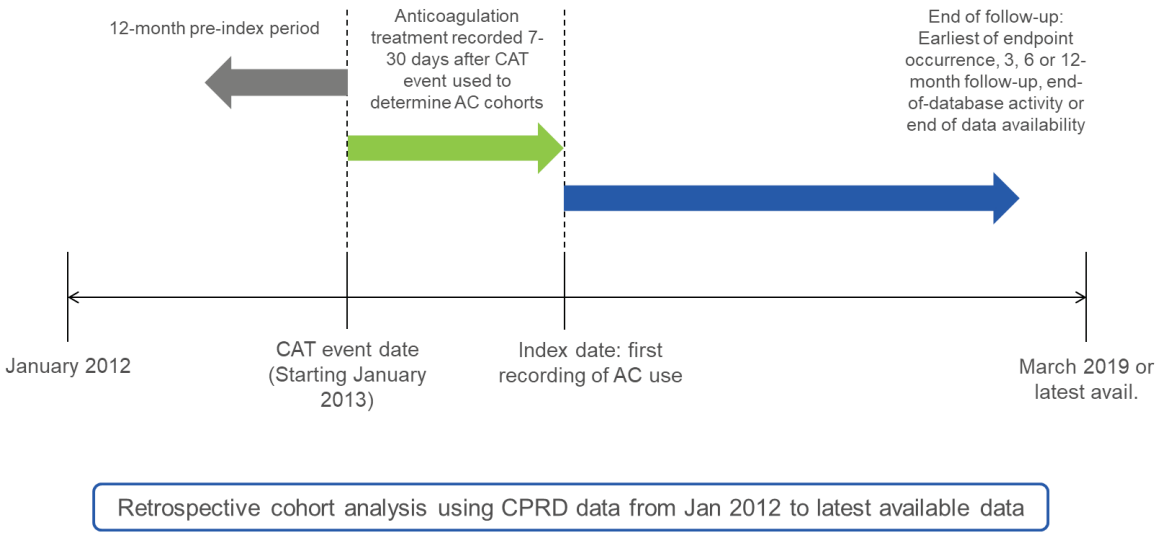
- Estimate duration of anticoagulation treatment and DOAC and LMWH discontinuation rates at 3-, 6- and 12-months and all available follow-up data.
- Conduct subgroup analyses on cancer specific populations (potential cancer types: breast, prostate, lung, ovarian, pancreatic, etc.).

9. Research methods

9.1 Study design

We will perform a retrospective cohort analysis using CPRD GOLD and Aurum HES-linked datasets, from January 2013 through latest available data. Patient identification and flow is depicted in **Figure 1.**
Adults diagnosed with active (primary or metastatic) cancer experiencing a hospitalization or emergency department admission or a primary care visit with an incident VTE, being administered rivaroxaban or other DOACs or a LMWH will be included. CPRD and their linked databases do not include information on in-hospital medication use. Patient discharge with anticoagulation supply is routine practice. However, neither the type of AC use, the date of medication start nor the amount of supply are recorded in CPRD or linked databases. Therefore, the first AC recording by the GP, between day 7 and day 30 after index date, will be used to define the type and duration of AC use and to allocate patients with acute VTE to the respective exposure, i.e. DOAC or LMWH. The 7-30 days window has been selected based on previous studies in this population [2, 4]. Subjects will need to be registered with their primary care practitioner (PCP) for at least 12-months prior to the acute CAT event.
Active cancer in this study will be defined as cancer being actively treated, diagnosed within 6-months prior of the index CAT or associated with metastatic disease (regardless of time from initial cancer diagnosis). We will exclude patients with an indication for OAC use to treat other conditions (i.e. atrial fibrillation, prophylaxis after hip/knee replacement in the last three months, stable coronary or peripheral artery disease, long-term VTE prophylaxis) or use of OAC during the 12-months prior to the CAT.

Figure 1: Schematic of VTE analysis



9.2 Setting

General Practice setting in the UK (CPRD GOLD and Aurum HES-linked databases). The CPRD databases contain longitudinal routinely-collected electronic health records (EHR data) from UK primary care practices. GP practices use two different software systems (in structure and clinical coding), and due to these differences, data are provided as two separate primary care databases that can be pooled (CPRD GOLD and Aurum) and general practices duplicated in GOLD and Aurum can be identified and removed accordingly. The databases (GOLD and Aurum) capture information on: demographic characteristics, diagnoses and symptoms, drug exposures, vaccination history, laboratory tests referrals to hospital and specialist care and can be linked to national secondary care databases like Hospital Episode Statistics (HES) as well as death registration data [5-7].

CPRD databases contain information of patients of all ages to provide a representative sample of UK patients with CAT.

9.2.1 Study population

The study population of interest will be adults diagnosed with active (primary or metastatic) cancer experiencing a hospitalization or emergency department admission or a primary care visit with an incident VTE, being administered rivaroxaban or other DOACs or a LMWH on or after January 1, 2013. We will identify the first record of anticoagulant therapy between day 7 and day 30 following CAT diagnosis. Subjects will need to be registered with their PCP for at least 12-months prior to the acute CAT event. Patients with cancer diagnoses and/or cancer-specific therapies including chemotherapy, radiotherapy, hormonal therapy and immunotherapy will be identified. Active cancer will be assumed to last 180 days following a cancer diagnosis or therapy recording. Active cancer episodes will be extended for 180 days from the day of the subsequent cancer-specific recording if it is recorded within the initial active cancer episode. Metastatic cancers will assumed to be active ever since first recording.

9.2.2 Study time frame

We will use CPRD GOLD and Aurum EHR data from January 1, 2013 through latest available data (currently March 2019).

- Patient identification period: The patient identification period will be restricted to January 1, 2013 through latest available data as shown in the figure above.
- Cohort entry: CAT diagnosis, hospitalization or emergency department admission or primary care visit with an incident VTE event.
- Index date: The date of first rivaroxaban (or any DOAC) or LMWH use according to registered prescription 7-30 days after CAT event (new-user design).
- Pre-index eligibility period: Patients will be required to have at least 12-months of EHR registration prior to the CAT event.
- Post-index eligibility period: There will be no minimum post-index eligibility requirement for patient identification.
- Follow-up period: There will be a minimum of 3 months and maximum 12-months follow-up period. Patients will be followed from the first recording of AC use (7-30 days after CAT event) until the end of eligibility.

9.2.3 Selection criteria

To be included in the study patients will have to:

- Be ≥18 years of age at the time of anticoagulation initiation
- Have active cancer and acute DVT and/or PE
- Treated with rivaroxaban (or any DOAC) or LMWH as their first recorded anticoagulant prescription 7 to 30 days post-acute CAT event diagnosis
- Have been active in the data set for at least 12-months prior to the index event and had at least one provider visit in the 12-months prior to the acute VTE event

We will exclude patients with:

- Evidence of atrial fibrillation, recent hip/knee replacement (with 90 days of CAT), ongoing VTE treatment, valvular heart disease defined as any rheumatic heart disease, mitral stenosis or mitral valve repair/replacement
- History of inferior vena cava filter before cohort entry
- VKA use between cohort entry and index day (initiation of DOAC or LMWH)
- Evidence of any type of therapeutic anticoagulation use during all available look-back period per written prescription or patient self-report
- Initiation of rivaroxaban or other DOACs or LMWH during the study period at non-therapeutic doses (e.g., enoxaparin at a dose other than 1 mg/kg twice daily or 1.5 mg/kg once daily; dalteparin at a dose other than 200 IU/kg of total body weight)
- Pregnancy
- Recording indicative of palliative care before cohort entry
- Any clinically-relevant bleeding-related d hospitalization or VTE recurrence between the initial CAT and the start of observation

9.2.4 Representativeness

The CPRD primary care dataset is one of the largest databases of longitudinal medical records from primary care in the world. Patients included in CPRD GOLD and Aurum are broadly representative of the UK general population in terms of age, sex and ethnicity. The CPRD is very widely used internationally for epidemiological research.

9.3 Variables

9.3.1 Exposure definition

Newly-initiated on rivaroxaban (or any DOAC) or LMWH per recorded written prescription on day 7-30 post-acute CAT event diagnosis. Patient self-report of medication use, over-the-counter medications are not registered in UK CPRD data. On-treatment analysis will be performed in the UK- CPRD databases. The vast majority of written prescriptions are filled in primary care in the UK with instructions, and we will be able to define patterns of treatment (stopping, continuous, switching, reinitiating, etc.).

Analysis at 3-, 6 and 12-months will be performed to assess the potential impact of the early anticoagulation discontinuation.

9.3.2 Outcomes definition

The study outcomes will be defined based on Read codes and ICD-9/10-CM diagnosis and procedure codes or laboratory, vital sign and other patient observation results.
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 Office of National Statistics ONS [4, 8].
A random sample of identified potential VTE recurrences and significant bleeding events will be manually reviewed by utilizing patient summaries/profiles including HES APC, HES Outpatient, ONS death registration data (DRD) and PCP recorded symptoms, signs, laboratory tests, diagnostic and therapeutic procedures, medication use, discharge diagnoses, and cause of death to confirm the that outcomes have been appropriately identified.

Primary outcomes

- The risk of recurrent VTE at 3-months
- Composite of any major bleeding or clinically-relevant non-major bleeding-related hospitalization (per the ISTH criteria [9, 10] for identification of bleeding-associated hospitalizations) at 3-months
- All-cause mortality at 3-months

Secondary outcomes

- Recurrent VTE at 6- and 12-months post-index VTE

- Composite of any major or clinically-relevant nonmajor bleeding-related hospitalization at 6- and 12-months post-index VTE, including:
    - Intracranial hemorrhage (ICH)
    - Critical organ bleeding (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial bleeding or intramuscular with compartment syndrome)
    - Extracranial bleeding-related hospitalizations (including trauma-related)
- Composite of any major bleeding or clinically-relevant non-major bleeding-related hospitalization (per the ISTH criteria [9, 10] for identification of bleeding-associated hospitalizations) at 6 and 12-months
- Intracranial hemorrhage (ICH), critical organ bleeding and extracranial bleeding-related hospitalizations as separate outcomes
- All-cause mortality at 6- and 12-months
- Incidence rates of recurrent VTE, any clinically-relevant bleeding-related hospitalization and all cause-mortality in rivaroxaban, DOAC and LMWH patients experiencing CAT regardless of the bleeding risk associated with cancer type
- Duration of anticoagulation treatment and rivaroxaban, DOAC and LMWH discontinuation rates at 3-, 6-, 12-months and all available follow-up

9.3.3 Covariate definition

Patient baseline characteristics such as age, gender, comorbidities, cancer-specific data and comedications will be collected at the index date or from the last recorded value within the baseline period. The presence of characteristics will be assessed from patients' medical and pharmacy data in the baseline period (see Annex 1).

Demographic characteristics

- Sex
- Age
- Race
- Individual DOAC or LMWH used to treat CAT
- Number of days between CAT and first recording of anticoagulation use

Clinical characteristics

- Presence of the following clinical characteristics will be assessed from patients' medical and pharmacy data in the baseline period:
    - **Comorbidities/prior history/risk scores:**
        - Number of days from January 1, 2013 to qualifying CAT diagnosis
        - Cancer type(s) present at CAT diagnosis
        - Metastatic disease at time of CAT diagnosis
        - Active/recent treatment (within 3-months pre- or post-CAT diagnosis)
            - Chemotherapy/immunotherapy
            - Radiation therapy
            - Surgical
        - Initial anticoagulation therapy on day of CAT diagnosis
        - Intracranial bleeding
        - Systemic embolism
        - Deep vein thrombosis
        - Pulmonary embolism
        - Heart failure
        - Hypertension
        - Ischemic stroke/transient ischemic attack
        - Peripheral vascular disease
        - Myocardial infarction
        - Percutaneous coronary intervention
        - Coronary artery bypass grafting
        - Any major bleed

- Major adverse limb events (need for surgical or endovascular revascularization or limb amputation)
- Gastrointestinal bleeding
- Central venous catheter
- Liver disease
- Coagulopathy
- Gastroesophageal reflux disease/heartburn
- Anemia
- Asthma
- Chronic obstructive pulmonary disease
- Sleep apnea
- Smoker
- Alcohol abuse
- Anxiety
- Depression
- Lower extremity paralysis
- Psychosis
- Osteoarthritis
- Diverticulitis
- Crohn's disease or ulcerative colitis
- Active or treated *Helicobacter pylori*
- Hypothyroidism
- Recent major surgery within 12 weeks of index event
- Dementia
- Recent trauma (with 90-days)

- Primary hypercoagulable state (e.g., activated protein C resistance, prothrombin gene mutation, antiphospholipid syndrome, lupus anticoagulant syndrome and other primary thrombophilia (per Read code; ICD-9 or -10 coding provided in Annex 1))
- Prior history of VTE
- Varicose veins
- Chronic venous insufficiency (per Read code or ICD-9 /-10 coding provided in Annex 1)
- Acute coronary syndrome
- Carotid stenosis
- Pneumonia
- Osteoporosis
- Orthopedic surgery
- Rheumatoid arthritis/collagen vascular disease
- Proteinuria
- Ischemic (coronary) heart disease
- Number of hospitalizations for any cause during the baseline period
- Vascular disease (defined as myocardial infarction, peripheral artery disease or aortic plaque
- Frailty (per specific Frailty Score)

- **Comedications**
  - Aspirin
  - P2Y12 Inhibitors
  - Other antiplatelet agents
  - NSAIDs
  - COX-2-specific NSAIDs
  - ACE inhibitors or ARBs

- β-blockers
- Diltiazem
- Verapamil
- Dihydropyridine calcium channel blockers
- Loop diuretic
- Thiazide diuretic
- Digoxin
- Amiodarone
- Dronedarone
- Other antiarrhythmic drugs
- Statins
- Other cholesterol lowering drugs
- Metformin
- Sulfonylureas or glinides
- Thiazolidinediones
- Dipeptidyl peptidase-4 inhibitors
- Glucagon-like peptide-1 agonists
- Insulin
- Benzodiazepines
- SSRIs or SNRIs
- Other antidepressants
- Proton pump inhibitors
- Histamine-2 receptor antagonists
- Systemic corticosteroids
- Exogenous estrogen therapies

- Strong CYP3A4 inhibitors (e.g., protease inhibitors, -azole antifungals)
- Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, St. John's wort)
- Chemotherapy agents (various)

- Laboratory values and vital signs at baseline
  - SBP
  - DBP
  - Hemoglobin
  - D-Dimer
  - Serum creatinine
  - Reported eGFR
  - Height
  - Weight
  - Body mass index (BMI)
  - Platelet count

9.4 Data sources

CPRD collects fully-coded patient electronic health records from GP practices using the Vision® (CPRD GOLD) or EMIS® (CPRD Aurum) software systems. Due to some differences in structure and clinical coding in these two systems, these data are provided as two separate primary care databases that can be pooled. The CPRD GOLD is a computerized primary care database containing anonymized records for more than 5.4 million active patients who are registered with participating primary care practices in the UK, which represents approximately 8% of the UK population. It contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK, also information about consultant referrals and hospitalizations, laboratory test results and diagnoses procedures (http://www.cprd.com/intro.asp). The CPRD also includes information recorded by GPs on patient demographics, lifestyle factors and detailed information on prescriptions written by the PCP.

The CPRD Aurum database contains longitudinal routinely-collected electronic health records from primary care practices in England. The database captures information on: Demographic characteristics, Diagnoses

and symptoms, prescriptions, tests, referrals to hospital and specialist care. The key strengths of CPRD Aurum are its size and coverage (complementing CPRD GOLD), longitudinal follow-up, representativeness, and standard linkages to national secondary care databases like Hospital Episode Statistics (HES) as well as deprivation and death registration data [6, 7].

CPRD data are linkable, at least partially, with other health care data sets (e.g., hospitalization -HES and national mortality data). Briefly, Hospital Episode Statistics (HES) are data collected from National Health Service (NHS) hospitals in England by the Secondary Uses Services (SUS), a programme that supports secondary care in the NHS. HES data include details of all hospital care funded by the NHS in England. It contains: admitted patient care data from 1997 onwards, outpatient attendance data from 2003 onwards and accident and Emergency (A&E) data from 2007 onwards. The full HES dataset contains more than 400 fields, although in most cases many of these are not completed by the hospital, either because they are not applicable or recording is not mandatory.

For the present study we will request linkage to different sources to obtain valid and complete information:

1.- HES Admitted Patient Care (HES APC) : Complete hospital episode information (admission and discharge dates, diagnoses (identifying primary diagnosis), specialists seen under and procedures undertaken) for each linked patient with a hospitalization record. This is necessary if we do not want to miss any study hospitalized outcome.

2.- HES Accident and Emergency (HES A&E) data of patients attending hospitals that may be further be hospitalized. From all information recorded we are specially interest in: A&E diagnosis.

3.- Death Registration data contains data from the Office for National Statistics (ONS) and includes information on the official date and causes of death (using ICD codes). This is important to ascertain potential outcomes that may not be in previous sources, but can identify patients dying from the outcome we are studying.

We will request approval to obtain the three linked data sources (HES APC, HES A&E, ONS Death registration) to ascertain all potential study outcome of interest resulting in a hospitalization or being the cause of death. On the other hand we will not request The HES Outpatient (HES OP), as data completeness is an issue in some OP fields and outpatient information may not add relevant clinical information of use for our outcome definitions.

Patients registered in CPRD database are age, sex, and geographically representative of the UK population, and has been extensively validated for use in epidemiological studies [5]. Updated, valid, linked data are available through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency

Research at the CPRD requires approval from the CPRD Independent Scientific Advisory Committee (ISAC).

The Read classification is used to code specific diagnoses [11, 12] and a drug dictionary based on data from the Gemscript classification is used to record prescriptions [13]. Currently, active patients included in CPRD-GOLD are over 3 million and the corresponding number in Aurum approximates 13 million.

9.5 Study size

Based on an incidence rate of VTE of 131.5 per 100,000 person-years and assuming that 18.6% of VTEs are associated with active cancer (1) and that 50% of patients with CAT have a recording for DOACs or LMWH within 30 days after initial VTE, we expect our cohort to include approximately 5,600 patients with CAT. Assuming a mean follow-up of 0.6 years following first CAT (according to the high mortality risk in these patients and the restriction to the first year following CAT) and incidence rates of 11.8 VTE recurrences, 14.4 significant bleeds and 80.0 deaths from any cause per 100 person-years, we expect to identify approximately 390 VTE recurrences, 480 significant bleeds and 2670 deaths from any cause within the first year after CAT. Based on the matching related fixed proportion of DOAC to LMWH users in our study cohort and the numbers mentioned above, this study would detect a significant difference between DOAC and LMWH users with 5% significance level and a power of 80% if the estimated HR is lower than 0.75, 0.77 or 0.89 respectively for VTE recurrence, serious bleeding or death from any cause. This is consistent with the HR of recurrent VTE ≤0.43 (supported by SELECT-D [14] and Costa et al. [15]) or with a more conservative HR (HR=0.71) as seen in the Hokusai VTE cancer trial for edoxaban (DOAC) compared to dalteparin (LMWH) [16].

9.6 Data management

- Raw and processed data files will be maintained by The Institute for Epidemiology, Statistics and Informatics (IfESI) on a secured network assessable server and made available only to members of IfESI's research team.
- IfESI and LIRN have developed standard definitions based on different medical and product dictionaries. All new code sets for hospital discharge diagnoses, in-hospital procedures, GP-recorded clinical diagnoses and prescribed medications and lab tests will be prepared by two physicians from

LIRN and IfESI. Existing and new code sets are reviewed for recentness, accuracy and completeness.

- Database management and analyses will be conducted using Stata 14 (StataCorp LP, College Station, Texas).

9.7 Data analysis

Baseline characteristics will be analyzed using descriptive statistics. Categorical data will be reported as percentages and continuous data as medians with accompanying 25%, 75% ranges or means ± standard deviations (SDs). Descriptive analysis will be performed for each of the three distinct cancer cohorts listed above, namely, (1) the cohort of cancer patients without gastrointestinal and genitourinary cancers, (2) the cohort defined by the ISTH CAT guidelines (in acute CAT patients without a malignant neoplasm associated with a high risk of bleeding) and (3) an all cancer type cohort.

To adjust for potential confounding between the rivaroxaban (or DOAC) and LMWH cohorts, propensity scores will be calculated using a multivariable logistic regression model. The propensity score model will include commonly used variables and accepted risk factors for differential anticoagulation exposure identified at baseline including demographics, comorbidities, laboratory values, vital signs, other clinical observations and outpatient medication use (prescription and over-the-counter). All clinical characteristics listed in section 9.3.3 of this protocol will be included in the propensity score model. Propensity scores will then be used to assign weight to individual patients in the analysis using an overlap weighting approach. Overlap weighting assigns weights to patients that are proportional to their probability of belonging to the opposite treatment cohort. By design, overlap weighting results in the exact balance of all variables included in the propensity score model. This method of adjustment retains all patients in the dataset (unlike propensity score matching) and gives less weight to patients with extreme propensity scores (which is often a concern with inverse probability weighting).

Propensity scores will be estimated based upon commonly used variables and accepted risk factors for differential anticoagulation exposure identified during the baseline period including demographics, comorbidities, laboratory and vital signs and concurrent outpatient co-medication use. All clinical characteristics listed in section 9.3.3 of this protocol will be included in the propensity score model. Given the retrospective nature of the data analysis, the presence of a comorbid disease diagnosis will be identified based upon the recording of the specific comorbid read codes. Missing data for covariates will occur when an existing co-morbidity or co-medication is not recorded in the database. In such case we will assume that the respective patient did not suffer from the respective co-morbidity/did not use the respective co-

medication. Information on time varying variables e.g. BMI and smoking status will assumed to be constant unless a different variable entry is recorded. Whenever meaningful, missing data will be presented in separate categories labelled “not stated” or "unknown". No imputation will be performed for potentially missing outcomes/endpoint data. Separate propensity score models will be fit once for the primary analysis and for each subgroup analysis.

Propensity score matching operates by taking each treated study participant and finding the closest propensity score match among controls within a calliper (or bound). Conventional IPTW assigns a weight of 1/PS for treated and 1/(1 − PS) for untreated patients, allowing individuals with underrepresented characteristics to count more in the analysis. IPTW can produce inflated variance estimates which can be addressed through a simple stabilization of weights (multiplying propensity scores of each participant by the relative proportion of the specific cohort makes up of the total study population). In observational data, in which the initial differences in treatment groups may be large, these methods can modify the target population, fail to achieve good balance or substantially worsen precision. Overlap weighting assigns weights to each patient that are proportional to the probability of that patient belonging to the opposite treatment group. Specifically, treated patients are weighted by the probability of not receiving treatment (1 − PS) and untreated patients are weighted by the probability of receiving the treatment (PS). These weights are smaller for extreme PS values so that outliers who are nearly always treated (PS near 1) or never treated (PS near 0) do not dominate results and worsen precision, as occurs with IPTW. These outliers contribute relatively less to the result, while patients whose characteristics are compatible with either treatment contribute relatively more. The resulting target population mimics the characteristics. Overlap weighting also leads to exact balance on the mean of every measured covariate when the PS is estimated by a logistic regression. Like all PS-based methods, overlap weighting cannot adjust for patient characteristics that are not measured and included in the model for the PS. When initial imbalances in patient characteristics between treatment groups are modest, overlap weighting yields similar results to IPTW. The advantages of overlap weighting are greatest when comparator groups are initially very different. To test the robustness of our conclusions to various methods for confounding adjustment, we will also perform a number of sensitivity analyses e.g. *1:1* matching based on propensity scores.

Cox proportional hazards regression is a method for investigating the effect of variables upon the time a specified event takes to happen. We will fit Cox proportional hazards regression models (with robust estimators) to compare event rates over time for the rivaroxaban (or any DOAC) and LMWH cohorts in the Xarelto SmPC and CAT guidance cancer type cohorts. As propensity score based methods will be assumed to

balance key characteristics of the treatment cohorts, the only independent variable that will be included into Cox regression model will be anticoagulant received (rivaroxaban or DOAC or LMWH). Results of Cox regression will be reported as hazard ratios (HRs) with 95% confidence intervals (CIs).
We will use an intention-to-treat approach to analyze the data in which, patients will be evaluated based on the initial anticoagulant prescription registered and will be followed until endpoint occurrence, end-of-database activity, end of data availability or end of designated follow-up time (3-, 6- or 12-months), whichever comes first. Time from treatment initiation to end of follow-up will then be considered the time at risk. On-treatment analysis (patients will be followed until endpoint occurrence, end-of-database activity, end of data availability, end of designated follow-up time (3-, 6- or 12-months), anticoagulant discontinuation or switch, whichever comes first) will be performed as a sensitivity analysis. No adjustments for multiple hypothesis testing will be performed.

Subgroup analyses

Analysis of the recurrent VTE, any clinically-relevant bleeding-related hospitalization and all-cause mortality outcomes among patients prescribed with rivaroxaban and any DOAC (apixaban, dabigatran, edoxaban, rivaroxaban) versus patients prescribed with LMWH patients for acute CAT will be performed stratifying by cancer subtypes (specific subtypes dependent on available sample sizes). To limit the number of analyses performed (and the impact of multiple hypothesis testing), subgroup analyses will only be performed on the primary effectiveness and safety endpoints (recurrent VTE, any clinically-relevant bleeding-related hospitalization and all-cause mortality).

Further descriptive analyses

We will calculate incidence rates of recurrent VTE, any clinically-relevant bleeding-related hospitalization and all-cause mortality in rivaroxaban patients experiencing CAT regardless of the cancer type and associated bleeding risk. The duration of anticoagulation treatment and discontinuation rates at 3-, 6- and 12-months follow-up will be estimated based on instructions at prescriptions filled in CPRD.

Sensitivity analyses

Various sensitivity analyses will be performed to test the robustness of our study's conclusions. A sensitivity analysis will be performed whereby patients with cancer will need to be admitted to the hospital, emergency department or observation unit for acute DVT and/or PE on or after January 1, 2013 in order to better estimate the "contemporary" comparative effectiveness and safety of the two treatment cohorts/strategies. We will perform 1:1 propensity score matching of rivaroxaban and LMWH patients and

analyze data using a proportional hazards models for the subdistribution of competing risk (competing risk model) to compare event incidences over time for the cohorts. An "on-treatment" approach (patients censored at the first event, anticoagulant discontinuation or switch or end of data availability) will also be performed as the CPRD GOLD and Aurum EHR contain prescription instructions commonly used to identify continuous anticoagulation use. Analysis at 6 and 12-months will be performed.

9.8 Quality control

- All coding (Read medical codes, SNOMED codes, OPCS, ICD-codes and product codes) will be 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 [4],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.
- A random sample of identified potential VTE recurrences and significant bleeding events will be manually reviewed by utilizing 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 the that both exposure (anticoagulant) and outcomes have been appropriately identified.

The external partners IfESI and LIRN will follow 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

9.9 Limitations of the research methods

As with any secondary data source, CPRD databases have limitations. Key limitations include:

- Misclassification of exposures can negatively impact the internal validity of observational studies.
- In general, in database analyses, the absence of information is taken as an indication of absence of the condition. Missing values may occur in a small proportion for some lifestyle habits. In this case, individuals with missing values will be kept in the analysis and a separate category will be created for missing values of that variable.
- DOAC prescriptions started in-hospital or events in the immediate post-discharge period are likely to be missed in the CPRD UK databases. This might induce some exposure misclassification that we expect to be non-differential between patients prescribed OACS and those prescribed LWMH. This might introduce some bias towards the null in study estimates. While bias towards the null is generally considered as conservative in effectiveness analyses, it is considered as anticonservative in safety analyses (tends to conclude treatment strategies are similar even if they are not). This will be taken into account when interpreting study results.
- In database analyses where randomization is not possible, such PS based methods such as weighting or matching serve to harmonize comparison groups with respect to patient characteristics. However, residual confounding caused by e.g. unmeasured factors, missing data, miscoding or tactical coding issues, etc. may be present.

- CPRD captures prescriptions recorded by the PCP, but do not capture if a patient filled their prescription and/or took it. The study is thus designed as an intention-to-treat approach, subsequent recording of anticoagulants will be evaluated to estimate time on anticoagulation treatment and discontinuation rates as exploratory outcomes.
- No adjustment for multiplicity hypothesis testing will be performed.

9.10 Other aspects

None.

10. Protection of human subjects

The study will be conducted in accordance with Good Pharmacoepidemiology Practices [17]. In this investigation we will use a medical record linkage database where the information of patients is anonymized and there is no need to obtain informed consent from patients. The study protocol is dependent on approval by the independent review of CPRD's Research Data Governance (RDG) process. CPRD protects the confidentiality of patient data implementing the following processes, as listed in their webpage [18]:

- *CPRD has ethics approval from the Health Research Authority to support research using anonymised patient data*
- *CPRD must complete an annual NHS Data Security and Protection Toolkit assessment to demonstrate that it meets the required standard for holding data securely*
- *Once CPRD receives anonymised data from a GP practice, we ensure the data is fully compliant with the Information Commissioner's Office (ICO) anonymisation code of practice and that patient privacy is protected*
- *The identity of GP practices that have contributed data is concealed*
- *The data CPRD holds can only be used for public health research*
- *Only bona fide researchers can receive the data*
- *Checks are conducted on organisations carrying out and funding the research to assess whether they are suitable to receive CPRD data*

- *Requests by researchers to access the data are reviewed via the CPRD RDG Process to ensure the research benefits public health*
- *Researchers must adhere to robust terms and conditions governing how the anonymised data is used.*

11. Management and reporting of 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 adverse events/reactions will be summarized in the study report, where applicable.

12. Plans for disseminating and communicating study results

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/ presentations at medical congresses (congresses/journals to be selected following consultation with Bayer AG) and will follow the International Committee of Medical Journal Editors guidelines.

Where applicable, this study's reporting will follow the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE) guidance.

This study will be registered at "www.clinicaltrials.gov" and in in the EU PAS register at "http://www.encepp.eu/encepp_studies/indexRegister.shtml".

13. References

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Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	Final version and date (if available)*
Read coding lists (detailed list of variables and coding)	Annex 2:"Read Codes_VTE_OSCAR_UK_cancer protocol.pdf"*24 June 2021*

Annex 2: Read codes

Read_Codes_VTE_OSCAR_UK_cancer protocol.pdf

Annex 3: Signature pages

This protocol is electronically signed in the study management system

Signature page- OS Conduct Responsible

Title	**OSCAR-UK: O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban **– U**nited **K**ingdom Cohort
Protocol version and date	V 1.0, 18 August 2021
IMPACT study number	22020
Study type / Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
EU PAS register number	NA
Medicinal product	Direct factor Xa inhibitor, B01AF01 rivaroxaban Direct acting Oral Anticoagulants (DOACs): factor Xa inhibitors: rivaroxaban, apixaban, edoxaban; factor IIa inhibitor dabigatran
Comparator	Low molecular weight heparin (LMWH) (Dalteparin, Enoxaparin, Tinzaparin)
Study Initiator and Funder	Bayer AG

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol

Printed Name: PPD

Signature, Date: PPD

Signature page- Qualified Person responsible for Pharmacovigilance (QPPV)

Title	**OSCAR-UK: O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban **– U**nited **K**ingdom Cohort
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Signature, Date: PPD

Signature page- OS Safety Lead

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Signature, Date: PPD

Signature page- OS Medical Expert

Title	**OSCAR-UK: O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban **– U**nited **K**ingdom Cohort
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Signature page- OS Medical Expert

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Study Initiator and Funder	Bayer AG

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol

Printed Name: PPD

Signature, Date: PPD

Signature page- OS Researcher, IEG

Title	**OSCAR-UK: O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban **– U**nited **K**ingdom Cohort
Protocol version and date	V 1.0, 18 August 2021
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Comparator	Low molecular weight heparin (LMWH) (Dalteparin, Enoxaparin, Tinzaparin)
Study Initiator and Funder	Bayer AG

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol

Printed Name: PPD

Signature, Date: PPD

Signature page- External OS Epidemiologist

Title	**OSCAR-UK: O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban **– U**nited **K**ingdom Cohort
Protocol version and date	V 1.0, 18 August 2021
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Comparator	Low molecular weight heparin (LMWH) (Dalteparin, Enoxaparin, Tinzaparin)
Study Initiator and Funder	Bayer AG

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol

Printed Name: PPD

Signature, Date: PPD

Signature page- External OS Statistician

Title	**OSCAR-UK: O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban **– U**nited **K**ingdom Cohort
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