Reference Number: RD-SOP-1216
Supplement Version: 3

Observational Study/Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	Observational Study of Cancer Associated Thrombosis for Rivaroxaban in SwEden (OSCAR-SE)
Report version and date	v 1.0, 12 April 2023
IMPACT study number	21616
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Registration number EUPAS43355 in the EU PAS register
Active substance	Direct factor Xa inhibitors B01AF01 rivaroxaban, B01AF02 apixaban, B01AF03 edoxaban Direct thrombin inhibitors B01AE07 dabigatran etexilate Vitamin K antagonist B01AA03 warfarin Heparins (B01AB)
Medicinal product	Rivaroxaban
Product reference	N/A
Procedure number	N/A
Comparator	Apixaban, dabigatran, edoxaban, warfarin, heparins
Study Initiator and Funder	Bayer AG, Müllerstrasse 173, 13353 Berlin
Research question and objectives	Research questions related to occurrence of VTE and treatments for VTE in patients with cancer in Sweden The objectives are: 1. To estimate the risk of recurrent VTE, major bleeding (defined as a bleeding leading to hospitalization) and all-cause mortality in individuals with cancer not

	associated with a high risk of bleeding (see Appendix 1), in Sweden 2. To describe the anticoagulation treatments for VTE including the choice of drug and duration of treatment 3. To estimate the risk of a recurrent VTE, major bleeding and all-cause mortality by type of anticoagulation treatment (LMWH, VKA or DOAC) as independent outcomes 4. To compare incidence rates of recurrent VTE, major bleeding and death in subjects treated with rivaroxaban versus LMWH; and DOACs versus LMWH
Country of study	Sweden
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Marketing authorization holder(s)	Bayer AG, Müllerstrasse 173, 13353 Berlin
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1. Abstract

Acronym/Title	Observational Studies in Cancer Associated Thrombosis for Rivaroxaban in SwEden (OSCAR-SE)
Report version and date **Author**	v 1.0, 12 April 2023 PPD Karolinska Institutet PPD Karolinska Institutet
IMPACT study number	21616
Keywords	Cancer associated thromboembolism, direct acting anticoagulants, low molecular weight heparin, major bleeding, recurrent venous thromboembolism, all-cause mortality
Rationale and background	Cancer is one of the leading causes of death globally and is known to increase the risk of Venous Thromboembolism (VTE) including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). Cancer Associated Thrombosis (CAT) is a major cause of morbidity and mortality in patients with cancer. During recent years treatment options for VTE in patients with cancer have expanded to include direct acting oral anticoagulants (DOACs) as an alternative treatment to Low Weight Molecular Heparins (LWMH) in patients with cancer after careful consideration of the risk of bleeding and possible interaction with cancer therapies. While their cancer is active, patients remain at increased risk of VTE. For reasons of convenience and route of administration, DOACs provide a less burdensome alternative to LMWH and are likely to improve adherence. However, there is a need to better understand how DOACs are used to treat VTE in patients with cancer, in particular in relation to cancer therapies, duration of use and risks of recurrent VTE events, major bleeding and death.
Research question and objectives	The research questions were to examine the occurrence of recurrent VTE, major bleeding and death; and associated treatments for VTE among subjects with cancer in Sweden. Patients with cancer with higher risk of bleeding were excluded. The objectives were: 1. To estimate the risk of recurrent VTE, major bleeding and all-cause mortality in individuals with cancer not associated with a high risk of bleeding (including upper gastrointestinal cancer, malignant immunoproliferative diseases and leukemia, see Appendix 1) in Sweden

	2. To describe the anticoagulation treatments for VTE including the choice of drug and duration of treatment 3. To estimate the risk of a recurrent VTE, major bleeding and all-cause mortality by type of anticoagulation treatment (LMWH, VKA or DOAC) as independent outcomes 4. To compare incidence rates of recurrent VTE, major bleeding and death in subjects treated with rivaroxaban versus LMWH; and DOACs versus LMWH
Study design	Cohort study
Setting	All residents in Sweden diagnosed with cancer from 2013 through 2019 were identified through the Swedish Cancer Register (SCR) and linked to other national health registers (National Patient Register [NPR], Prescribed Drug Register [PDR], Total Population Register [TPR], and Cause of Death Register [CDR]).
Subjects and study size, including dropouts	All patients diagnosed with cancer in Sweden from year 2013 to 2019 were identified. We observed 555,558 cases of cancer, of whom 12,685 had a first VTE. After applying inclusion and exclusion criteria, 8,058 individuals entered the study.
Variables and data sources	Type of cancer was identified through ICD10 codes C00-C97 (malignant neoplasms) including data on cancer stage and type at diagnosis. Baseline characteristics including demographic information as well as data on comorbidities through ICD10 codes (see Appendix 1) from hospitalizations and open care visits to specialists were collected. We obtained information on prescribed drugs through ATC codes (see Appendix 1) to capture dispensed prescriptions of DOACs, VKA and LMWH as well as other relevant medicines including cancer treatments, whenever available. ICD10 codes to identify the outcomes DVT, PE, VTE, major bleeding are presented in Appendix 1. The outcome all-cause mortality was identified from date of death registered in CDR. Data source was the Swedish health registries including the Swedish Cancer Register, the National Patient Register, the Prescribed Drug Register, and the Cause of Death Register.
Results	In total, 8,058 adult eligible individuals were recorded with cancer between 2013 and 2019 in SCR, and with CAT registered in NPR within 183 days of their cancer diagnosis. The comparative analyses included 5,737 individuals of whom 556 used DOACs and 5,181 used LMWH. Among the DOAC users, 283 used rivaroxaban.

	For recurrent VTE, the cumulative incidence proportions varied between 3.5% and 8.4%, the incidence rates varied between 54 events per 1000 person-years and 241 events per 1000 person-years. For major bleeding, the cumulative incidence proportions varied between 4.5% and 7.7%, the incidence rates varied between 24 events per 1000 person-years and 89 events per 1000 person-years, the cumulative incidence function varied between 0.8% and 6.7%. For all-cause mortality, the cumulative incidence proportions varied between 11.3% and 52.5%, the incidence rates varied between 263 events per 1000 person-years and 894 events per 1000 person-years, the cumulative incidence varied between 11.3% and 53.5%. The number of patients treated with DOACs has increased 10 times from 2013 and onwards, for LMWH the number of patients have been constant over time, approximately 750 per year. The number of patients treated with VKA has decreased from 52 patients in 2013 to 6 patients in 2019. The use of LMWH decreased from 88% at study start to 45% after 2 years. The use DOACs were mainly represented by apixaban and rivaroxaban. The use of apixaban increased from 4% at initiation to 20% after 2 years, correspondingly the use of rivaroxaban went from 5% at study start to 19% after 2 years. The duration of use of DOACs were mainly evenly distributed over the studied lengths. Rivaroxaban showed somewhat higher proportions for the longer durations, 57.9% of patients treated with rivaroxaban used it for more than 6 months, whereas 47.8% of those treated LMWH used it more than 6 months. VKAs were mostly used for a short time, less than 3 months (74%). In individuals under LMWH treatment, recurrent VTE cumulative incidence proportions varied between 3.8% and 8.7%; recurrent VTE incidence rates varied between 57 events per 1000 person-years and 228 events per 1000 person-years; and cumulative incidence functions for recurrent VTE varied between 4% and 11%. Under LMWH treatment, major bleeding cumulative incidence proportions varied between 0.9% and 4.9%; major bleeding incidence rates varied between 22 events per 1000 person-years and 95 events per 1000 person-years; and cumulative incidence functions for major bleeding varied between 0.9% and 6.8%. Under LMWH treatment, all-cause mortality cumulative incidence proportions varied between 12.2% and 56.4%; all-cause mortality incidence rates varied between 289 events per 1000 person-years and 980 events per 1000 person-years; and

	cumulative incidence functions for all-cause mortality varied between 12.2% and 57.4%. In individuals under DOAC treatment, recurrent VTE cumulative incidence proportions varied between 0.5% and 11.4%; recurrent VTE incidence rates varied between 11 events per 1000 person-years and 399 events per 1000 person-years; and cumulative incidence functions for recurrent VTE varied between 0.5% and 13%. Under DOAC treatment, major bleeding cumulative incidence proportions varied between 0.4% and 13%; major bleeding incidence rates varied between 12 events per 1000 person-years and 95 events per 1000 person-years; and cumulative incidence functions for major bleeding varied between 0.4% and 14.4%. Under DOAC treatment, all-cause mortality cumulative incidence proportions varied between 0.7% and 28%; all-cause mortality incidence rates varied between 27 events per 1000 person-years and 401 events per 1000 person-years; and cumulative incidence functions for all-cause mortality varied between 0.7% and 29.1%. In individuals under rivaroxaban treatment, recurrent VTE cumulative incidence proportions varied between 1.0% and 11.1%; recurrent VTE incidence rates varied between 11 events per 1000 person-years and 391 events per 1000 person-years; and cumulative incidence functions for recurrent VTE varied between 1% and 12%. Under rivaroxaban treatment, major bleeding cumulative incidence proportions varied between 0.5% and 10%; major bleeding incidence rates varied between 15 events per 1000 person-years and 57 events per 1000 person-years; and cumulative incidence functions for major bleeding varied between 0.5% and 11.1%. Under rivaroxaban treatment, all-cause mortality cumulative incidence proportions varied between 1.3% and 24%; all-cause mortality incidence rates varied between 26 events per 1000 person-years and 265 events per 1000 person-years; and cumulative incidence functions for all-cause mortality varied between 1.3% and 25.4%. Incidence rates of bleeding or recurrent VTE comparing DOACs and LMWH were similar, all hazards ratios were close to one. For the comparison of all-cause mortality between DOACs and LMWH all results were statistically significant favoring DOACs. A similar pattern was found comparing rivaroxaban with LMWH, all hazards ratios were close to one except for all-cause mortality favoring rivaroxaban.
Discussion	Results indicate that DOACs and rivaroxaban was associated with similar risks of major bleeding and recurrent VTE as

	LMWH. The all-cause mortality was lower in patients treated with DOACs and rivaroxaban as compared to LMWH, worth noting a likely effect of residual confounding why results for all-cause mortality should be interpreted with caution. We conclude that rivaroxaban may serve as alternative to LMWH in treating patients with cancer-associated thrombosis.
Marketing Authorization Holder(s)	Bayer AG, Müllerstrasse 173, 13353 Berlin

2. List of abbreviations

APX	Apixaban
ATC	Anatomical Therapeutic Chemical (Classification System)
CAT	Cancer Associated Thrombosis
CDR	Cause of Death Register
CI	Confidence Interval
CIF	Cumulative Incidence Function
CIP	Cumulative Incidence Proportion
DBG	Dabigatran
DEGURBA	Degree of Urbanization
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
EDX	Edoxaban
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
IR	Incidence Rate
ITT	Intention To Treat
LMWH	Low Molecular Weight Heparin
MAH	Marketing Authorization Holder
N/A	Not Applicable
NE	Not Estimable
NPR	National Patient Register
OAC	Oral Anticoagulant
OS	Observational Study
OT	On Treatment
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PDR	Prescribed Drug Register

PE	Pulmonary Embolism
PY	Person-Years
RCT	Randomized Clinical Trial
REF	Reference
RVX	Rivaroxaban
SAP	Statistical Analysis Plan
SCR	Swedish Cancer Register
STROBE	Strengthening The Reporting Of Observational Studies In Epidemiology
TNM	Tumor (T), Nodes (N), and Metastases (M)
TPR	Total Population Register
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WHO	World Health Organization

3. Investigators

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4. Other responsible parties

4.1 Study Team (internal or external)

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Role: PPD (internal)

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Role: PPD (external)

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Role: PPD
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Role: PPD (external)
Name: PPD

Contact details of the responsible parties are available upon request.

5. Milestones

Milestone	Planned date	Actual Date	Comments
Study start	September 2021	15 November 2021	None
Completion of the analysis	February 2022	October 2022	None
Registration in the EU PAS register	October 2021	19 November 2021	None
Final report of study results	August 2022	April 2023	None

6. Rationale and background

Cancer is the second leading cause of death globally, accounting for about 9.6 million deaths in 2018 according to WHO [1]. Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a serious complication and a leading cause of death in patients with cancer [2]. Whether or not the long-term mortality is increased in case of survival the initial VTE is less clear [3]. Risk of VTE is 4- to 7-fold higher in patients with cancer compared to the general population [4]. This corresponds to an incidence rate ranging between 2 to 12 cases per 100 person-years [5]. The pathogenesis of VTE in cancer is complex and multifactorial, including general prothrombotic factors, process induced by malignant cells, and cancer- as well as therapy-related factors [6, 7]. The risk of recurrent events is also increased in patients with cancer as well as the risk of major bleeding when treated with antithrombotic and cancer specific treatments.

Cancer is a complex group of several diseases and treatment choices are many depending on the mix of cells stage of each individual cancer and patient preference in therapeutic choices. The occurrence of VTE in cancer complicates several anti-cancer treatments, for example chemotherapy because of increased risk of bleeding via a potential drug-drug interaction effect [8]. For thromboprophylaxis, an individual assessment to identify patients with cancer at high risk of VTE who may benefit the most is recommended [9]. Individual considerations depending on the type of tumor and individual patient risk profile must be considered when treating individuals with cancer.

The recommended treatments of VTE in patients with cancer have changed recently. Low molecular weight heparin (LMWH) used to be the standard of care for VTE for short-term treatment and Vitamin K Antagonists (VKA) for long-term treatment [8, 10, 11]. However, VKA introduces serious potential problems for patients with cancer including risks of drug interactions, malnutrition, vomiting, kidney and liver dysfunction and chemotherapy-induced thrombocytopenia, consequently potentially resulting in suboptimal anticoagulation treatment and may even be harmful for the patient [12]. In addition, RCTs found that warfarin was associated with an increase in the composite

of major bleeding or recurrent VTE, as well as an increase in mortality as compared to LMWH in a 3-months treatment trial; and an increase in recurrent VTE and no statistically significant difference in major bleeding in a trial with 6-months treatment period. Although meta-analyses confirmed the role of LMWH in both the initial anticoagulation period and in the long-term, in reality the patient adherence was low in long-term treatment studies [12].

In more recent studies, rivaroxaban, edoxaban and apixaban have been associated with decreased recurrence of VTE, but with increased occurrence of major bleeding as compared to LMWH in randomized trials for 6-month and up to 12-month treatment periods in patients with cancer [13-17]. Patients with gastrointestinal cancers have been reported to be at increased risk of major bleeding [14, 15]. Rivaroxaban, apixaban and edoxaban are DOACs recommended as alternatives to LMWH in patients with cancer with an acute diagnosis of VTE and a low risk of bleeding considering also possible interactions with current cancer therapy [8, 10, 11]. A shared decision-making with patients is recommended, considering the potential lower risk of recurrences associated with DOACs but higher bleeding risk as compared to LMWH, according to the guideline [18]. Additionally, patient convenience and preference attributes are likely to play important roles in patient treatment adherence and therapeutic effectiveness.

The duration of anticoagulation treatment in patients with cancer remain an open question. Most RCTs have evaluated a maximum duration of 6 months after an acute thrombotic event. A minimum of 6 months treatment period is recommended and even longer treatment duration when risk factors of VTE recurrence are present [10, 19]. Preventing VTE recurrence must be balanced versus increased risk of major bleeding during anticoagulation therapy. A recent meta-analysis of all observational studies found that treatment duration was longer for DOACs than for LMWH which may support the idea that administration of DOACs may result in better patient adherence in particular for extended treatment duration [20].

Previous studies on all cancer have observed estimates of recurrent VTE ranging from 1% to 8.9% for studies with 3 months follow-up time and 4.0% to 13.2% for studies with 6-month follow-up time, according to the authors [21]. A recent meta-analysis of six observational studies investigating recurrent VTE in patients with cancer (all sites) treated with rivaroxaban found an average cumulative incidence for 6 months (most studies) to be 4.2% (95% confidence interval 4.1%-26.2%) [22].

One strength with the current study is the population-based design covering all recorded cases of cancer in Sweden during a specified time period, allowing estimation of an overall risk of recurrent VTE in patients with cancer suffering from VTE, as well as allowing restricted analysis to certain common cancer sites, such as breast cancer in women and prostate cancer in men. This study also constitutes the basis for examinations of the risk of recurrent VTE in other common cancers of sufficient sample size.

The present study examined the incidence of VTE recurrence and treatment practices in patients diagnosed with cancer and VTE based on data from available registries in Sweden through record-linkage by the unique person identification number.

7. Research question and objectives

7.1 Primary objective

The main objectives are:

1. To estimate the risk of the independent outcomes recurrent VTE, major bleeding and all-cause mortality in individuals with cancer not associated with a high risk of bleeding (including upper gastrointestinal cancer, malignant immunoproliferative diseases and leukemia, see Appendix 1) in Sweden
2. To describe the anticoagulation treatments for VTE including the choice of drug and duration of treatment
3. To estimate the risk of a recurrent VTE, major bleeding and all-cause mortality by type of anticoagulation treatment (LMWH, VKA or DOAC) as three independent outcomes
4. To compare incidence rates of the independent outcomes recurrent VTE, major bleeding and all-cause mortality in patients treated with rivaroxaban versus LMWH; and DOACs versus LMWH

8. Amendments and updates

None

9. Research methods

9.1 Study design

This study was designed as a cohort study based on available data sources in Sweden. All individuals with a diagnosis of cancer associated thrombosis (CAT) defined as VTE within 6 months of date of cancer diagnosis was identified and followed until date of recurrent VTE event, bleeding or death, or end of follow-up. The first VTE after the cancer diagnosis was the index event. The date of the index VTE determined the index date, which is used as start of the follow-up time.

The 15-year lookback prior to the index date was referred to as the baseline period, used for identification of covariates. In general, comorbidities were searched for within 15 years before the index date and comedications were searched for within 1 year before the index date.

9.2 Setting

All residents in Sweden diagnosed with cancer at any time during the time period from 2013 through 2019 was identified through the national Swedish Cancer Register (SCR) and linked to other national health registers (National Patient Register [NPR], Prescribed Drug Register [PDR], Total Population Register [TPR], and Cause of Death Register [CDR]).

9.3 Subjects

The study population included in this study is nationally representative for all residents in Sweden.

9.3.1 Inclusion criteria

All adult patients with database coverage and with a cancer diagnosis recorded in SCR followed by a VTE diagnosis recorded in NPR (in- or outpatient) was included in the study through the following inclusion criteria.

- a resident in Sweden of 18+ years of age
- a Swedish Person Identification Number
- a diagnosis of cancer ((ICD10 = C00-C97) in the Swedish Cancer Register during 2013-2019
- a diagnosis of VTE within 6 months following the cancer diagnosis date

9.3.2 Exclusion criteria

Patients with probable other indication than VTE, already treated with OACs or with a cancer associated with elevated risk of bleeding was excluded through the following exclusion criteria.

- a diagnosis of atrial fibrillation, total hip or knee replacement or acute coronary syndrome (for evaluation of treatment patterns) before the date of VTE diagnosis
- a dispensed prescription for any OAC before the date of VTE diagnosis
- a cancer diagnosis associated with high bleeding risk, including upper gastrointestinal cancer, malignant immunoproliferative diseases and leukemia (see Appendix 1)

9.4 Variables

9.4.1 Exposure definition

A filled prescription of any anticoagulant (low molecular weight heparin, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, or vitamin K antagonist) from a Swedish pharmacy defined the exposure. Patients were classified to the type of anticoagulant(s) dispensed during the first four weeks after the index CAT date. Duration of an individual prescription was based on all dispensed prescriptions any time after index CAT using information on pack size and the numbers of packs dispensed. An episode of use was defined by summing the lengths of individual consecutive prescriptions including a defined grace period of 14 days. The focus in this study was on the first continuous episode of anticoagulant use. Exposure duration was classified into ≤3 months, >3 to 6 months, >6 to 9 months and >9 months irrespective of anticoagulant type.

9.4.2 Outcomes definition

Three different outcomes were investigated, i.e. recurrent VTE, major bleeding, and all-cause mortality.

The recurrent VTE outcome was defined as a diagnosis of DVT or PE (See Appendix 1) recorded as main diagnosis at discharge from hospital, based on the National Patient Register.

Major bleeding was defined as a diagnosis of intracranial, gastrointestinal, urogenital or other bleeding (See Appendix 1) recorded as a main diagnosis at discharge from hospital based on the National Patient Register.

All-cause mortality was retrieved from the Cause of Death Register.

9.4.3 Case validation

Cases of recurrent VTE and major bleedings defined from the Patient register and deaths from the Cause of Death register were not individually validated in this study. Several validation studies of the Swedish registries have been performed previously [23-26]. Death is a hard outcome with good accuracy, several systems are interlinked to ascertain accuracy. Major bleeding defined as being hospitalized with main diagnosis has been evaluated in a validation study with convincing accuracy [26]. The accuracy in VTE diagnosis is likely to vary depending on if the diagnosis is DVT or PE, the latter is more accurate [25]. It is also likely to vary by geographical area in Sweden driven by the presence of physicians with special interest in VTE. The results from a small study in northern Sweden indicated that the predictive value was relatively low, especially for DVT [25].

9.4.4 Covariate definition

The study cohort of patients with cancer who had experienced an index CAT was described at baseline. The variables displayed were age (at index CAT), baseline comorbidities defined as a diagnosis from the National Patient register (look-back of 15 years up until date of CAT) as well as concomitant medications defined by filled prescriptions from the Prescribed Drug register (look-back of 1 year before CAT). Comorbidities of interest are cancer, cardiovascular disease (myocardial infarction, coronary artery disease, peripheral artery disease, diabetes mellitus, hyperlipidemia, and major bleeding). The medications of interest are antiplatelet drugs, anticoagulants, antihypertensive drugs, statins, anti-diabetic agents, non-steroidal anti-inflammatory drugs, oral steroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, antidepressants, and antipsychotic drugs.

Aggregated Tumor, Nodes, and Metastases (TNM) score was calculated from TNM staging and grading, where T denotes size and extent of the tumor, N denotes number of nearby lymph nodes affected, and M denotes presence of metastases. For simplicity, the maximum grading/staging over dimensions was chosen. For values of TNM, see Dimension.

Table 1: Description of the TNM staging and grading system for cancer

Dimension	Value	Meaning
T	TX	Cannot be measured
	T0	Cannot be found
	T1, T2, T3,	Size and/or extent
N	NX	Cannot be measured
	N0	No lymph node involvement
	N1, N2, N3	Number of lymph nodes
M	MX	Metastasis cannot be
	M0	No metastases
	M1	Metastases

Combinations containing only missing values and/or TX, NX, MX were classified as missing. Combinations containing only missing values and/or TX, NX, MX, T0, N0, M0 with at least one zero were classified as severity 0 (undetermined). Combinations containing only missing values and/or TX, NX, MX, T0, N0, M0, T1, N1, M1 with at least one '1' were classified as severity 1 (small tumor). Combinations containing T2 and/or N2 were classified as severity 2 (medium tumor). Combinations containing T3 and/or N3 were classified as severity 3 (larger tumor). Combinations containing T4 were classified as severity 4 (big tumor).

9.5 Data sources and measurement

This is a record-linkage study containing information from national Swedish health registries covering 10 million inhabitants, the entire population in Sweden. These registries are owned and governed by the National Board of Health and Welfare. For all individuals with cancer information was linked from the sources described below.

Reporting to the Swedish Cancer Register is mandatory in Sweden and captures all incident primary tumors diagnosed in Sweden since 1958. The National Patient Register contains data on all hospitalizations as well as open care visits to specialists, this register has a national coverage since 1987. The Prescribed Drug Register includes information on all prescribed drugs dispensed from pharmacies. The start of PDR was July 1, 2005. The Cause of Death Register holds information on date and causes of death, including underlying as well as up to 30 contributory causes of death.

An ethical application was submitted to the national ethical committee. Similarly, a scientific application was submitted to the national board of health and welfare asking for permission to obtain the necessary record linkages and release of data from named sources. All analyses was conducted on pseudo-anonymized individual data.

9.6 Bias

Results from observational, non-interventional studies are at risk of bias and likely to be affected by confounding factors. This section describes how bias was addressed in the statistical analysis.

Confounding is present when one or more factors influence both the outcome of interest and the exposure under study. As a consequence of this, instead of observing the direct effect of the exposure on the outcome, the resulting effect will be conflated by the presence of confounders. Therefore, analysis of observational studies must adjust for the presence of confounding.

Bias can be defined as an error in the collection, analysis or information leading to results or conclusions that are systematically different from the truth.

Propensity score overlap weighting was used to control for confounding in the analysis [27]. For each patient, the propensity score is the probability of receiving treatment given the observed covariates. The overlap weighting method assigns statistical weights to observations and creates a pseudo-population with exact balance in the mean of the variables used for adjustment, focus on the patients with most overlap in the observed covariates, and minimizes the variance of the estimated treatment effect.

Another source of error originates from misclassification. Two main types are misclassification of exposure, i.e. drugs used, as well as of outcomes, i.e. bleedings or recurrent VTE. Misclassification of study drug (LMWH, DOAC or rivaroxaban) is likely non-existent or minimal since the exposure is based on filled prescriptions from pharmacies, where electronic recording from prescriptions take place. Though treatments administered in hospital as requisitioned drugs are not covered by the Swedish national health registers. Misclassification of study outcomes will exist to some extent, mainly because many physicians are involved in assigning diagnoses in routine health care. To minimize this source of bias, the study outcomes were restricted to diagnoses registered at discharge after hospitalization, thus restricted to clinically relevant disease states. Another source affecting the classification of bleedings are the fact that the National Board of Health and Welfare has truncated the fourth digit of ICD-codes for gastrointestinal diagnoses meaning we cannot distinguish if a perforation or a bleeding took place for a gastrointestinal bleeding, thus the study is somewhat over-

recording gastrointestinal bleeding. The misclassification of gastrointestinal bleedings most likely resulted in reduced specificity, i.e. some patients would falsely have been classified as having a bleed. Since the misclassification of gastrointestinal bleedings is likely to be independent of drug, and if hypothetically rivaroxaban was truly associated with an increased risk of gastrointestinal bleeding as compared to LMWH, the over-recording would have led to hazards ratios closer to unity for gastrointestinal bleeding, but only marginally impacted results for major bleeding in total.

9.7 Study size

All persons with cancer not associated with a high risk of bleeding (per section 6.1 of the Xarelto® SmPC and international treatment guidelines, see Appendix 1) in Sweden and a CAT diagnosis during 2013-2019, and thereby fulfilling the inclusion criteria were included in the study (see section 9.3).

9.8 Data transformation

The data files released from the national board of health and welfare and all documentation including study protocol, ethics committee approval, national board of health and welfare approval, computer programs and all related other documentation was kept at the Centre for Pharmacoepidemiology accessed only by staff involved in the study. All material was archived for at least 10 years.

9.9 Statistical methods

9.9.1 Descriptive analyses

Baseline characteristics was reported using descriptive statistics. These characteristics cover demographics, comorbidities, concomitant medications as well as details of the primary cancer, including type and aggregated TNM.

9.9.2 Analysis of exposure

The anticoagulation treatment (section 9.3.1) initiated after index CAT was summarized. The number and proportion of patients was presented as well as the duration of initial therapy. Subsequent changes of the anticoagulation treatment was presented similarly (i.e. 2nd treatment, 3rd treatment, etc.). Sankey plots visualized the paths of treatment. The follow-up ended at the date of recurrent VTE, bleeding, death, emigration, or end of follow-up, whichever comes first.

9.9.3 Analysis of outcomes

The cumulative incidence function was computed for each of the outcomes

- recurrent VTE
- major bleeding
- all-cause mortality.

It was summarized for 3, 6, 12, and 24 months after index CAT together with corresponding 95% confidence intervals.

The incidence rate and 95% Poisson confidence intervals was calculated for the same time points. It is the number of cases of a specific outcome divided by the person-years of observation.

In general, the follow-up time will end at the date of a certain outcome of interest, death, emigration, or end of follow-up, whichever comes first. For all-cause mortality death is the outcome, but for recurrent VTE and major bleeding individuals are censored at death.

The cumulative incidence proportions as well as the incidence rates was presented overall, by subgroups and types of initial anticoagulation treatment.

For the latter, two types of analyses was applied. First, similar to an intention-to-treat analysis, patients was followed regardless of whether they were still treated with the anticoagulation they started on. Second, an analysis censoring follow-up time at the end of supply or switch to another anticoagulation therapy, in addition to date of a certain outcome of interest, emigration, death or end of follow-up, whichever came first.

9.9.4 Time to event analysis

The comparisons of the independent outcomes recurrent VTE, major bleeding, and all-cause mortality between treatment groups applied propensity score (PS) overlap weights [28]. 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). The propensity score model included all variables presented in section 9.7.1. Propensity score models was set up independently of each other for both planned comparisons, rivaroxaban vs LMWH, and DOAC vs LMWH.

Subsequently, Cox proportional hazards regression models was applied to compare time to event for the outcomes of interest between treatment groups. Overlap weight was incorporated in the regression models, robust variance estimate was applied. As propensity score-based methods are assumed to balance key characteristics of the treatment cohorts, the only independent variable that was included into the Cox regression models was anticoagulant received. As before, an intention-to-treat as well as a censored follow-up approach was applied.

A patient is considered as censored if the outcome of interest has not been observed by time of death, emigration, or end of follow-up, whichever comes first. To note, a patient will not be censored at time of death when outcome “all-cause mortality” is evaluated.

As a further sensitivity analysis, death was considered as a competing risk for the outcomes recurrent VTE and major bleeding. Cumulative incidences and Fine-Gray regressions [29] was computed using the PS overlap weights.

9.9.5 Main summary measures

Cumulative incidence (incidence proportion), incidence rates, cumulative incidence function, and hazard ratios.

9.9.6 Main statistical methods

Propensity score modelling via logistic regression and computation of overlap weights. Overlap weighted Cox proportional hazard and Fine-Gray regression. Kaplan-Meier survivor function.

9.9.7 Missing values

It is assumed that general demographic information is complete for all patients. Sex and age are guaranteed to be complete since these are a part of the unique personal identification number. If information on a particular confounding variable was provided, patients was coded as not having the

factor if there were no evidence for its presence (i.e., values for confounder variables was coded as '0' rather than 'missing' if data on that confounder was not observed). Missing data were not imputed but could be allocated to a missing category. Specifically, no imputation was performed for potentially missing outcomes/endpoint data.

9.9.8 Sensitivity analyses

As part of sensitivity analysis of the competing risk of death on recurrent VTE and major bleeding, the sub-hazard ratios between treatment groups was estimated with Fine-Gray regression. As with Cox regression, overlapping weights was used for the adjustment.

9.9.9 Amendments to the statistical analysis plan

None

9.10 Quality control

All study relevant information, such as documents, data sets, computer scripts, was archived at the Centre for PharmacoEpidemiology, Karolinska Institutet according to local requirements, considering possible audits and inspections from the sponsor or local authorities. Study relevant information will also be archived at Bayer (see Data Management section).

10. Results

Below all objectives described in the protocol and the statistical analysis plan are addressed.

10.1 Participants

In total, 8,058 adult individuals recorded with cancer between 2013 and 2019 in SCR, and with a subsequent CAT registered in NPR within 183 days of their cancer diagnosis were included and followed up until 2020. Individuals with database coverage less than 183 days, aged less than 18 years, with excluding diagnoses, with excluding treatments or with high bleeding risk cancer types were excluded.

For the comparative analyses, also individuals not dispensing DOAC or LMWH within 28 days of their index CAT were excluded, resulting in 5,737 included individuals of whom 556 used DOACs and 5,181 used LMWH. Among the DOAC users, 283 used rivaroxaban. Thus, 25.5% (n=2056) of patients did not fill a prescription of anticoagulation within 28 days after being discharged from hospital.

See Figure 1 for a flowchart illustrating the identification of the study population.

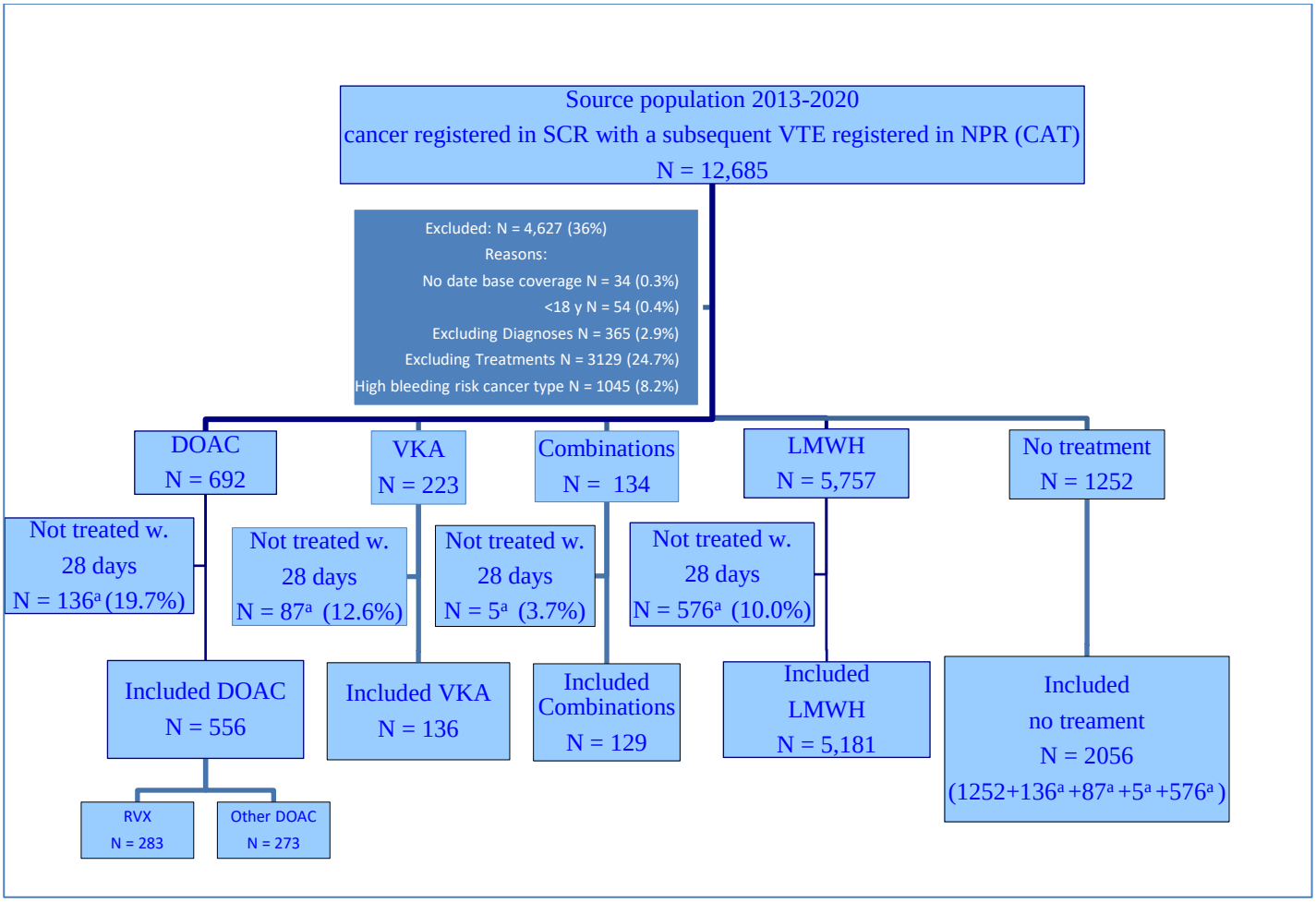

Figure 1. ***Flowchart of patient selection***
a = individuals filling their prescription later than 28 days after diagnosis are included in the no treatment group.

The proportion of patients 65 years or older varied between 66% and 86%, with a higher proportion of elderly treated with VKA and a lower proportion of elderly treated with LMWH. The proportion of females varied between 41% and 57%, with a lower proportion of females treated with VKA and a higher proportion of females treated with LMWH. The proportion of included patients varied over study years, with more DOAC treated included late, and less VKA treated included late, whereas the inclusion of LMWH users were relatively constant over time. The majority of index CATs were PE, varying between 55% (LMWH) and 65% (VKA). Overall, the predominant cancer sites were digestive organs (29%), respiratory and intrathoracic organs (18%) and breast (10%). For DOAC and VKA, also male genital organs were commonly included, 18% and 24%, respectively. For elementary baseline characteristics see Table 2, for further baseline characteristics see Appendix 3, Table 1 and Table 2.

Table 2. Baseline characteristics by observed treatment, frequency (proportion), before exclusion on treatment, ISTH cancers only, treatment within 28 days after index CAT.

Variable	Value	Total	DOAC	RVX[a]	LMWH	VKA	COMBO[b]	NONE[c]
Total number		**8058**	**556**	**283**	**5181**	**136**	**129**	**2056**

Variable	Value	Total	DOAC	RVX[a]	LMWH	VKA	COMBO[b]	NONE[c]
Age at index date	<65	2475 (31%)	152 (27%)	78 (28%)	1739 (34%)	19 (14%)	39 (30%)	526 (26%)
	>=65	5583 (69%)	404 (73%)	205 (72%)	3442 (66%)	117 (86%)	90 (70%)	1530 (74%)
Sex	Female	4448 (55%)	282 (51%)	137 (48%)	2952 (57%)	56 (41%)	49 (38%)	1109 (54%)
	Male	3610 (45%)	274 (49%)	146 (52%)	2229 (43%)	80 (59%)	80 (62%)	947 (46%)
Inclusion year	2013	1187 (15%)	12 (2%)	12 (4%)	766 (15%)	52 (38%)	47 (36%)	310 (15%)
	2014	1171 (15%)	46 (8%)	40 (14%)	744 (14%)	36 (26%)	35 (27%)	310 (15%)
	2015	1145 (14%)	77 (14%)	49 (17%)	746 (14%)	18 (13%)	18 (14%)	286 (14%)
	2016	1163 (14%)	79 (14%)	37 (13%)	753 (15%)	12 (9%)	12 (9%)	307 (15%)
	2017	1186 (15%)	118 (21%)	56 (20%)	746 (14%)	5 (4%)	4 (3%)	313 (15%)
	2018	1190 (15%)	122 (22%)	50 (18%)	769 (15%)	7 (5%)	7 (5%)	285 (14%)
	2019	1016 (13%)	102 (18%)	39 (14%)	657 (13%)	6 (4%)	6 (5%)	245 (12%)
Type of index CAT	DVT	3066 (38%)	200 (36%)	102 (36%)	2122 (41%)	39 (29%)	54 (42%)	651 (32%)
	PE	4585 (57%)	333 (60%)	171 (60%)	2828 (55%)	89 (65%)	69 (53%)	1266 (62%)
	Both	407 (5%)	23 (4%)	10 (4%)	231 (4%)	8 (6%)	6 (5%)	139 (7%)
Cancer type	Oral Cavity and Pharynx	120 (1%)	8 (1%)	2 (0.7%)	67 (1%)	3 (2%)	5 (4%)	37 (2%)
	Digestive Organs	2324 (29%)	103 (19%)	52 (18%)	1561 (30%)	30 (22%)	17 (13%)	613 (30%)
	Respiratory and Intrathoracic Organs	1456 (18%)	41 (7%)	14 (5%)	946 (18%)	11 (8%)	14 (11%)	444 (22%)
	Bone and Articular Cartilage	18 (0.2%)	1 (0.2%)	0 (0%)	11 (0.2%)	0 (0%)	0 (0%)	6 (0.3%)
	Malignant Melanoma	162 (2%)	51 (9%)	37 (13%)	51 (1%)	9 (7%)	11 (9%)	40 (2%)
	Mesothelial and Soft Tissue	82 (1%)	5 (0.9%)	2 (0.7%)	57 (1%)	0 (0%)	0 (0%)	20 (1%)
	Breast	808 (10%)	67 (12%)	30 (11%)	606 (12%)	15 (11%)	15 (12%)	105 (5%)
	Female Genital Organs	551 (7%)	33 (6%)	14 (5%)	382 (7%)	5 (4%)	5 (4%)	126 (6%)
	Male Genital Organs	553 (7%)	100 (18%)	58 (20%)	265 (5%)	32 (24%)	28 (22%)	128 (6%)
	Urinary Tract	485 (6%)	38 (7%)	17 (6%)	321 (6%)	8 (6%)	10 (8%)	108 (5%)
	Eye, Brain and Other Parts of Central Nervous System	550 (7%)	51 (9%)	27 (10%)	350 (7%)	12 (9%)	10 (8%)	127 (6%)
	Thyroid and Other Endocrine Glands	69 (0.9%)	16 (3%)	11 (4%)	30 (0.6%)	3 (2%)	4 (3%)	16 (0.8%)
	Ill-Defined, Secondary and Unspecified	344 (4%)	3 (0.5%)	1 (0.4%)	188 (4%)	3 (2%)	3 (2%)	147 (7%)

Variable	Value	Total	DOAC	RVX[a]	LMWH	VKA	COMBO[b]	NONE[c]
	Lymphoid, Hematopoietic and Related Tissue	536 (7%)	39 (7%)	18 (6%)	346 (7%)	5 (4%)	7 (5%)	139 (7%)

a = Rivaroxaban (RVX) is a DOAC and included in the total only once
b = Combinations (COMBO), i.e., dispensing of more than one class on the same date, will be excluded from comparative analyses. The exact combinations are given in the table below.
c = No treatment (NONE) means none of DOAC, VKA or LMWH, or no dispensing of ATC-code beginning with B01

Extra table 1: Exact combinations purchased at the same date. Data lacks information on instructions to the patient, i.e. there is no information on how the different drugs are supposed to be used.

Drugs dispensed at same date	Frequency	Percent
Apixaban + Dalteparin	3	2.33
Apixaban + Tinzaparin	3	2.33
Dabigatran + Dalteparin	3	2.33
Dabigatran + Enoxaparin	2	1.55
Dalteparin + Edoxaban	1	0.78
Dalteparin + Rivaroxaban	2	1.55
Dalteparin + Warfarin	67	51.94
Enoxaparin + Warfarin	7	5.43
Rivaroxaban + Tinzaparin	1	0.78
Tinzaparin + Warfarin	40	31.01
Total	129	100

10.2 Risk of recurrent VTE, major bleeding and all-cause mortality

Objective #1 to estimate the risk of the independent outcomes recurrent VTE (Table 3), major bleeding (Table 4) and all-cause mortality (Table 5) in individuals with cancer (excluding lip, upper GI, NMSC, lymphomas and leukemia cancers) in Sweden was addressed by calculating overall cumulative incidence proportions, incidence rates and cumulative incidence functions by different subgroups and time windows, detailed results are given in Appendix 3, Table 3 to 5. Individuals who started one study treatment (LMWH, DOAC or VKA) within 4 weeks after CAT within the study period were included, in total 5,873 patients.

For recurrent VTE, the cumulative incidence proportions varied between 3.5% for DVT at 0-3 months and 8.4% for PE at 0-24 months (Table 3). The incidence rates for recurrent VTE varied between 54 events per 1000 person-years for DVT at 0-24 months and 241 events per 1000 person-years for PE at 0-3 months. For all patients and for all subgroups, incidence rates of recurrent VTE showed a decreasing trend over accumulating follow-up time. The cumulative incidence function for recurrent VTE varied between 3.7% for DVT at 0-3 months and 10.8% for PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time. See Table 3, for additional subgroup incidences see Appendix 3, Table 3.

Table 3. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for recurrent VTE.

Subgroup	Value	Time (month)	Cumulative incidence (CI)	N events	T person-time (years)	Incidence rates (CI) per 1000 PY	Cumulative Incidence Function (%) [a] (CI)
Overall		0-3	4.5 (4.0-5.1)	264	1279	206.4 (182.3-232.9)	4.6 (4.1-5.2)
		0-6	5.1 (4.5-5.7)	298	2349	126.9 (112.9-142.1)	5.4 (4.8-6.0)
		0-12	6.4 (5.7-7.0)	373	4165	89.5 (80.7-99.1)	7.3 (6.6-8.0)

Subgroup	Value	Time (month)	Cumulative incidence (CI)	N events	T person-time (years)	Incidence rates (CI) per 1000 PY	Cumulative Incidence Function (%) [a] (CI)
		0-24	7.7 (7.0-8.4)	450	6933	64.9 (59.1-71.2)	9.8 (8.9-10.7)
Age	<65 years	0-3	4.4 (3.5-5.4)	84	431	195.0 (155.5-241.4)	4.5 (3.7-5.6)
		0-6	5.0 (4.0-6.0)	95	808	117.6 (95.1-143.7)	5.2 (4.3-6.3)
		0-12	6.2 (5.1-7.4)	118	1470	80.3 (66.5-96.2)	6.8 (5.7-8.1)
		0-24	7.5 (6.4-8.8)	144	2528	57.0 (48.0-67.1)	9.0 (7.7-10.5)
	>=65 years	0-3	4.5 (3.9-5.2)	180	848	212.2 (182.4-245.6)	4.7 (4.1-5.4)
		0-6	5.1 (4.5-5.9)	203	1540	131.8 (114.3-151.2)	5.5 (4.8-6.3)
		0-12	6.4 (5.7-7.2)	255	2696	94.6 (83.3-106.9)	7.5 (6.7-8.5)
		0-24	7.7 (6.9-8.6)	306	4405	69.5 (61.9-77.7)	10.2 (9.2-11.5)
Sex	Female	0-3	4.3 (3.6-5.1)	142	720	197.2 (166.1-232.5)	4.4 (3.8-5.2)
		0-6	4.9 (4.2-5.7)	161	1328	121.2 (103.2-141.5)	5.2 (4.4-6.0)
		0-12	6.2 (5.4-7.1)	205	2371	86.5 (75.0-99.2)	7.1 (6.2-8.1)
		0-24	7.4 (6.5-8.3)	243	3971	61.2 (53.7-69.4)	9.3 (8.2-10.5)
	Male	0-3	4.7 (3.9-5.6)	122	559	218.3 (181.2-260.6)	4.9 (4.1-5.8)
		0-6	5.3 (4.5-6.2)	137	1021	134.2 (112.7-158.7)	5.7 (4.8-6.7)
		0-12	6.5 (5.6-7.5)	168	1795	93.6 (80.0-108.9)	7.5 (6.5-8.7)
		0-24	8.0 (7.0-9.1)	207	2962	69.9 (60.7-80.1)	10.5 (9.1-12.0)
Type of index CAT	DVT	0-3	3.5 (2.8-4.3)	82	518	158.4 (126.0-196.6)	3.7 (3.0-4.5)
		0-6	4.4 (3.6-5.3)	103	950	108.4 (88.5-131.5)	4.8 (4.0-5.8)
		0-12	5.6 (4.7-6.6)	132	1697	77.8 (65.1-92.3)	6.6 (5.6-7.8)
		0-24	6.6 (5.6-7.6)	155	2866	54.1 (45.9-63.3)	8.5 (7.2-9.9)
	PE	0-3	5.2 (4.5-6.1)	170	705	241.2 (206.3-280.4)	5.4 (4.6-6.2)
		0-6	5.6 (4.8-6.4)	181	1295	139.8 (120.2-161.7)	5.8 (5.0-6.7)
		0-12	6.8 (6.0-7.7)	221	2283	96.8 (84.4-110.4)	7.6 (6.7-8.7)
		0-24	8.4 (7.5-9.4)	273	3756	72.7 (64.3-81.8)	10.8 (9.6-12.1)
	DVT+PE	0-3	4.6 (2.4-7.9)	12	57	212.4 (109.7-371.0)	4.6 (2.6-7.9)
		0-6	5.3 (3.0-8.8)	14	104	135.0 (73.8-226.6)	5.5 (3.3-9.2)
		0-12	7.6 (4.7-11.5)	20	185	108.0 (66.0-166.8)	8.9 (5.8-13.5)
		0-24	8.4 (5.3-12.4)	22	310	71.0 (44.5-107.5)	10.2 (6.8-15.2)

a = Cumulative incidence function estimated with the Kaplan-Meier method

Table 4 presents the results for major bleeding, the cumulative incidence proportions for all subjects varied between 4.5% at 0-3 months and 7.7% for 0-24 months follow-up. The cumulative incidence varied across the subgroups, surprisingly little by age and gender, and more markedly higher for PE as compared to DVT. All cumulative incidence proportions showed an increasing trend over accumulating time. The incidence rates for major bleeding varied between 24 events per 1000 person-years for age below 65 years at 0-24 months and 89 events per 1000 person-years for PE at 0-3 months. All incidence rates, except for DVT+PE, showed a decreasing trend over accumulating time. The cumulative incidence function for major bleeding varied between 0.8% for DVT+PE at 0-3 months and 6.7% for PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time. See Table 4, for additional subgroup incidences see Appendix 3, Table 4.

Table 4. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for major bleeding.

Subgroup	Value	Time (month)	Cumulative incidence (CI)	N events	T person-time (years)	Incidence rates (CI) per 1000 PY	Cumulative Incidence Function (%) [a] (CI)
Overall		0-3	1.7 (1.4-2.1)	101	1314	76.9 (62.6-93.4)	1.9 (1.5-2.2)
		0-6	2.6 (2.2-3.0)	152	2414	63.0 (53.4-73.8)	3.0 (2.5-3.5)
		0-12	3.4 (3.0-3.9)	200	4289	46.6 (40.4-53.6)	4.2 (3.6-4.8)
		0-24	4.2 (3.7-4.8)	247	7145	34.6 (30.4-39.2)	5.7 (5.0-6.5)
Age	<65 years	0-3	1.3 (0.8-1.9)	24	442	54.3 (34.8-80.7)	1.3 (0.9-2.0)
		0-6	1.8 (1.3-2.5)	35	834	42.0 (29.2-58.3)	2.0 (1.4-2.8)
		0-12	2.7 (2.0-3.6)	52	1525	34.1 (25.5-44.7)	3.2 (2.4-4.2)
		0-24	3.3 (2.5-4.2)	63	2628	24.0 (18.4-30.7)	4.1 (3.2-5.3)
	>=65 years	0-3	1.9 (1.5-2.4)	77	871	88.4 (69.7-110.4)	2.1 (1.7-2.6)
		0-6	3.0 (2.4-3.5)	117	1579	74.1 (61.3-88.8)	3.5 (2.9-4.1)
		0-12	3.7 (3.2-4.4)	148	2764	53.5 (45.3-62.9)	4.7 (4.0-5.5)
		0-24	4.6 (4.0-5.3)	184	4518	40.7 (35.1-47.1)	6.6 (5.7-7.6)
Sex	Female	0-3	1.7 (1.3-2.2)	56	739	75.8 (57.2-98.4)	1.8 (1.4-2.4)
		0-6	2.5 (2.0-3.1)	82	1363	60.2 (47.8-74.7)	2.8 (2.3-3.5)
		0-12	3.4 (2.8-4.0)	111	2436	45.6 (37.5-54.9)	4.1 (3.4-4.9)
		0-24	4.2 (3.5-4.9)	137	4079	33.6 (28.2-39.7)	5.5 (4.7-6.5)
	Male	0-3	1.7 (1.3-2.3)	45	575	78.3 (57.1-104.8)	1.9 (1.4-2.5)
		0-6	2.7 (2.1-3.4)	70	1051	66.6 (51.9-84.2)	3.2 (2.5-4.0)
		0-12	3.4 (2.8-4.2)	89	1852	48.0 (38.6-59.1)	4.3 (3.5-5.3)
		0-24	4.3 (3.5-5.1)	110	3067	35.9 (29.5-43.2)	6.0 (4.9-7.2)
Type of index CAT	DVT	0-3	1.4 (1.0-2.0)	34	528	64.4 (44.6-90.0)	1.6 (1.1-2.2)
		0-6	1.9 (1.4-2.5)	45	972	46.3 (33.8-61.9)	2.2 (1.6-2.9)
		0-12	2.7 (2.1-3.4)	63	1742	36.2 (27.8-46.3)	3.3 (2.6-4.2)
		0-24	3.3 (2.6-4.1)	78	2945	26.5 (20.9-33.1)	4.5 (3.6-5.6)
	PE	0-3	2.0 (1.5-2.5)	65	727	89.4 (69.0-113.9)	2.1 (1.7-2.7)
		0-6	3.2 (2.6-3.9)	104	1334	78.0 (63.7-94.5)	3.7 (3.0-4.4)
		0-12	4.0 (3.4-4.7)	130	2354	55.2 (46.1-65.6)	4.9 (4.1-5.7)
		0-24	4.9 (4.2-5.7)	160	3880	41.2 (35.1-48.1)	6.7 (5.7-7.8)
	Both	0-3	0.8 (0.1-2.7)	2	59	34.1 (4.1-123.3)	0.8 (0.2-3.1)
		0-6	1.1 (0.2-3.3)	3	108	27.8 (5.7-81.4)	1.3 (0.4-3.9)
		0-12	2.7 (1.1-5.4)	7	193	36.4 (14.6-74.9)	3.5 (1.7-7.4)
		0-24	3.4 (1.6-6.4)	9	320	28.1 (12.8-53.3)	5.0 (2.6-9.4)

a = Cumulative incidence function estimated with the Kaplan-Meier method

Table 5 presents results for all-cause mortality, the cumulative incidence proportions varied between 11.3% for age below 65 years at 0-3 months and 52.5% for age 65 years and older at 0-24 months. All cumulative incidence proportions showed an increasing trend over accumulating time. The incidence rates for all-cause mortality varied between 263 events per 1000 person-years for age below 65 years at 0-24 months and 894 events per 1000 person-years for age 65 years or older at 0-3 months. All incidence rates showed a decreasing trend over accumulating time. The cumulative incidence function

for all-cause mortality varied between 11.3% for age below 65 years at 0-3 months and 53.5% for age 65 years and older at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time. See Table 5, for additional subgroup incidences see Appendix 3, Table 5.

Table 5. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for all-cause mortality.

Subgroup	Value	Time (month)	Cumulative incidence (CI)	N events	T person -time (years)	Incidence rates (CI) per 1000 PY	Cumulative Incidence Function (%) [a] (CI)
Overall		0-3	17.1 (16.1-18.0)	1002	1325	756.0 (709.9-804.3)	17.1 (16.1-18.0)
		0-6	27.2 (26.1-28.3)	1597	2448	652.5 (620.8-685.3)	27.2 (26.1-28.4)
		0-12	38.1 (36.8-39.3)	2235	4372	511.2 (490.3-532.9)	38.1 (36.9-39.4)
		0-24	47.4 (46.1-48.7)	2784	7323	380.2 (366.2-394.6)	48.3 (47.1-49.7)
Age	<65 years	0-3	11.3 (9.9-12.8)	215	445	482.6 (420.3-551.6)	11.3 (9.9-12.8)
		0-6	19.8 (18.1-21.7)	379	843	449.7 (405.6-497.3)	19.8 (18.1-21.7)
		0-12	28.8 (26.8-30.9)	550	1546	355.8 (326.6-386.8)	28.8 (26.9-30.9)
		0-24	36.8 (34.6-39.0)	702	2673	262.6 (243.5-282.7)	37.6 (35.4-39.8)
	>=65 years	0-3	19.9 (18.6-21.1)	787	880	894.4 (833.0-959.1)	19.9 (18.7-21.1)
		0-6	30.7 (29.3-32.2)	1218	1605	758.9 (716.9-802.8)	30.7 (29.3-32.2)
		0-12	42.5 (41.0-44.1)	1685	2826	596.3 (568.2-625.5)	42.6 (41.1-44.1)
		0-24	52.5 (51.0-54.1)	2082	4650	447.8 (428.8-467.4)	53.5 (52.0-55.1)
Sex	Female	0-3	16.2 (14.9-17.5)	532	746	713.0 (653.7-776.2)	16.2 (15.0-17.5)
		0-6	25.8 (24.3-27.3)	848	1383	613.3 (572.7-656.0)	25.8 (24.3-27.3)
		0-12	36.1 (34.5-37.8)	1189	2485	478.5 (451.7-506.5)	36.2 (34.6-37.9)
		0-24	45.3 (43.6-47.0)	1491	4189	355.9 (338.1-374.4)	46.3 (44.5-48.0)
	Male	0-3	18.2 (16.7-19.7)	470	579	811.3 (739.6-888.1)	18.2 (16.8-19.7)
		0-6	29.0 (27.3-30.8)	749	1065	703.3 (653.9-755.6)	29.0 (27.3-30.8)
		0-12	40.5 (38.6-42.4)	1046	1887	554.4 (521.3-589.0)	40.5 (38.7-42.5)
		0-24	50.1 (48.1-52.0)	1293	3134	412.6 (390.4-435.7)	51.0 (49.1-53.0)
Type of index CAT	DVT	0-3	17.5 (16.0-19.1)	413	531	778.3 (705.0-857.1)	17.5 (16.0-19.1)
		0-6	26.7 (24.9-28.5)	630	981	642.2 (593.1-694.4)	26.7 (25.0-28.5)
		0-12	36.6 (34.6-38.6)	864	1764	489.8 (457.7-523.6)	36.7 (34.7-38.6)
		0-24	45.5 (43.5-47.5)	1074	2992	359.0 (337.8-381.1)	46.4 (44.3-48.4)
	PE	0-3	16.7 (15.4-18.0)	543	736	737.9 (677.2-802.7)	16.7 (15.5-18.0)
		0-6	27.6 (26.0-29.1)	896	1358	659.8 (617.3-704.5)	27.6 (26.1-29.1)
		0-12	39.2 (37.5-40.9)	1274	2412	528.1 (499.5-557.9)	39.3 (37.6-41.0)
		0-24	48.9 (47.1-50.6)	1588	4002	396.8 (377.6-416.9)	49.9 (48.1-51.6)
	Both	0-3	17.6 (13.2-22.7)	46	59	780.1 (571.1-1040.6)	17.6 (13.5-22.7)
		0-6	27.1 (21.8-32.9)	71	109	652.8 (509.8-823.4)	27.1 (22.1-32.9)
		0-12	37.0 (31.2-43.2)	97	196	496.1 (402.3-605.1)	37.0 (31.5-43.2)
		0-24	46.6 (40.4-52.8)	122	330	370.2 (307.5-442.1)	47.4 (41.5-53.8)

a = Cumulative incidence function estimated with the Kaplan-Meier method

Anticoagulation treatments for index CAT

As presented in Figure 1, as many as 2056 (25.5%) of 8058 patients did not fill a prescription of anticoagulation within 28 days after being discharged from hospital.

Objective #2 to describe the anticoagulation treatments for CAT including the choice of drug and duration of treatment was addressed by calculating numbers and proportions of patients in different treatment groups at given timepoints, and by tabulating duration of treatment by treatment group using the On-Treatment exposure definition.

The use of LMWH decreased from 88% at study start to 45% after 2 years. The use DOACs were mainly represented by apixaban and rivaroxaban (Table 6). The use of apixaban increased from 4% at initiation to 20% after 2 years, correspondingly rivaroxaban increased from 5% at study start to 19% after 2 years. Dispensing of more than one substance is not allowed at inclusion, but throughout the study between 3% and 6% of the study participants dispense more than one drug class (LMWH+VKA, LMWH+DOAC, DOAC+VKA) and/or different DOACs on the same date. See Table 6, and Appendix 3, Table 6 and Figure 1.

Table 6. Number (proportion) of patients in different treatment groups at given timepoints using treatment episodes constructed from all recorded dispensings.

Time (mon)	Total	LMWH	DOAC[a]	APX	DBG	EDX	RVX	VKA[b]	LMWH +VKA[a]	DOAC+ LMWH[a]	DOAC +VKA[a]
0	5873	5181 (88.2%)		245 (4.2%)	14 (0.2%)	14 (0.2%)	283 (4.8%)	136 (2.3%)			
3	5479	4487 (81.9%)	33 (0.6%)	259 (4.7%)	12 (0.2%)	21 (0.4%)	278 (5.1%)	150 (2.7%)	40 (0.7%)	197 (3.6%)	2 (0.0%)
6	4489	3471 (77.3%)	63 (1.4%)	268 (6.0%)	14 (0.3%)	26 (0.6%)	289 (6.4%)	157 (3.5%)	20 (0.4%)	177 (3.9%)	4 (0.1%)
12	2113	1359 (64.3%)	40 (1.9%)	231 (10.9%)	17 (0.8%)	21 (1.0%)	231 (10.9%)	141 (6.7%)	5 (0.2%)	66 (3.1%)	2 (0.1%)
24	884	400 (45.2%)	11 (1.2%)	173 (19.6%)	14 (1.6%)	15 (1.7%)	168 (19.0%)	84 (9.5%)	5 (0.6%)	11 (1.2%)	3 (0.3%)

APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban
a = dispenses different groups on same date. At overlaps DOACs are summed
b = not included in comparative analyses

In Table 7 the duration of first continuous treatment episode is shown. The duration of use of DOACs were mainly evenly distributed over the studied lengths 0-3, 3-6, 6-9 and more than 9 months with some skewness towards shorter use of less than 3 months (28%). Rivaroxaban showed somewhat higher proportions for the longer durations 6-9 months (27%) and more than 9 months (31%). Use of LMWH was either short, less than 3 months (31%), or long, more than 9 months (31%). VKAs were mostly used for a short time, less than 3 months (74%). See Table 7 and Appendix 3, Table 7.

Table 7. Duration of treatment by treatment group using OT definition, i.e. stop at switch or end of supply. Each patient contributes to one row, illustrating the distribution of durations within each class of drugs.

Duration	Total	DOAC	RVX[a]	LMWH	VKA
<=3 months	1874 (31.9%)	155 (27.9%)	57 (20.1%)	1619 (31.2%)	100 (73.5%)
>3 to 6 months	1239 (21.1%)	130 (23.4%)	62 (21.9%)	1085 (20.9%)	24 (17.6%)
>6 to 9 months	1035 (17.6%)	141 (25.4%)	77 (27.2%)	888 (17.1%)	6 (4.4%)
>9 months	1725 (29.4%)	130 (23.4%)	87 (30.7%)	1589 (30.7%)	6 (4.4%)

a=Rivaroxaban is a DOAC, included in the total only once

10.3 Risk of recurrent VTE, major bleeding and all-cause mortality by type of anticoagulation treatment

Objective #3 to estimate the risk of a recurrent VTE, major bleeding and all-cause mortality by type of anticoagulation treatment (LMWH, VKA or DOAC) as three independent outcomes was addressed by calculating cumulative incidence proportions, incidence rates and cumulative incidence functions by different subgroups and time windows, by treatment under ITT and OT exposure. An overview of the results under ITT exposure is given below in Table 7. The results for the OT exposure definition were similar, see Appendix 3, where also detailed results for both exposure definitions are given.

Table 8 shows recurrent VTE under DOAC treatment, the cumulative incidence proportions varied between 0.5% for index DVT at 0-3 months and 11.4% for index PE at 0-24 months. All cumulative incidence proportions showed an increasing trend over accumulating time, except for age less than 65 years and index DVT where there were no new events in the time-window 3-6 months and index DVT+PE where all events (n=2) happened in the time-window 0-3 months. The incidence rates for recurrent VTE varied between 11 events per 1000 person-years for DVT at 0-6 months and 399 events per 1000 person-years for DVT+PE at 0-3 months. All incidence rates showed a decreasing trend over accumulating time, except for DVT where the smallest incidence rate was observed at 0-6 months. The cumulative incidence function for recurrent VTE varied between 0.5% for DVT at 0-3 months and 13% for PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time, except for age less than 65 years and DVT where there were no new events in the time-window 3-6 months and DVT+PE where all events (n=2) happened in the time-window 0-3 months.

For recurrent VTE under LMWH treatment, the cumulative incidence proportions varied between 3.8% for DVT at 0-3 months and 8.7% for DVT+PE at 0-24 months. All cumulative incidence proportions showed an increasing trend over accumulating time. The incidence rates for recurrent VTE varied between 57 events per 1000 person-years for age below 65 years at 0-24 months and 228 events per 1000 person-years for PE at 0-3 months. All incidence rates showed a decreasing trend over accumulating time. The cumulative incidence function for recurrent VTE varied between 4.0% for DVT at 0-3 months and 11.0% for DVT+PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time. See Table 8, for additional subgroup incidences see Appendix 3, Table 8.

Table 8. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for recurrent VTE by treatment ITT exposure for DOAC and LMWH.

		DOAC					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
Overall	0-3	25	127	4.5 (2.9-6.6)	196.6 (127.2-290.2)	4.5 (3.1-6.7)	230	1121	4.4 (3.9-5.0)	205.2 (179.5-233.5)	4.6 (4.1-5.2)
	0-6	27	246	4.9 (3.2-7.0)	109.8 (72.3-159.7)	4.9 (3.4-7.1)	262	2043	5.1 (4.5-5.7)	128.3 (113.2-144.8)	5.4 (4.8-6.1)
	0-12	35	466	6.3 (4.4-8.6)	75.2 (52.4-104.6)	6.6 (4.8-9.1)	328	3583	6.3 (5.7-7.0)	91.5 (81.9-102.0)	7.4 (6.6-8.2)
	0-24	45	818	8.1 (6.0-10.7)	55.0 (40.1-73.6)	9.1 (6.9-12.1)	393	5896	7.6 (6.9-8.3)	66.7 (60.2-73.6)	9.9 (9.0-10.9)
Age <65 y	0-3	9	35	5.9 (2.7-10.9)	253.6 (115.9-481.4)	5.9 (3.1-11.1)	74	391	4.3 (3.4-5.3)	189.2 (148.6-237.6)	4.4 (3.5-5.5)
	0-6	9	70	5.9 (2.7-10.9)	128.1 (58.6-243.2)	5.9 (3.1-11.1)	85	729	4.9 (3.9-6.0)	116.5 (93.1-144.1)	5.2 (4.2-6.3)

		DOAC					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
	0-12	12	136	7.9 (4.1-13.4)	88.4 (45.7-154.4)	8.0 (4.6-13.6)	104	1317	6.0 (4.9-7.2)	79.0 (64.5-95.7)	6.6 (5.5-8.0)
	0-24	13	243	8.6 (4.6-14.2)	53.6 (28.5-91.6)	8.7 (5.1-14.5)	128	2254	7.4 (6.2-8.7)	56.8 (47.4-67.5)	8.9 (7.5-10.6)
Age ≥65 y	0-3	16	92	4.0 (2.3-6.4)	174.5 (99.7-283.4)	4.0 (2.5-6.5)	156	730	4.5 (3.9-5.3)	213.7 (181.5-250.0)	4.7 (4.0-5.5)
	0-6	18	176	4.5 (2.7-7.0)	102.5 (60.7-161.9)	4.6 (2.9-7.2)	177	1313	5.1 (4.4-5.9)	134.8 (115.6-156.1)	5.5 (4.8-6.4)
	0-12	23	330	5.7 (3.6-8.4)	69.7 (44.2-104.7)	6.1 (4.1-9.0)	224	2266	6.5 (5.7-7.4)	98.9 (86.3-112.7)	7.8 (6.9-8.9)
	0-24	32	576	7.9 (5.5-11.0)	55.6 (38.0-78.5)	9.4 (6.7-13.1)	265	3642	7.7 (6.8-8.6)	72.8 (64.3-82.1)	10.5 (9.3-11.9)
Female	0-3	14	64	5.0 (2.7-8.2)	219.6 (120.1-368.5)	5.0 (3.0-8.3)	124	644	4.2 (3.5-5.0)	192.6 (160.2-229.7)	4.3 (3.6-5.1)
	0-6	15	124	5.3 (3.0-8.6)	120.7 (67.5-199.0)	5.4 (3.3-8.8)	142	1180	4.8 (4.1-5.6)	120.4 (101.4-141.9)	5.1 (4.4-6.0)
	0-12	19	237	6.7 (4.1-10.3)	80.1 (48.2-125.0)	7.0 (4.5-10.8)	181	2088	6.1 (5.3-7.1)	86.7 (74.5-100.3)	7.1 (6.1-8.2)
	0-24	22	416	7.8 (5.0-11.6)	52.9 (33.1-80.1)	8.5 (5.6-12.6)	215	3471	7.3 (6.4-8.3)	61.9 (53.9-70.8)	9.3 (8.2-10.7)
Male	0-3	11	63	4.0 (2.0-7.1)	173.4 (86.6-310.3)	4.1 (2.3-7.2)	106	477	4.8 (3.9-5.7)	222.1 (181.8-268.6)	5.0 (4.1-6.0)
	0-6	12	122	4.4 (2.3-7.5)	98.7 (51.0-172.3)	4.5 (2.6-7.8)	120	863	5.4 (4.5-6.4)	139.0 (115.3-166.3)	5.8 (4.9-6.9)
	0-12	16	228	5.8 (3.4-9.3)	70.1 (40.1-113.8)	6.2 (3.8-9.9)	147	1495	6.6 (5.6-7.7)	98.3 (83.1-115.6)	7.8 (6.6-9.1)
	0-24	23	402	8.4 (5.4-12.3)	57.2 (36.3-85.8)	9.8 (6.6-14.4)	178	2425	8.0 (6.9-9.2)	73.4 (63.0-85.0)	10.8 (9.3-12.5)
Index DVT	0-3	1	47	0.5 (0.0-2.8)	21.1 (0.5-117.4)	0.5 (0.1-3.5)	81	461	3.8 (3.0-4.7)	175.8 (139.6-218.4)	4.0 (3.3-5.0)
	0-6	1	93	0.5 (0.0-2.8)	10.8 (0.3-60.0)	0.5 (0.1-3.5)	102	838	4.8 (3.9-5.8)	121.7 (99.2-147.7)	5.3 (4.4-6.5)
	0-12	3	179	1.5 (0.3-4.3)	16.8 (3.5-49.1)	1.6 (0.5-5.0)	128	1482	6.0 (5.1-7.1)	86.4 (72.1-102.7)	7.3 (6.1-8.6)
	0-24	5	322	2.5 (0.8-5.7)	15.5 (5.0-36.2)	2.9 (1.2-7.0)	149	2474	7.0 (6.0-8.2)	60.2 (50.9-70.7)	9.2 (7.8-10.8)
Index PE	0-3	22	75	6.6 (4.2-9.8)	294.5 (184.6-445.9)	6.7 (4.5-10.0)	139	611	4.9 (4.1-5.8)	227.6 (191.4-268.8)	5.0 (4.3-5.9)
	0-6	24	143	7.2 (4.7-10.5)	167.7 (107.5-249.6)	7.4 (5.0-10.8)	148	1115	5.2 (4.4-6.1)	132.8 (112.3-156.0)	5.5 (4.7-6.4)
	0-12	30	267	9.0 (6.2-12.6)	112.2 (75.7-160.2)	9.5 (6.7-13.3)	182	1943	6.4 (5.6-7.4)	93.7 (80.5-108.3)	7.3 (6.3-8.4)
	0-24	38	460	11.4 (8.2-15.3)	82.6 (58.4-113.4)	13.0 (9.6-17.6)	224	3162	7.9 (7.0-9.0)	70.8 (61.9-80.8)	10.4 (9.1-11.9)
Index DVT + PE	0-3	2	5	8.7 (1.1-28.0)	399.0 (48.3-1441.2)	8.7 (2.2-30.5)	10	50	4.3 (2.1-7.8)	202.0 (96.8-371.4)	4.3 (2.4-7.9)
	0-6	2	10	8.7 (1.1-28.0)	201.2 (24.4-726.7)	8.7 (2.2-30.5)	12	90	5.2 (2.7-8.9)	133.6 (69.1-233.4)	5.5 (3.1-9.4)
	0-12	2	20	8.7 (1.1-28.0)	102.4 (12.4-369.8)	8.7 (2.2-30.5)	18	158	7.8 (4.7-12.0)	114.1 (67.6-180.3)	9.4 (6.0-14.7)
	0-24	2	36	8.7 (1.1-28.0)	56.0 (6.8-202.2)	8.7 (2.2-30.5)	20	259	8.7 (5.4-13.1)	77.1 (47.1-119.1)	11.0 (7.2-16.8)

T Time (month)

N events
PY person-time (years)
CIP Cumulative incidence proportion
IR Incidence rates per 1000 PY
CIF Cumulative Incidence Function (%) estimated with the Kaplan-Meier method
CI Confidence Intervals
N.E. non-estimable

For recurrent VTE under rivaroxaban treatment, the cumulative incidence proportions varied between 1.0% for DVT at 0-3 months and 11.1% for PE at 0-24 months (Table 9). All cumulative incidence proportions showed an increasing trend over accumulating time, except for age below 65 years where there were no events in the time-window 3-6 months, and females and DVT where there were no events in the time window 3-12 months. The incidence rates for recurrent VTE varied between 11 events per 1000 person-years for DVT at 0-12 months and 391 events per 1000 person-years for age below 65 years at 0-3 months. All incidence rates showed a decreasing trend over accumulating time.

The cumulative incidence function for recurrent VTE varied between 1.0% for DVT at 0-3 months and 12.0% for PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time, except for age below 65 years where there were no events in the time-window 3-6 months, and females and DVT where there were no events in the time window 3-12 months. There were no events observed for DVT+PE, therefore the requested measures were non-estimable. See Table 9, for additional subgroup incidences see Appendix 3, Table 9.

Table 9. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for recurrent VTE by treatment ITT exposure for rivaroxaban and LMWH.

		Rivaroxaban					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
Overall	0-3	12	66	4.2 (2.2-7.3)	181.1 (93.6-316.3)	4.3 (2.5-7.4)	230	1121	4.4 (3.9-5.0)	205.2 (179.5-233.5)	4.6 (4.1-5.2)
	0-6	13	129	4.6 (2.5-7.7)	100.5 (53.5-171.9)	4.7 (2.7-7.9)	262	2043	5.1 (4.5-5.7)	128.3 (113.2-144.8)	5.4 (4.8-6.1)
	0-12	17	248	6.0 (3.5-9.4)	68.7 (40.0-109.9)	6.2 (3.9-9.8)	328	3583	6.3 (5.7-7.0)	91.5 (81.9-102.0)	7.4 (6.6-8.2)
	0-24	21	447	7.4 (4.7-11.1)	47.0 (29.1-71.8)	8.0 (5.3-12.0)	393	5896	7.6 (6.9-8.3)	66.7 (60.2-73.6)	9.9 (9.0-10.9)
Age <65 y	0-3	7	18	9.0 (3.7-17.6)	391.1 (157.3-805.9)	9.0 (4.4-17.9)	74	391	4.3 (3.4-5.3)	189.2 (148.6-237.6)	4.4 (3.5-5.5)
	0-6	7	35	9.0 (3.7-17.6)	198.2 (79.7-408.4)	9.0 (4.4-17.9)	85	729	4.9 (3.9-6.0)	116.5 (93.1-144.1)	5.2 (4.2-6.3)
	0-12	8	69	10.3 (4.5-19.2)	116.6 (50.3-229.7)	10.3 (5.3-19.5)	104	1317	6.0 (4.9-7.2)	79.0 (64.5-95.7)	6.6 (5.5-8.0)
	0-24	8	125	10.3 (4.5-19.2)	63.9 (27.6-126.0)	10.3 (5.3-19.5)	128	2254	7.4 (6.2-8.7)	56.8 (47.4-67.5)	8.9 (7.5-10.6)
Age ≥65 y	0-3	5	48	2.4 (0.8-5.6)	103.3 (33.6-241.2)	2.5 (1.0-5.8)	156	730	4.5 (3.9-5.3)	213.7 (181.5-250.0)	4.7 (4.0-5.5)
	0-6	6	94	2.9 (1.1-6.3)	63.8 (23.4-138.9)	3.0 (1.4-6.5)	177	1313	5.1 (4.4-5.9)	134.8 (115.6-156.1)	5.5 (4.8-6.4)
	0-12	9	179	4.4 (2.0-8.2)	50.3 (23.0-95.5)	4.6 (2.4-8.7)	224	2266	6.5 (5.7-7.4)	98.9 (86.3-112.7)	7.8 (6.9-8.9)
	0-24	13	322	6.3 (3.4-10.6)	40.4 (21.5-69.1)	7.2 (4.2-12.1)	265	3642	7.7 (6.8-8.6)	72.8 (64.3-82.1)	10.5 (9.3-11.9)
Female	0-3	4	32	2.9 (0.8-7.3)	123.3 (33.6-315.8)	2.9 (1.1-7.6)	124	644	4.2 (3.5-5.0)	192.6 (160.2-229.7)	4.3 (3.6-5.1)

		Rivaroxaban					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
	0-6	4	64	2.9 (0.8-7.3)	62.7 (17.1-160.5)	2.9 (1.1-7.6)	142	1180	4.8 (4.1-5.6)	120.4 (101.4-141.9)	5.1 (4.4-6.0)
	0-12	4	124	2.9 (0.8-7.3)	32.4 (8.8-82.9)	2.9 (1.1-7.6)	181	2088	6.1 (5.3-7.1)	86.7 (74.5-100.3)	7.1 (6.1-8.2)
	0-24	5	223	3.6 (1.2-8.3)	22.4 (7.3-52.2)	3.8 (1.6-9.0)	215	3471	7.3 (6.4-8.3)	61.9 (53.9-70.8)	9.3 (8.2-10.7)
Male	0-3	8	34	5.5 (2.4-10.5)	236.4 (102.0-465.7)	5.5 (2.8-10.8)	106	477	4.8 (3.9-5.7)	222.1 (181.8-268.6)	5.0 (4.1-6.0)
	0-6	9	65	6.2 (2.9-11.4)	137.4 (62.8-260.8)	6.3 (3.3-11.7)	120	863	5.4 (4.5-6.4)	139.0 (115.3-166.3)	5.8 (4.9-6.9)
	0-12	13	124	8.9 (4.8-14.7)	104.8 (55.8-179.2)	9.3 (5.5-15.5)	147	1495	6.6 (5.6-7.7)	98.3 (83.1-115.6)	7.8 (6.6-9.1)
	0-24	16	223	11.0 (6.4-17.2)	71.6 (40.9-116.3)	12.0 (7.5-18.9)	178	2425	8.0 (6.9-9.2)	73.4 (63.0-85.0)	10.8 (9.3-12.5)
DVT	0-3	1	25	1.0 (0.0-5.3)	40.8 (1.0-227.2)	1.0 (0.1-6.8)	81	461	3.8 (3.0-4.7)	175.8 (139.6-218.4)	4.0 (3.3-5.0)
	0-6	1	49	1.0 (0.0-5.3)	20.6 (0.5-114.7)	1.0 (0.1-6.8)	102	838	4.8 (3.9-5.8)	121.7 (99.2-147.7)	5.3 (4.4-6.5)
	0-12	1	95	1.0 (0.0-5.3)	10.5 (0.3-58.5)	1.0 (0.1-6.8)	128	1482	6.0 (5.1-7.1)	86.4 (72.1-102.7)	7.3 (6.1-8.6)
	0-24	2	179	2.0 (0.2-6.9)	11.2 (1.4-40.4)	2.2 (0.6-8.6)	149	2474	7.0 (6.0-8.2)	60.2 (50.9-70.7)	9.2 (7.8-10.8)
PE	0-3	11	39	6.4 (3.3-11.2)	280.0 (139.8-501.0)	6.5 (3.7-11.5)	139	611	4.9 (4.1-5.8)	227.6 (191.4-268.8)	5.0 (4.3-5.9)
	0-6	12	76	7.0 (3.7-11.9)	158.3 (81.8-276.5)	7.1 (4.1-12.3)	148	1115	5.2 (4.4-6.1)	132.8 (112.3-156.0)	5.5 (4.7-6.4)
	0-12	16	143	9.4 (5.4-14.7)	112.3 (64.2-182.3)	9.7 (6.1-15.4)	182	1943	6.4 (5.6-7.4)	93.7 (80.5-108.3)	7.3 (6.3-8.4)
	0-24	19	250	11.1 (6.8-16.8)	76.1 (45.8-118.9)	12.0 (7.8-18.3)	224	3162	7.9 (7.0-9.0)	70.8 (61.9-80.8)	10.4 (9.1-11.9)
DVT + PE	0-3	0	2	N.E.	N.E.	N.E.	10	50	4.3 (2.1-7.8)	202.0 (96.8-371.4)	4.3 (2.4-7.9)
	0-6	0	5	N.E.	N.E.	N.E.	12	90	5.2 (2.7-8.9)	133.6 (69.1-233.4)	5.5 (3.1-9.4)
	0-12	0	10	N.E.	N.E.	N.E.	18	158	7.8 (4.7-12.0)	114.1 (67.6-180.3)	9.4 (6.0-14.7)
	0-24	0	19	N.E.	N.E.	N.E.	20	259	8.7 (5.4-13.1)	77.1 (47.1-119.1)	11.0 (7.2-16.8)

T Time (month)
N events
PY person-time (years)
CIP Cumulative incidence proportion
IR Incidence rates per 1000 PY
CIF Cumulative Incidence Function (%) estimated with the Kaplan-Meier method
CI Confidence Intervals
N.E. non-estimable

Table 10 presents results for major bleeding under DOAC treatment, the cumulative incidence proportions varied between 0.4% for females at 0-3 months and 13.0% for DVT+PE at 0-24 months. All cumulative incidence proportions showed an increasing trend over accumulating time, except for age below 65 years where all events were observed in two time-windows 0-3 months and 6-12 months and DVT where no events were observed in the time-window 3-6 months. The incidence rates for

major bleeding under DOAC treatment varied between 12 events per 1000 person-years for age below 65 years at 0-24 months and 95 events per 1000 person-years for DVT+PE at 0-12 months. All incidence rates, except for age 65 years and older, females, DVT and PE, showed a decreasing trend over accumulating time. The cumulative incidence function for major bleeding under DOAC treatment varied between 0.4% for females at 0-3 months and 14.4% for DVT+PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time, except age below 65 years and DVT. There were no events observed for DVT+PE at 0-3 months and at 0-6 months, therefore the requested measures were non-estimable. See Table 9.

For major bleeding under LMWH treatment, the cumulative incidence proportions varied between 0.9% for DVT+PE at 0-3 months and 4.9% for PE at 0-24 months (Table 9). All cumulative incidence proportions showed an increasing trend over accumulating time. The incidence rates for major bleeding under LMWH treatment varied between 22 events per 1000 person-years for DVT+PE at 0-24 months and 95 events per 1000 person-years for age 65 years or older at 0-3 months. All incidence rates showed a decreasing trend over accumulating time. The cumulative incidence function for major bleeding under LMWH treatment varied between 0.9% for DVT+PE at 0-3 months and 6.8% for PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time. See Table 10, for additional subgroup incidences see Appendix 3, Table 10.

Table 10. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for major bleeding by treatment ITT exposure for DOAC and LMWH.

		DOAC					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
Overall	0-3	5	131	0.9 (0.3-2.1)	38.0 (12.4-88.8)	0.9 (0.4-2.2)	93	1150	1.8 (1.5-2.2)	80.9 (65.3-99.1)	1.9 (1.6-2.4)
	0-6	8	254	1.4 (0.6-2.8)	31.5 (13.6-62.0)	1.5 (0.8-3.0)	141	2096	2.7 (2.3-3.2)	67.3 (56.6-79.3)	3.2 (2.7-3.7)
	0-12	14	483	2.5 (1.4-4.2)	29.0 (15.8-48.6)	2.8 (1.7-4.7)	181	3682	3.5 (3.0-4.0)	49.2 (42.3-56.9)	4.3 (3.8-5.0)
	0-24	22	852	4.0 (2.5-5.9)	25.8 (16.2-39.1)	4.9 (3.2-7.3)	218	6063	4.2 (3.7-4.8)	36.0 (31.3-41.1)	5.8 (5.1-6.6)
Age <65 y	0-3	2	37	1.3 (0.2-4.7)	53.9 (6.5-194.5)	1.3 (0.3-5.2)	22	401	1.3 (0.8-1.9)	54.9 (34.4-83.1)	1.3 (0.9-2.0)
	0-6	2	74	1.3 (0.2-4.7)	27.2 (3.3-98.1)	1.3 (0.3-5.2)	33	752	1.9 (1.3-2.7)	43.9 (30.2-61.7)	2.1 (1.5-2.9)
	0-12	3	144	2.0 (0.4-5.7)	20.8 (4.3-60.9)	2.0 (0.7-6.1)	49	1363	2.8 (2.1-3.7)	35.9 (26.6-47.5)	3.3 (2.5-4.4)
	0-24	3	259	2.0 (0.4-5.7)	11.6 (2.4-33.9)	2.0 (0.7-6.1)	60	2334	3.5 (2.6-4.4)	25.7 (19.6-33.1)	4.4 (3.4-5.7)
Age ≥65 y	0-3	3	94	0.7 (0.2-2.2)	31.8 (6.6-93.0)	0.8 (0.2-2.4)	71	749	2.1 (1.6-2.6)	94.8 (74.0-119.5)	2.3 (1.8-2.9)
	0-6	6	180	1.5 (0.5-3.2)	33.2 (12.2-72.4)	1.6 (0.7-3.5)	108	1345	3.1 (2.6-3.8)	80.3 (65.9-97.0)	3.7 (3.1-4.5)
	0-12	11	339	2.7 (1.4-4.8)	32.4 (16.2-58.0)	3.1 (1.7-5.6)	132	2319	3.8 (3.2-4.5)	56.9 (47.6-67.5)	4.9 (4.1-5.8)
	0-24	19	593	4.7 (2.9-7.2)	32.0 (19.3-50.0)	6.1 (3.9-9.5)	158	3729	4.6 (3.9-5.3)	42.4 (36.0-49.5)	6.6 (5.6-7.7)
Female	0-3	1	67	0.4 (0.0-2.0)	15.0 (0.4-83.5)	0.4 (0.1-2.6)	53	659	1.8 (1.3-2.3)	80.4 (60.2-105.2)	1.9 (1.5-2.5)
	0-6	2	130	0.7 (0.1-2.5)	15.4 (1.9-55.6)	0.8 (0.2-3.0)	78	1208	2.6 (2.1-3.3)	64.6 (51.1-80.6)	3.0 (2.4-3.7)

		DOAC					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
	0-12	6	249	2.1 (0.8-4.6)	24.1 (8.9-52.5)	2.4 (1.1-5.3)	103	2138	3.5 (2.9-4.2)	48.2 (39.3-58.4)	4.3 (3.5-5.2)
	0-24	10	438	3.5 (1.7-6.4)	22.8 (10.9-42.0)	4.4 (2.4-8.1)	124	3549	4.2 (3.5-5.0)	34.9 (29.1-41.7)	5.6 (4.7-6.7)
Male	0-3	4	65	1.5 (0.4-3.7)	61.8 (16.8-158.3)	1.5 (0.6-4.0)	40	491	1.8 (1.3-2.4)	81.5 (58.2-111.0)	2.0 (1.5-2.7)
	0-6	6	124	2.2 (0.8-4.7)	48.3 (17.7-105.2)	2.3 (1.0-5.1)	63	889	2.8 (2.2-3.6)	70.9 (54.5-90.7)	3.4 (2.6-4.3)
	0-12	8	235	2.9 (1.3-5.7)	34.1 (14.7-67.2)	3.2 (1.6-6.3)	78	1544	3.5 (2.8-4.3)	50.5 (39.9-63.1)	4.4 (3.6-5.5)
	0-24	12	414	4.4 (2.3-7.5)	29.0 (15.0-50.6)	5.3 (3.0-9.2)	94	2514	4.2 (3.4-5.1)	37.4 (30.2-45.7)	6.1 (4.9-7.5)
DVT	0-3	2	48	1.0 (0.1-3.6)	42.1 (5.1-152.1)	1.0 (0.3-4.1)	32	471	1.5 (1.0-2.1)	68.0 (46.5-96.0)	1.7 (1.2-2.4)
	0-6	2	93	1.0 (0.1-3.6)	21.6 (2.6-77.9)	1.0 (0.3-4.1)	43	861	2.0 (1.5-2.7)	50.0 (36.2-67.3)	2.3 (1.7-3.2)
	0-12	4	179	2.0 (0.5-5.0)	22.4 (6.1-57.2)	2.2 (0.8-5.7)	59	1527	2.8 (2.1-3.6)	38.6 (29.4-49.8)	3.5 (2.7-4.5)
	0-24	5	323	2.5 (0.8-5.7)	15.5 (5.0-36.2)	2.8 (1.2-6.7)	73	2551	3.4 (2.7-4.3)	28.6 (22.4-36.0)	4.8 (3.8-6.0)
PE	0-3	3	78	0.9 (0.2-2.6)	38.2 (7.9-111.7)	0.9 (0.3-2.9)	59	628	2.1 (1.6-2.7)	93.9 (71.5-121.2)	2.2 (1.7-2.9)
	0-6	6	150	1.8 (0.7-3.9)	39.9 (14.6-86.8)	1.9 (0.9-4.2)	95	1143	3.4 (2.7-4.1)	83.1 (67.3-101.6)	3.9 (3.2-4.8)
	0-12	8	284	2.4 (1.0-4.7)	28.2 (12.2-55.6)	2.6 (1.3-5.2)	117	1992	4.1 (3.4-4.9)	58.7 (48.6-70.4)	5.1 (4.3-6.1)
	0-24	14	492	4.2 (2.3-7.0)	28.4 (15.5-47.7)	5.4 (3.2-9.1)	139	3244	4.9 (4.1-5.8)	42.9 (36.0-50.6)	6.8 (5.7-8.0)
DVT + PE	0-3	0	5	N.E.	N.E.	N.E.	2	51	0.9 (0.1-3.1)	39.1 (4.7-141.3)	0.9 (0.2-3.5)
	0-6	0	11	N.E.	N.E.	N.E.	3	93	1.3 (0.3-3.7)	32.3 (6.7-94.4)	1.5 (0.5-4.5)
	0-12	2	21	8.7 (1.1-28.0)	95.4 (11.6-344.7)	9.3 (2.4-32.4)	5	164	2.2 (0.7-5.0)	30.6 (9.9-71.3)	2.8 (1.2-6.8)
	0-24	3	37	13.0 (2.8-33.6)	80.8 (16.7-236.3)	14.4 (4.9-38.3)	6	268	2.6 (1.0-5.6)	22.4 (8.2-48.7)	3.7 (1.6-8.1)

T Time (month)
N events
PY person-time (years)
CIP Cumulative incidence proportion
IR Incidence rates per 1000 PY
CIF Cumulative Incidence Function (%) estimated with the Kaplan-Meier method
CI Confidence Intervals
N.E. non-estimable

Table 11 shows major bleeding under rivaroxaban treatment, the cumulative incidence proportions varied between 0.5% for age 65 years or older at 0-3 months and 10.0% for DVT+PE at 0-24 months. All cumulative incidence proportions, except ages 65 years or below and DVT, showed an increasing trend over accumulating time. The incidence rates for major bleeding under rivaroxaban treatment varied between 15 events per 1000 person-years for age below 65 years at 0-24 months and 57 events per 1000 person-years for males at 0-3 months. Only the incidence rates for males and DVT showed a clear decreasing trend over accumulating time. The cumulative incidence function for major

bleeding under rivaroxaban treatment varied between 0.5% for ages 65 and above at 0-3 months and 11.1% for DVT+PE at 0-24 months. All cumulative incidence functions except ages 65 years or below and DVT, showed an increasing trend over accumulating time. There were no events observed for females during the first 6 months and for DVT+PE during the first 12 months, therefore the requested measures were non-estimable. See Table 11, for additional subgroup incidences see Appendix 3, Table 11.

Table 11. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for major bleeding by treatment ITT exposure for rivaroxaban and LMWH.

		Rivaroxaban					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
Overall	0-3	2	68	0.7 (0.1-2.5)	29.4 (3.6-106.2)	0.7 (0.2-2.9)	93	1150	1.8 (1.5-2.2)	80.9 (65.3-99.1)	1.9 (1.6-2.4)
	0-6	3	133	1.1 (0.2-3.1)	22.5 (4.7-65.9)	1.1 (0.4-3.3)	141	2096	2.7 (2.3-3.2)	67.3 (56.6-79.3)	3.2 (2.7-3.7)
	0-12	6	256	2.1 (0.8-4.6)	23.5 (8.6-51.1)	2.3 (1.0-5.0)	181	3682	3.5 (3.0-4.0)	49.2 (42.3-56.9)	4.3 (3.8-5.0)
	0-24	10	460	3.5 (1.7-6.4)	21.7 (10.4-40.0)	4.2 (2.3-7.7)	218	6063	4.2 (3.7-4.8)	36.0 (31.3-41.1)	5.8 (5.1-6.6)
Age <65 y	0-3	1	19	1.3 (0.0-6.9)	52.2 (1.3-291.0)	1.3 (0.2-8.8)	22	401	1.3 (0.8-1.9)	54.9 (34.4-83.1)	1.3 (0.9-2.0)
	0-6	1	38	1.3 (0.0-6.9)	26.3 (0.7-146.4)	1.3 (0.2-8.8)	33	752	1.9 (1.3-2.7)	43.9 (30.2-61.7)	2.1 (1.5-2.9)
	0-12	2	74	2.6 (0.3-9.0)	26.9 (3.3-97.1)	2.6 (0.7-10.0)	49	1363	2.8 (2.1-3.7)	35.9 (26.6-47.5)	3.3 (2.5-4.4)
	0-24	2	135	2.6 (0.3-9.0)	14.8 (1.8-53.5)	2.6 (0.7-10.0)	60	2334	3.5 (2.6-4.4)	25.7 (19.6-33.1)	4.4 (3.4-5.7)
Age ≥65 y	0-3	1	49	0.5 (0.0-2.7)	20.5 (0.5-114.0)	0.5 (0.1-3.4)	71	749	2.1 (1.6-2.6)	94.8 (74.0-119.5)	2.3 (1.8-2.9)
	0-6	2	95	1.0 (0.1-3.5)	21.1 (2.5-76.1)	1.0 (0.3-4.0)	108	1345	3.1 (2.6-3.8)	80.3 (65.9-97.0)	3.7 (3.1-4.5)
	0-12	4	181	2.0 (0.5-4.9)	22.1 (6.0-56.5)	2.1 (0.8-5.6)	132	2319	3.8 (3.2-4.5)	56.9 (47.6-67.5)	4.9 (4.1-5.8)
	0-24	8	325	3.9 (1.7-7.5)	24.6 (10.6-48.5)	4.8 (2.4-9.5)	158	3729	4.6 (3.9-5.3)	42.4 (36.0-49.5)	6.6 (5.6-7.7)
Female	0-3	0	33	N.E.	N.E.	N.E.	53	659	1.8 (1.3-2.3)	80.4 (60.2-105.2)	1.9 (1.5-2.5)
	0-6	0	65	N.E.	N.E.	N.E.	78	1208	2.6 (2.1-3.3)	64.6 (51.1-80.6)	3.0 (2.4-3.7)
	0-12	2	126	1.5 (0.2-5.2)	15.9 (1.9-57.3)	1.6 (0.4-6.2)	103	2138	3.5 (2.9-4.2)	48.2 (39.3-58.4)	4.3 (3.5-5.2)
	0-24	4	227	2.9 (0.8-7.3)	17.6 (4.8-45.0)	3.5 (1.3-9.2)	124	3549	4.2 (3.5-5.0)	34.9 (29.1-41.7)	5.6 (4.7-6.7)
Male	0-3	2	35	1.4 (0.2-4.9)	57.4 (7.0-207.4)	1.4 (0.4-5.5)	40	491	1.8 (1.3-2.4)	81.5 (58.2-111.0)	2.0 (1.5-2.7)
	0-6	3	68	2.1 (0.4-5.9)	44.4 (9.1-129.6)	2.1 (0.7-6.5)	63	889	2.8 (2.2-3.6)	70.9 (54.5-90.7)	3.4 (2.6-4.3)
	0-12	4	130	2.7 (0.8-6.9)	30.9 (8.4-79.0)	2.9 (1.1-7.6)	78	1544	3.5 (2.8-4.3)	50.5 (39.9-63.1)	4.4 (3.6-5.5)
	0-24	6	233	4.1 (1.5-8.7)	25.8 (9.5-56.1)	4.8 (2.1-10.3)	94	2514	4.2 (3.4-5.1)	37.4 (30.2-45.7)	6.1 (4.9-7.5)

		Rivaroxaban					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
DVT	0-3	1	25	1.0 (0.0-5.3)	40.6 (1.0-226.4)	1.0 (0.1-6.8)	32	471	1.5 (1.0-2.1)	68.0 (46.5-96.0)	1.7 (1.2-2.4)
	0-6	1	49	1.0 (0.0-5.3)	20.5 (0.5-114.5)	1.0 (0.1-6.8)	43	861	2.0 (1.5-2.7)	50.0 (36.2-67.3)	2.3 (1.7-3.2)
	0-12	2	95	2.0 (0.2-6.9)	21.0 (2.5-75.9)	2.0 (0.5-7.9)	59	1527	2.8 (2.1-3.6)	38.6 (29.4-49.8)	3.5 (2.7-4.5)
	0-24	3	177	2.9 (0.6-8.4)	16.9 (3.5-49.5)	3.2 (1.0-9.6)	73	2551	3.4 (2.7-4.3)	28.6 (22.4-36.0)	4.8 (3.8-6.0)
PE	0-3	1	41	0.6 (0.0-3.2)	24.4 (0.6-136.0)	0.6 (0.1-4.3)	59	628	2.1 (1.6-2.7)	93.9 (71.5-121.2)	2.2 (1.7-2.9)
	0-6	2	79	1.2 (0.1-4.2)	25.2 (3.0-90.9)	1.2 (0.3-4.8)	95	1143	3.4 (2.7-4.1)	83.1 (67.3-101.6)	3.9 (3.2-4.8)
	0-12	4	151	2.3 (0.6-5.9)	26.5 (7.2-67.9)	2.6 (1.0-6.7)	117	1992	4.1 (3.4-4.9)	58.7 (48.6-70.4)	5.1 (4.3-6.1)
	0-24	6	265	3.5 (1.3-7.5)	22.6 (8.3-49.3)	4.4 (2.0-9.5)	139	3244	4.9 (4.1-5.8)	42.9 (36.0-50.6)	6.8 (5.7-8.0)
DVT + PE	0-3	0	2	N.E.	N.E.	N.E.	2	51	0.9 (0.1-3.1)	39.1 (4.7-141.3)	0.9 (0.2-3.5)
	0-6	0	5	N.E.	N.E.	N.E.	3	93	1.3 (0.3-3.7)	32.3 (6.7-94.4)	1.5 (0.5-4.5)
	0-12	0	10	N.E.	N.E.	N.E.	5	164	2.2 (0.7-5.0)	30.6 (9.9-71.3)	2.8 (1.2-6.8)
	0-24	1	18	10.0 (0.3-44.5)	55.4 (1.4-308.4)	11.1 (1.6-56.7)	6	268	2.6 (1.0-5.6)	22.4 (8.2-48.7)	3.7 (1.6-8.1)

T Time (month)
N events
PY person-time (years)
CIP Cumulative incidence proportion
IR Incidence rates per 1000 PY
CIF Cumulative Incidence Function (%) estimated with the Kaplan-Meier method
CI Confidence Intervals
N.E. non-estimable

Table 12 displays results for all-cause mortality under DOAC treatment, the cumulative incidence proportions varied between 0.7% for age below 65 years at 0-3 months and 28.0% for age 65 years and older at 0-24 months. All cumulative incidence proportions, except DVT+PE, showed an increasing trend over accumulating time. The incidence rates for all-cause mortality under DOAC treatment varied between 27 events per 1000 person-years for age below 65 years at 0-3 months and 401 events per 1000 person-years for age 65 years or older at 0-3 months. All incidence rates, except for age below 65 years, showed a decreasing trend over accumulating time. The cumulative incidence function for all-cause mortality under DOAC treatment varied between 0.7% for age below 65 years at 0-3 months and 29.1% for age 65 years and older at 0-24 months. All cumulative incidence functions, except DVT+PE, showed an increasing trend over accumulating time. See Table 11.

For all-cause mortality under LMWH treatment, the cumulative incidence proportions varied between 12.2% for age below 65 years at 0-3 months and 56.4% for age 65 years and older at 0-24 months. All cumulative incidence proportions showed an increasing trend over accumulating time. The incidence rates for all-cause mortality under LMWH treatment varied between 289 events per 1000 person-years for age below 65 years at 0-24 months and 980 events per 1000 person-years for

age 65 years or older at 0-3 months. All incidence rates showed a decreasing trend over accumulating time. The cumulative incidence function for all-cause mortality under LMWH treatment varied between 12.2% for age below 65 years at 0-3 months and 57.4% for age 65 years and older at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time. See Table 12, for additional subgroup incidences see Appendix 3, Table 12.

Table 12. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for all-cause mortality by treatment ITT exposure for DOAC and LMWH.

		DOAC					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
Overall	0-3	39	132	7.0 (5.0-9.5)	295.4 (210.1-403.9)	7.0 (5.2-9.5)	955	1161	18.4 (17.4-19.5)	822.7 (771.3-876.5)	18.4 (17.4-19.5)
	0-6	65	257	11.7 (9.1-14.7)	253.4 (195.6-323.0)	11.7 (9.3-14.7)	1522	2127	29.4 (28.1-30.6)	715.4 (679.9-752.3)	29.4 (28.2-30.6)
	0-12	94	490	16.9 (13.9-20.3)	191.9 (155.0-234.8)	17.0 (14.1-20.3)	2125	3757	41.0 (39.7-42.4)	565.6 (541.8-590.2)	41.1 (39.7-42.4)
	0-24	127	869	22.8 (19.4-26.6)	146.2 (121.9-174.0)	23.8 (20.4-27.7)	2628	6220	50.7 (49.4-52.1)	422.5 (406.5-439.0)	51.7 (50.3-53.0)
Age <65 y	0-3	1	37	0.7 (0.0-3.6)	26.8 (0.7-149.5)	0.7 (0.1-4.6)	213	404	12.2 (10.7-13.9)	527.7 (459.2-603.5)	12.2 (10.8-13.9)
	0-6	4	74	2.6 (0.7-6.6)	53.9 (14.7-137.9)	2.6 (1.0-6.9)	374	760	21.5 (19.6-23.5)	492.4 (443.7-544.9)	21.5 (19.7-23.5)
	0-12	9	145	5.9 (2.7-10.9)	62.0 (28.3-117.6)	5.9 (3.1-11.1)	540	1383	31.1 (28.9-33.3)	390.5 (358.3-424.9)	31.1 (29.0-33.3)
	0-24	14	261	9.2 (5.1-15.0)	53.7 (29.3-90.0)	9.6 (5.8-15.8)	686	2378	39.4 (37.1-41.8)	288.5 (267.3-310.9)	40.3 (38.0-42.6)
Age ≥65 y	0-3	38	95	9.4 (6.7-12.7)	401.0 (283.8-550.5)	9.4 (6.9-12.7)	742	757	21.6 (20.2-23.0)	979.9 (910.7-1053.1)	21.6 (20.2-23.0)
	0-6	61	182	15.1 (11.8-19.0)	334.7 (256.0-429.9)	15.1 (12.0-19.0)	1148	1368	33.4 (31.8-35.0)	839.3 (791.4-889.3)	33.4 (31.8-35.0)
	0-12	85	345	21.0 (17.2-25.3)	246.6 (197.0-305.0)	21.1 (17.4-25.4)	1585	2374	46.0 (44.4-47.7)	667.6 (635.1-701.3)	46.1 (44.5-47.8)
	0-24	113	608	28.0 (23.6-32.6)	185.9 (153.2-223.6)	29.1 (24.8-33.9)	1942	3842	56.4 (54.7-58.1)	505.4 (483.2-528.4)	57.4 (55.7-59.1)
Female	0-3	18	67	6.4 (3.8-9.9)	269.5 (159.7-425.9)	6.4 (4.1-9.9)	509	666	17.2 (15.9-18.7)	764.1 (699.2-833.5)	17.2 (15.9-18.7)
	0-6	28	130	9.9 (6.7-14.0)	214.6 (142.6-310.2)	9.9 (7.0-14.1)	814	1227	27.6 (26.0-29.2)	663.6 (618.8-710.8)	27.6 (26.0-29.2)
	0-12	44	251	15.6 (11.6-20.4)	175.5 (127.5-235.6)	15.7 (11.9-20.5)	1136	2185	38.5 (36.7-40.3)	519.9 (490.1-551.1)	38.5 (36.8-40.3)
	0-24	59	443	20.9 (16.3-26.1)	133.2 (101.4-171.8)	21.8 (17.3-27.2)	1418	3654	48.0 (46.2-49.9)	388.0 (368.1-408.8)	49.0 (47.1-50.8)
Male	0-3	21	65	7.7 (4.8-11.5)	322.0 (199.3-492.2)	7.7 (5.1-11.5)	446	495	20.0 (18.4-21.7)	901.5 (819.7-989.2)	20.0 (18.4-21.7)
	0-6	37	126	13.5 (9.7-18.1)	293.6 (206.7-404.6)	13.5 (10.0-18.1)	708	901	31.8 (29.8-33.7)	786.1 (729.2-846.2)	31.8 (29.9-33.7)
	0-12	50	239	18.2 (13.9-23.3)	209.0 (155.1-275.5)	18.3 (14.2-23.4)	989	1572	44.4 (42.3-46.5)	629.0 (590.5-669.5)	44.4 (42.4-46.5)
	0-24	68	426	24.8 (19.8-30.4)	159.7 (124.0-202.5)	25.9 (21.0-31.7)	1210	2566	54.3 (52.2-56.4)	471.6 (445.4-498.9)	55.2 (53.1-57.3)
DVT	0-3	12	48	6.0 (3.1-10.2)	251.5 (130.0-439.4)	6.0 (3.5-10.3)	400	474	18.9 (17.2-20.6)	844.8 (764.0-931.8)	18.9 (17.2-20.6)
	0-6	18	93	9.0 (5.4-13.9)	192.7 (114.2-304.5)	9.0 (5.8-13.9)	610	869	28.7 (26.8-30.7)	702.0 (647.4-760.0)	28.8 (26.9-30.7)
	0-12	27	180	13.5 (9.1-19.0)	149.8 (98.7-217.9)	13.5 (9.5-19.1)	834	1547	39.3 (37.2-41.4)	539.1 (503.1-577.0)	39.4 (37.3-41.5)
	0-24	35	327	17.5 (12.5-23.5)	106.9 (74.5-148.7)	17.9 (13.2-24.1)	1033	2594	48.7 (46.5-50.8)	398.3 (374.4-423.3)	49.6 (47.5-51.8)

		DOAC					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
PE	0-3	26	79	7.8 (5.2-11.2)	329.8 (215.5-483.3)	7.8 (5.4-11.3)	510	636	18.0 (16.6-19.5)	802.1 (734.0-874.8)	18.0 (16.7-19.5)
	0-6	46	152	13.8 (10.3-18.0)	302.2 (221.3-403.1)	13.8 (10.5-18.0)	842	1165	29.8 (28.1-31.5)	723.0 (675.0-773.6)	29.8 (28.1-31.5)
	0-12	65	288	19.5 (15.4-24.2)	225.6 (174.1-287.5)	19.6 (15.7-24.3)	1196	2044	42.3 (40.5-44.1)	585.1 (552.5-619.3)	42.3 (40.5-44.2)
	0-24	89	502	26.7 (22.0-31.8)	177.5 (142.5-218.4)	28.2 (23.5-33.6)	1478	3352	52.3 (50.4-54.1)	441.0 (418.8-464.1)	53.2 (51.3-55.1)
DVT + PE	0-3	1	5	4.3 (0.1-21.9)	182.6 (4.6-1017.5)	4.3 (0.6-27.1)	45	52	19.5 (14.6-25.2)	873.5 (637.1-1168.8)	19.5 (14.9-25.2)
	0-6	1	11	4.3 (0.1-21.9)	91.8 (2.3-511.3)	4.3 (0.6-27.1)	70	94	30.3 (24.4-36.7)	745.3 (581.0-941.6)	30.3 (24.8-36.7)
	0-12	2	21	8.7 (1.1-28.0)	93.1 (11.3-336.4)	8.7 (2.2-30.5)	95	166	41.1 (34.7-47.8)	571.7 (462.5-698.8)	41.1 (35.1-47.8)
	0-24	3	40	13.0 (2.8-33.6)	75.7 (15.6-221.1)	13.5 (4.6-36.3)	117	275	50.6 (44.0-57.3)	425.5 (351.9-510.0)	51.5 (45.2-58.2)

T Time (month)
N events
PY person-time (years)
CIP Cumulative incidence proportion
IR Incidence rates per 1000 PY
CIF Cumulative Incidence Function (%) estimated with the Kaplan-Meier method
CI Confidence Intervals
N.E. non-estimable

For all-cause mortality under rivaroxaban treatment, the cumulative incidence proportions varied between 1.3% for age below 65 years at 0-6 months and 24.0% for PE at 0-24 months (Table 12). All cumulative incidence proportions showed an increasing trend over accumulating time. The incidence rates for all-cause mortality under rivaroxaban treatment varied between 26 events per 1000 person-years for age below 65 years at 0-6 months and 265 events per 1000 person-years for age 65 years or older at 0-3 months. All incidence rates, except age below 65, females and DVT, showed a decreasing trend over accumulating time. The cumulative incidence function for all-cause mortality under rivaroxaban treatment varied between 1.3% for age below 65 years at 0-6 months and 25.4% for PE at 0-24 months. All cumulative incidence functions showed an increasing trend over accumulating time. There were no events observed for DVT+PE during 24 months and for age below 65 years during the first 3 months, therefore the requested measures were non-estimable. See Table 13, for additional subgroup incidences see Appendix 3, Table 13.

Table 13. Cumulative incidence (incidence proportion), incidence rates and cumulative incidence function by time for all-cause mortality by treatment ITT exposure for rivaroxaban and LMWH.

		rivaroxaban					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
Overall	0-3	13	68	4.6 (2.5-7.7)	190.4 (101.4-325.6)	4.6 (2.7-7.8)	955	1161	18.4 (17.4-19.5)	822.7 (771.3-876.5)	18.4 (17.4-19.5)
	0-6	21	134	7.4 (4.7-11.1)	156.7 (97.0-239.6)	7.4 (4.9-11.2)	1522	2127	29.4 (28.1-30.6)	715.4 (679.9-752.3)	29.4 (28.2-30.6)
	0-12	38	259	13.4 (9.7-18.0)	146.8 (103.9-201.5)	13.5 (10.0-18.0)	2125	3757	41.0 (39.7-42.4)	565.6 (541.8-590.2)	41.1 (39.7-42.4)
	0-24	54	468	19.1 (14.7-24.2)	115.3 (86.6-150.4)	19.9 (15.6-25.1)	2628	6220	50.7 (49.4-52.1)	422.5 (406.5-439.0)	51.7 (50.3-53.0)
Age <65 y	0-3	0	19	N.E.	N.E.	N.E.	213	404	12.2 (10.7-13.9)	527.7 (459.2-603.5)	12.2 (10.8-13.9)

		rivaroxaban					LMWH				
Group	**T**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**	**N**	**PY**	**CIP (CI)**	**IR (CI)**	**CIF (CI)**
	0-6	1	38	1.3 (0.0-6.9)	26.1 (0.7-145.2)	1.3 (0.2-8.8)	374	760	21.5 (19.6-23.5)	492.4 (443.7-544.9)	21.5 (19.7-23.5)
	0-12	5	75	6.4 (2.1-14.3)	66.3 (21.5-154.8)	6.4 (2.7-14.7)	540	1383	31.1 (28.9-33.3)	390.5 (358.3-424.9)	31.1 (29.0-33.3)
	0-24	7	137	9.0 (3.7-17.6)	51.2 (20.6-105.4)	9.3 (4.6-18.7)	686	2378	39.4 (37.1-41.8)	288.5 (267.3-310.9)	40.3 (38.0-42.6)
Age ≥65 y	0-3	13	49	6.3 (3.4-10.6)	265.0 (141.1-453.2)	6.3 (3.7-10.7)	742	757	21.6 (20.2-23.0)	979.9 (910.7-1053.1)	21.6 (20.2-23.0)
	0-6	20	96	9.8 (6.1-14.7)	209.1 (127.7-323.0)	9.8 (6.4-14.7)	1148	1368	33.4 (31.8-35.0)	839.3 (791.4-889.3)	33.4 (31.8-35.0)
	0-12	33	183	16.1 (11.3-21.9)	179.9 (123.9-252.7)	16.2 (11.8-22.0)	1585	2374	46.0 (44.4-47.7)	667.6 (635.1-701.3)	46.1 (44.5-47.8)
	0-24	47	332	22.9 (17.4-29.3)	141.7 (104.1-188.5)	23.8 (18.4-30.4)	1942	3842	56.4 (54.7-58.1)	505.4 (483.2-528.4)	57.4 (55.7-59.1)
Female	0-3	5	33	3.6 (1.2-8.3)	150.6 (48.9-351.4)	3.6 (1.5-8.5)	509	666	17.2 (15.9-18.7)	764.1 (699.2-833.5)	17.2 (15.9-18.7)
	0-6	8	65	5.8 (2.6-11.2)	122.3 (52.8-241.0)	5.8 (3.0-11.3)	814	1227	27.6 (26.0-29.2)	663.6 (618.8-710.8)	27.6 (26.0-29.2)
	0-12	17	127	12.4 (7.4-19.1)	134.3 (78.3-215.1)	12.5 (8.0-19.4)	1136	2185	38.5 (36.7-40.3)	519.9 (490.1-551.1)	38.5 (36.8-40.3)
	0-24	22	229	16.1 (10.3-23.3)	96.2 (60.3-145.7)	16.8 (11.3-24.4)	1418	3654	48.0 (46.2-49.9)	388.0 (368.1-408.8)	49.0 (47.1-50.8)
Male	0-3	8	35	5.5 (2.4-10.5)	228.1 (98.5-449.5)	5.5 (2.8-10.7)	446	495	20.0 (18.4-21.7)	901.5 (819.7-989.2)	20.0 (18.4-21.7)
	0-6	13	69	8.9 (4.8-14.7)	189.5 (100.9-324.1)	8.9 (5.3-14.8)	708	901	31.8 (29.8-33.7)	786.1 (729.2-846.2)	31.8 (29.9-33.7)
	0-12	21	132	14.4 (9.1-21.1)	158.8 (98.3-242.8)	14.4 (9.6-21.2)	989	1572	44.4 (42.3-46.5)	629.0 (590.5-669.5)	44.4 (42.4-46.5)
	0-24	32	240	21.9 (15.5-29.5)	133.4 (91.2-188.3)	22.7 (16.6-30.6)	1210	2566	54.3 (52.2-56.4)	471.6 (445.4-498.9)	55.2 (53.1-57.3)
DVT	0-3	3	25	2.9 (0.6-8.4)	121.1 (25.0-354.0)	2.9 (1.0-8.8)	400	474	18.9 (17.2-20.6)	844.8 (764.0-931.8)	18.9 (17.2-20.6)
	0-6	4	49	3.9 (1.1-9.7)	81.5 (22.2-208.7)	3.9 (1.5-10.1)	610	869	28.7 (26.8-30.7)	702.0 (647.4-760.0)	28.8 (26.9-30.7)
	0-12	9	96	8.8 (4.1-16.1)	93.6 (42.8-177.6)	8.9 (4.7-16.3)	834	1547	39.3 (37.2-41.4)	539.1 (503.1-577.0)	39.4 (37.3-41.5)
	0-24	13	181	12.7 (7.0-20.8)	71.9 (38.3-123.0)	12.9 (7.7-21.2)	1033	2594	48.7 (46.5-50.8)	398.3 (374.4-423.3)	49.6 (47.5-51.8)
PE	0-3	10	41	5.8 (2.8-10.5)	243.7 (116.8-448.1)	5.8 (3.2-10.6)	510	636	18.0 (16.6-19.5)	802.1 (734.0-874.8)	18.0 (16.7-19.5)
	0-6	17	80	9.9 (5.9-15.4)	212.5 (123.8-340.2)	9.9 (6.3-15.5)	842	1165	29.8 (28.1-31.5)	723.0 (675.0-773.6)	29.8 (28.1-31.5)
	0-12	29	153	17.0 (11.7-23.4)	189.9 (127.1-272.7)	17.0 (12.2-23.6)	1196	2044	42.3 (40.5-44.1)	585.1 (552.5-619.3)	42.3 (40.5-44.2)
	0-24	41	269	24.0 (17.8-31.1)	152.4 (109.4-206.7)	25.4 (19.3-33.0)	1478	3352	52.3 (50.4-54.1)	441.0 (418.8-464.1)	53.2 (51.3-55.1)
DVT + PE	0-3	0	2	N.E.	N.E.	N.E.	45	52	19.5 (14.6-25.2)	873.5 (637.1-1168.8)	19.5 (14.9-25.2)
	0-6	0	5	N.E.	N.E.	N.E.	70	94	30.3 (24.4-36.7)	745.3 (581.0-941.6)	30.3 (24.8-36.7)
	0-12	0	10	N.E.	N.E.	N.E.	95	166	41.1 (34.7-47.8)	571.7 (462.5-698.8)	41.1 (35.1-47.8)
	0-24	0	19	N.E.	N.E.	N.E.	117	275	50.6 (44.0-57.3)	425.5 (351.9-510.0)	51.5 (45.2-58.2)

T Time (month)
N events
PY person-time (years)
CIP Cumulative incidence proportion

IR Incidence rates per 1000 PY
CIF Cumulative Incidence Function (%) estimated with the Kaplan-Meier method
CI Confidence Intervals
N.E. non-estimable

Complete analysis using OT definition are presented in the Appendix 3, Result Tables 14 to 19. Tables 14, 16 and 18 in Appendix 3 present the comparison using OT definition between DOACs and LMWH with respect to recurrent VTE, major bleeding and all-cause mortality respectively. Tables 15, 17 and 19 in Appendix 3 present the comparison using OT definition between rivaroxaban and LMWH with respect to recurrent VTE, major bleeding and all-cause mortality respectively.

10.4 Comparisons of incidence rates of recurrent VTE, major bleeding and all-cause mortality

Objective #4 was to compare incidence rates of the independent outcomes recurrent VTE, major bleeding and all-cause mortality in patients treated with DOACs versus LMWH (Table 14); and rivaroxaban versus LMWH (Table 15). We estimated hazard ratios from Cox proportional hazards regression and sub-hazard ratios from Fine-Gray regression models with death as competing risk. All estimates are given both as unweighted (adjusted for sex and age) and weighted (PS overlap weighted), and repeated under ITT and OT exposure. Results under ITT exposure are given below (Table 14 and Table 15), for OT exposure and further details are presented in Appendix 3 Table 20 (HR from Cox regression models) and 21 (sub-HR from Fine-Gray regression model). Variable balance before and after adjusting with overlap PS-weighting, standardized differences are presented in Appendix 3 Figures 2 and 3.

For the comparison of major bleeding between DOACs and LMWH no results had a confidence interval not including unity, but hazard ratios were most often slightly below unity, thus favored DOACs. When considering death as a competing risk, all sub-hazard ratios were closer to unity than the corresponding hazard ratio, still favoring DOACs for short follow-up times, but moving towards no difference for longer follow-up times and broader confidence intervals. Differences between unweighted and weighted results were marginal. OT analysis shown similar HR and sub-HR with overlapping confidence intervals among ITT and OT approaches, but slightly higher effect favoring DOACs in the OT approach. Unweighted and weighted HR CI excluded 1 at 0-6 and 0-12 months. See Table 14, for additional information including ITT and OT exposure see Appendix 3, Table 20 and 21.

For the comparison of recurrent VTE between DOACs and LMWH no results were statistically significant, and all hazard ratios were close to 1. When considering death as a competing risk, all sub-hazard ratios were higher than the corresponding hazard ratio and confidence intervals broader. OT analysis shown similar results with overlapping confidence intervals among ITT and OT approaches. See Table 14, for additional information including ITT and OT exposure see Appendix 3, Table 20 and 21.

For the comparison of all-cause mortality between DOACs and LMWH all results were statistically significant favoring DOACs. For all-cause death a more pronounced difference was observed between unweighted and weighted results, reflecting stronger influence by confounding in unweighted results. As death was considered competing risk, no results from Fine-Gray regression are possible. OT analysis shown similar HR with overlapping confidence intervals among ITT and OT approaches, but slightly higher effect favoring DOACs in the OT approach. See Table 14, for additional information including ITT and OT exposure see Appendix 3, Table 20 and 21.

Table 14. Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for major bleeding, recurrent VTE, and all-cause mortality; DOAC vs LMWH under ITT exposure. N (DOAC) = 566, N (LMWH) = 5181. LMWH is the reference group in all HR and sHR.

Follow-up (months)	Group	N events	T person-years	IR (CI)	Unweighted HR (CI)*	Weighted HR (CI)	Unweighted sub-HR (CI)*	Weighted sub-HR (CI)
Recurrent VTE								
0-3	DOAC	25	127	196.6 (127.2-290.2)	0.98 (0.65-1.49)	0.96 (0.59-1.56)	1.00 (0.66-1.52)	0.96 (0.49-1.89)
	LMWH	230	1121	205.2 (179.5-233.5)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-6	DOAC	27	246	109.8 (72.34-159.7)	0.90 (0.61-1.35)	0.89 (0.56-1.42)	0.95 (0.64-1.41)	0.91 (0.48-1.72)
	LMWH	262	2043	128.3 (113.2-144.8)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-12	DOAC	35	466	75.18 (52.36-104.6)	0.88 (0.62-1.25)	0.91 (0.61-1.35)	0.98 (0.69-1.39)	0.95 (0.54-1.65)
	LMWH	328	3583	91.55 (81.91-102.0)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-24	DOAC	45	818	55.00 (40.12-73.59)	0.89 (0.65-1.22)	0.90 (0.63-1.29)	1.06 (0.78-1.44)	0.97 (0.58-1.60)
	LMWH	393	5896	66.66 (60.23-73.59)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
Overall	DOAC	56	1396	40.12 (30.31-52.10)	0.92 (0.70-1.22)	0.94 (0.68-1.29)	1.15 (0.87-1.52)	1.05 (0.66-1.66)
	LMWH	473	10524	44.95 (40.99-49.19)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
Major bleeding								
0-3	DOAC	5	131	38.04 (12.35-88.77)	0.45 (0.18-1.10)	0.45 (0.17-1.17)	0.48 (0.19-1.17)	0.45 (0.13-1.54)
	LMWH	93	1150	80.87 (65.27-99.07)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-6	DOAC	8	254	31.48 (13.59-62.04)	0.44 (0.22-0.90)	0.48 (0.22-1.05)	0.49 (0.24-1.01)	0.50 (0.18-1.38)
	LMWH	141	2096	67.26 (56.62-79.32)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-12	DOAC	14	483	28.96 (15.83-48.59)	0.59 (0.34-1.01)	0.65 (0.36-1.17)	0.69 (0.40-1.20)	0.69 (0.31-1.54)
	LMWH	181	3682	49.16 (42.26-56.86)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-24	DOAC	22	852	25.81 (16.18-39.08)	0.72 (0.47-1.12)	0.77 (0.47-1.26)	0.91 (0.59-1.41)	0.86 (0.43-1.71)
	LMWH	218	6063	35.96 (31.34-41.06)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
Overall	DOAC	31	1464	21.18 (14.39-30.06)	0.82 (0.57-1.18)	0.86 (0.56-1.31)	1.08 (0.75-1.56)	1.00 (0.54-1.84)
	LMWH	273	10918	25.00 (22.13-28.15)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
All-cause mortality								
0-3	DOAC	39	132	295.4 (210.1-403.9)	0.32 (0.23-0.44)	0.65 (0.46-0.91)	Competing risk	
	LMWH	955	1161	822.7 (771.3-876.5)	1.00 (REF)	1.00 (REF)		

Follow-up (months)	Group	N events	T person-years	IR (CI)	Unweighted HR (CI)*	Weighted HR (CI)	Unweighted sub-HR (CI)*	Weighted sub-HR (CI)
0-6	DOAC	65	257	253.4 (195.6-323.0)	0.32 (0.25-0.41)	0.60 (0.46-0.79)		
	LMWH	1522	2127	715.4 (679.9-752.3)	1.00 (REF)	1.00 (REF)		
0-12	DOAC	94	490	191.9 (155.0-234.8)	0.32 (0.26-0.39)	0.57 (0.45-0.71)		
	LMWH	2125	3757	565.6 (541.8-590.2)	1.00 (REF)	1.00 (REF)		
0-24	DOAC	127	869	146.2 (121.9-174.0)	0.33 (0.28-0.39)	0.57 (0.47-0.68)		
	LMWH	2628	6220	422.5 (406.5-439.0)	1.00 (REF)	1.00 (REF)		
Overall	DOAC	153	1502	101.9 (86.38-119.4)	0.34 (0.29-0.40)	0.56 (0.47-0.66)		
	LMWH	3084	11309	272.7 (263.2-282.5)	1.00 (REF)	1.00 (REF)		

* Adjusted for sex and age.

Table 15 presents results for comparisons of major bleeding between rivaroxaban and LMWH. No results were statistically significant, but all hazard ratios, except for overall follow-up, favored rivaroxaban. When considering death as a competing risk, all sub-hazard ratios were higher than the corresponding hazard ratio, still favoring rivaroxaban for short follow-up times, but favoring LMWH for overall follow-up time. OT analysis shown similar HR and subHR with overlapping confidence intervals among ITT and OT approaches, but slightly higher effect favoring rivaroxaban in the OT approach.

For the comparison of recurrent VTE between rivaroxaban and LMWH no results were statistically significant, but all hazard ratios favored rivaroxaban. When considering death as a competing risk, all sub-hazard ratios were higher than the corresponding hazard ratio, but still favoring rivaroxaban. OT analysis shown similar results with overlapping confidence intervals among ITT and OT approaches.

For the comparison of all-cause mortality between rivaroxaban and LMWH all results were statistically significant favoring rivaroxaban. OT analysis shown similar HR with overlapping confidence intervals among ITT and OT approaches, but slightly higher effect favoring rivaroxaban in the OT approach. As death was considered competing risk, no results from Fine-Gray regression are possible.

For additional information including ITT and OT exposure see Appendix 3, Table 20 and 21.

Table 15. Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for recurrent VTE, Major bleeding and all-cause mortality; rivaroxaban vs LMWH under ITT exposure. N (RVX) = 283, N (LMWH) = 5181. LMWH is the reference group in all HR and sHR.

Follow-up (months)	Group	N events	T person-years	IR (CI)	Unweighted HR (CI)*	Weighted HR (CI)	Unweighted sub-HR (CI)*	Weighted sub-HR (CI)
Major bleeding								
0-3	RVX	2	68	29.39 (3.56-106.2)	0.35 (0.09-1.40)	0.40 (0.09-1.74)	0.37 (0.09-1.51)	0.41 (0.06-2.92)
	LMWH	93	1150	80.87	1.00	1.00	1.00	1.00

Follow-up (months)	Group	N events	T person -years	IR (CI)	Unweighted HR (CI)*	Weighted HR (CI)	Unweighted sub-HR (CI)*	Weighted sub-HR (CI)
				(65.27-99.07)	(REF)	(REF)	(REF)	(REF)
0-6	RVX	3	133	22.55 (4.65-65.90)	0.32 (0.10-0.99)	0.42 (0.12-1.38)	0.36 (0.12-1.14)	0.44 (0.09-2.16)
	LMWH	141	2096	67.26 (56.62-79.32)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-12	RVX	6	256	23.46 (8.61-51.06)	0.48 (0.21-1.08)	0.62 (0.26-1.49)	0.59 (0.26-1.32)	0.68 (0.20-2.33)
	LMWH	181	3682	49.16 (42.26-56.86)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-24	RVX	10	460	21.73 (10.42-39.97)	0.62 (0.33-1.17)	0.71 (0.35-1.46)	0.81 (0.43-1.52)	0.81 (0.28-2.32)
	LMWH	218	6063	35.96 (31.34-41.06)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
	RVX	17	872	19.51 (11.36-31.23)	0.80 (0.50-1.30)	1.04 (0.60-1.82)	1.13 (0.70-1.84)	1.27 (0.53-3.02)
Overall	LMWH	273	10918	25.00 (22.13-28.15)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
Recurrent VTE								
0-3	RVX	12	66	181.1 (93.55-316.3)	0.91 (0.51-1.63)	0.80 (0.40-1.60)	0.94 (0.52-1.68)	0.81 (0.33-2.02)
	LMWH	230	1121	205.2 (179.5-233.5)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-6	RVX	13	129	100.5 (53.53-171.9)	0.84 (0.48-1.46)	0.75 (0.38-1.45)	0.89 (0.51-1.56)	0.77 (0.32-1.83)
	LMWH	262	2043	128.3 (113.2-144.8)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-12	RVX	17	248	68.66 (40.00-109.9)	0.81 (0.50-1.32)	0.77 (0.43-1.35)	0.93 (0.57-1.51)	0.81 (0.38-1.74)
	LMWH	328	3583	91.55 (81.91-102.0)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
0-24	RVX	21	447	47.00 (29.09-71.84)	0.78 (0.50-1.21)	0.73 (0.44-1.23)	0.96 (0.62-1.48)	0.80 (0.40-1.61)
	LMWH	393	5896	66.66 (60.23-73.59)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
	RVX	25	850	29.41 (19.03-43.41)	0.73 (0.49-1.10)	0.70 (0.44-1.13)	0.98 (0.65-1.46)	0.80 (0.42-1.53)
Overall	LMWH	473	10524	44.95 (40.99-49.19)	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
All-cause mortality								
0-3	RVX	13	68	190.4 (101.4-325.6)	0.21 (0.12-0.36)	0.47 (0.27-0.83)	Competing risk	
	LMWH	955	1161	822.7 (771.3-876.5)	1.00 (REF)	1.00 (REF)		
0-6	RVX	21	134	156.7 (97.01-239.6)	0.20 (0.13-0.31)	0.41 (0.26-0.65)		
	LMWH	1522	2127	715.4 (679.9-752.3)	1.00 (REF)	1.00 (REF)		
0-12	RVX	38	259	146.8 (103.9-201.5)	0.24 (0.18-0.33)	0.48 (0.34-0.67)		
	LMWH	2125	3757	565.6 (541.8-590.2)	1.00 (REF)	1.00 (REF)		

Follow-up (months)	Group	N events	T person -years	IR (CI)	Unweighted HR (CI)*	Weighted HR (CI)	Unweighted sub-HR (CI)*	Weighted sub-HR (CI)
0-24	RVX	54	468	115.3 (86.59-150.4)	0.26 (0.20-0.34)	0.48 (0.36-0.64)		
	LMWH	2628	6220	422.5 (406.5-439.0)	1.00 (REF)	1.00 (REF)		
Overall	RVX	70	896	78.11 (60.89-98.68)	0.28 (0.22-0.35)	0.50 (0.39-0.64)		
	LMWH	3084	11309	272.7 (263.2-282.5)	1.00 (REF)	1.00 (REF)		

* Adjusted for sex and age.

The analyses were repeated in subgroups of patients with DVT or PE as their index CAT, respectively. The patterns are consistent with the analysis for the whole group (DVT and/or PA as index VAT) for recurrent VTE, major bleeding and all-cause mortality. HR and sub-HR were similar for recurrent VTE and major bleeding, with broader confidence intervals estimated with the Fine-Gray approach compared to the conventional proportional hazards Cox regression model.

The results under ITT exposure are presented as forest plots in the following Figures 2 to 13. Fine-Grey sub-HR estimates were in general closer to unity and with broader confidence intervals than corresponding Cox regression HR estimates. The only outstanding difference from the overall results were for the sub-groups of DVT and PE as index VTE. For DOACs as compared with LMWH, a statistically reduced adjusted HR estimated with Cox analysis of recurrent VTE at 2-years follow-up was found. For rivaroxaban versus LMWH, a lower HR, with confidence interval not crossing 1, of recurrent VTE with the Cox regression as well as Fine Grey analyses at 2-years follow-up and overall follow-up. For the sub-group with PE as index VTE, all CIs for the HR estimates contained 1, and the point estimates were slightly above unity.

Figure 2: Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for recurrent VTE; DOAC vs LMWH under ITT exposure in the subgroup of patients with index CAT = DVT.

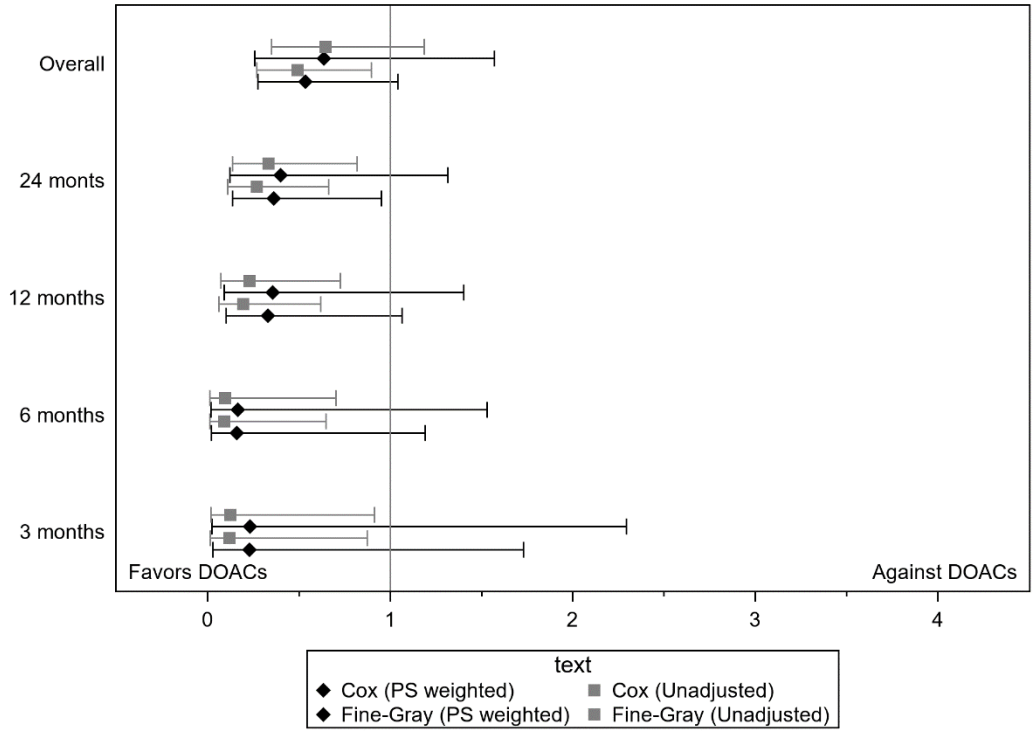

Figure 3: Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for recurrent VTE; RIVA vs LMWH under ITT exposure in the subgroup of patients with index CAT = DVT.

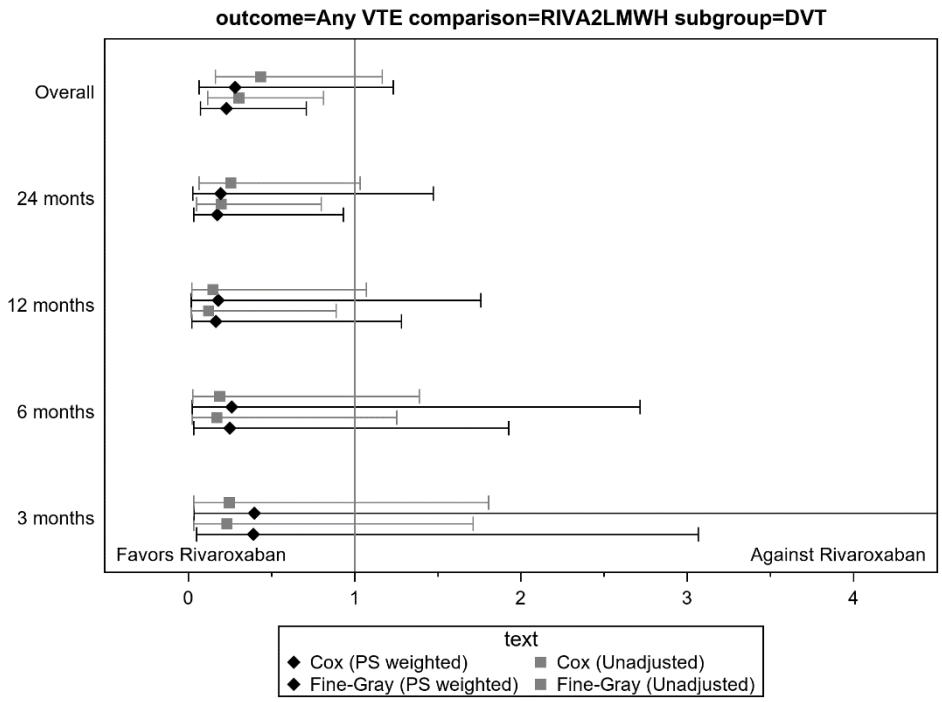

Figure 4: Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for major bleeding; DOAC vs LMWH under ITT exposure in the subgroup of patients with index CAT = DVT.

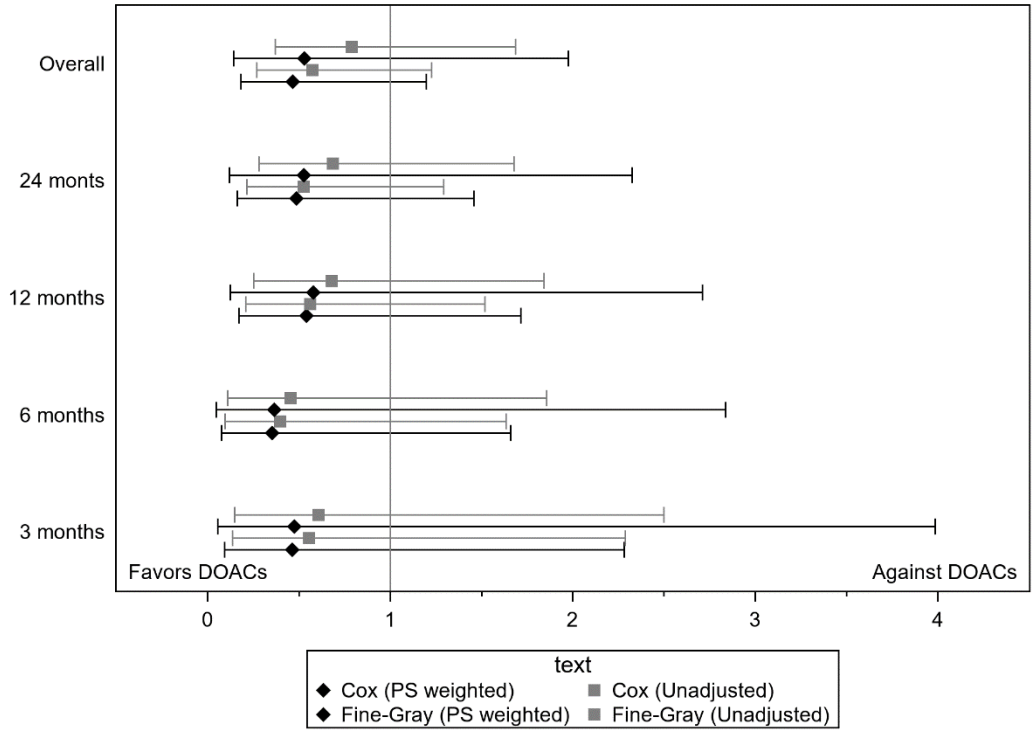

Figure 5: Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for major bleeding; RIVA vs LMWH under ITT exposure in the subgroup of patients with index CAT = DVT.

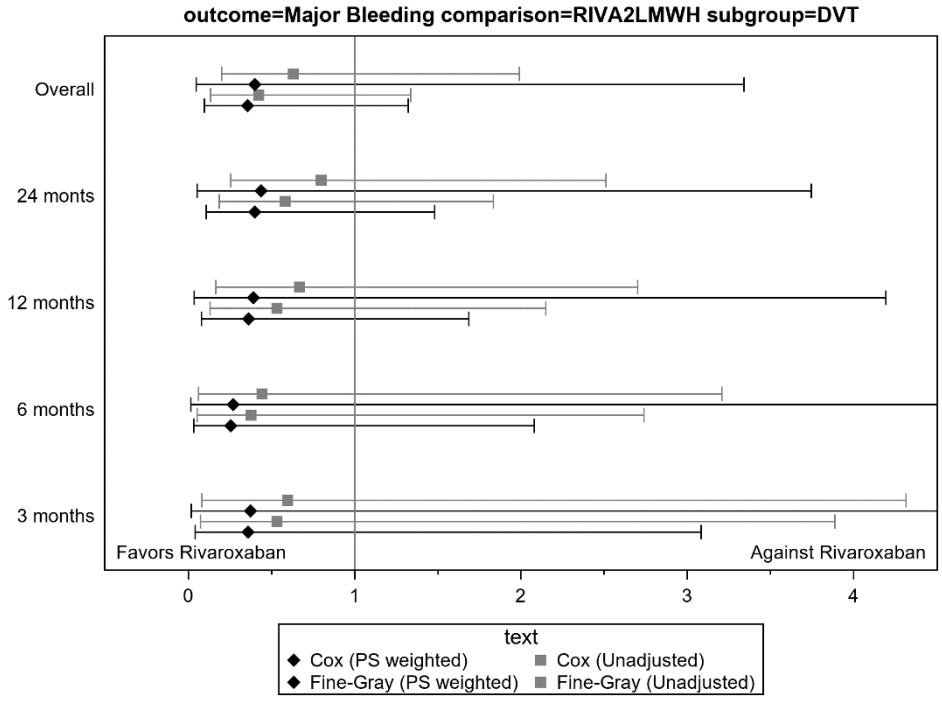

Figure 6: Crude and adjusted hazard ratios from Cox regression for all-cause mortality; DOAC vs LMWH under ITT exposure in the subgroup of patients with index CAT = DVT.

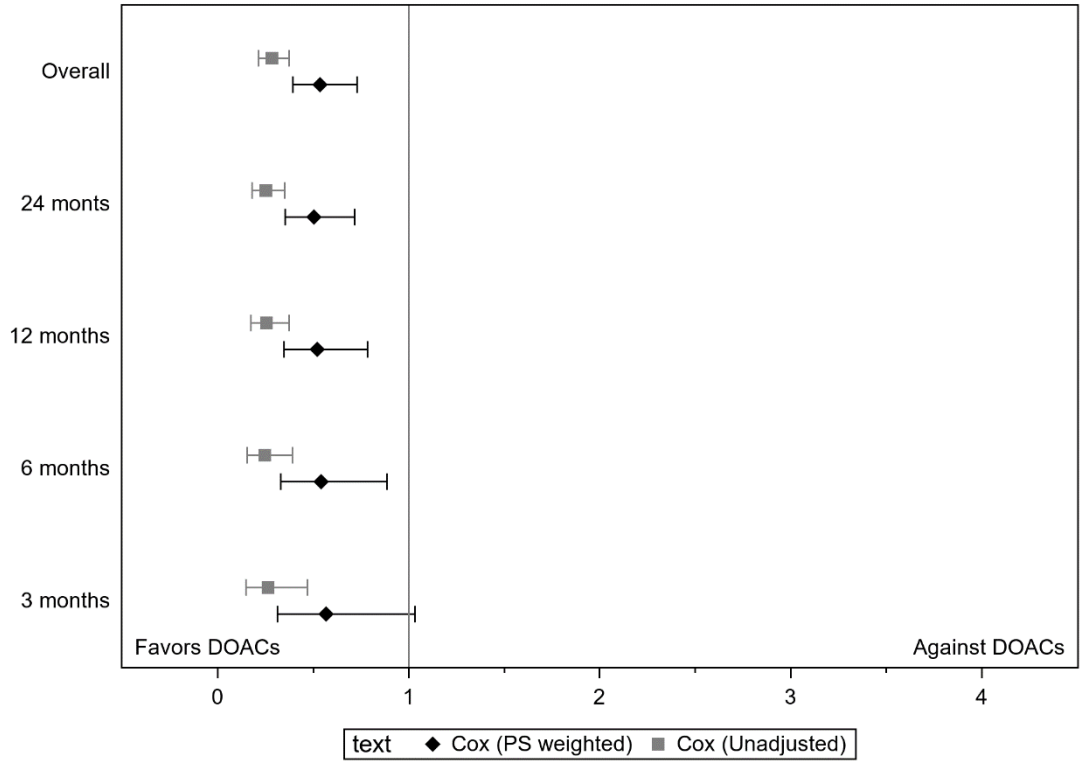

Figure 7: Crude and adjusted hazard ratios from Cox regression for all-cause mortality; RIVA vs LMWH under ITT exposure in the subgroup of patients with index CAT = DVT

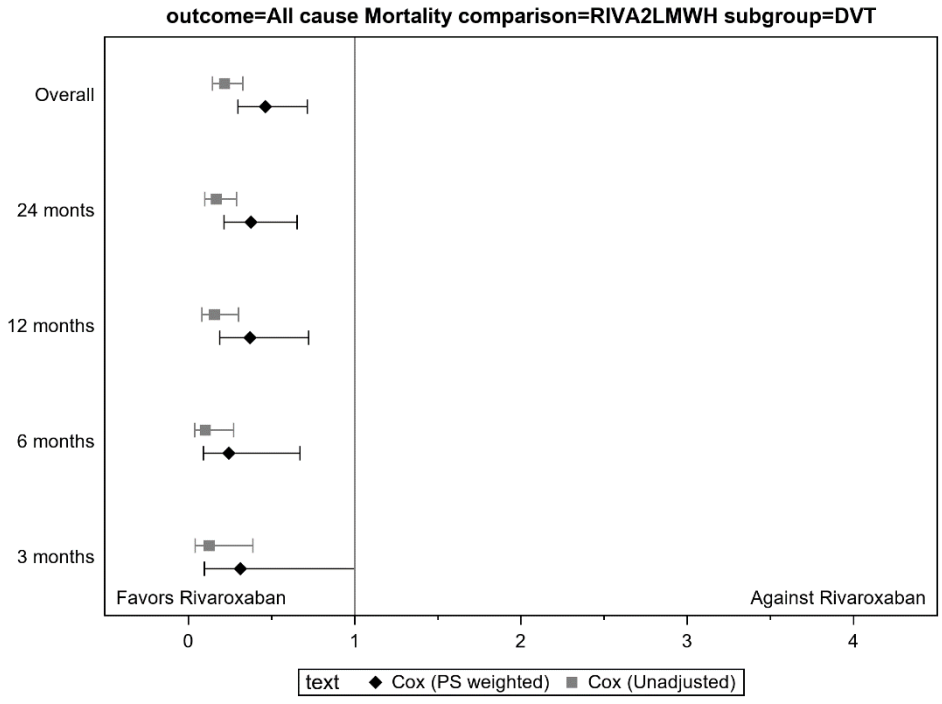

Figure 8: Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for recurrent VTE; DOAC vs LMWH under ITT exposure in the subgroup of patients with index CAT = PE.

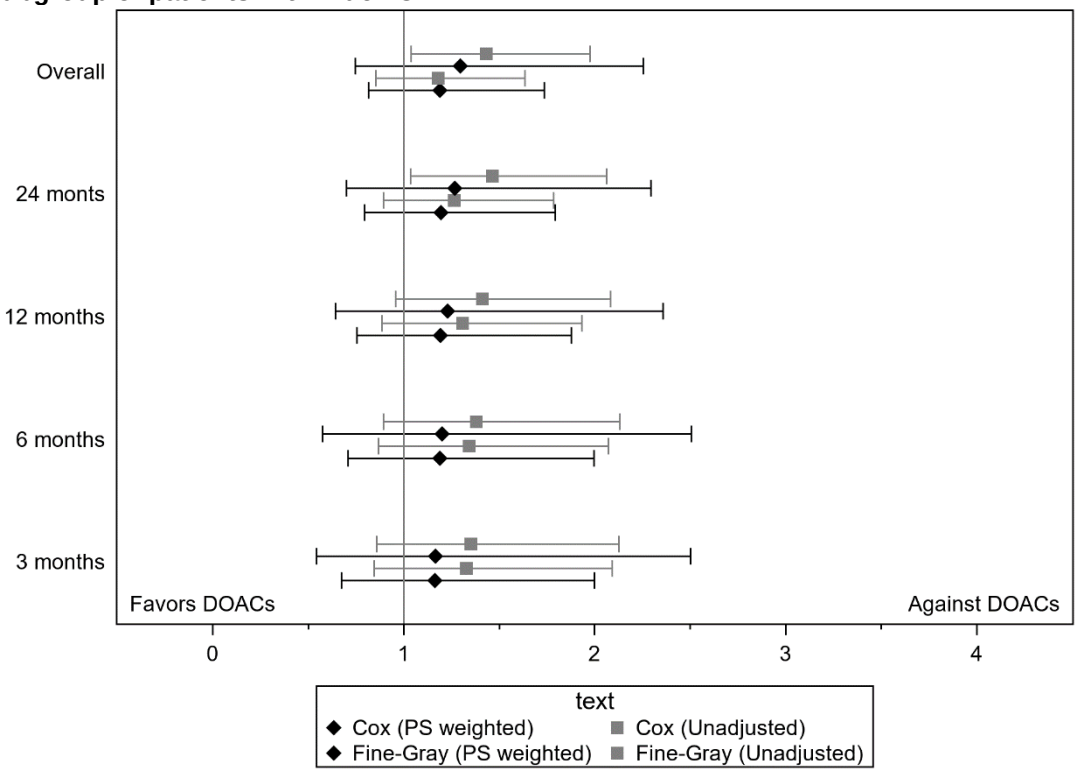

Figure 9: Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for recurrent VTE; RIVA vs LMWH under ITT exposure in the subgroup of patients with index CAT = PE.

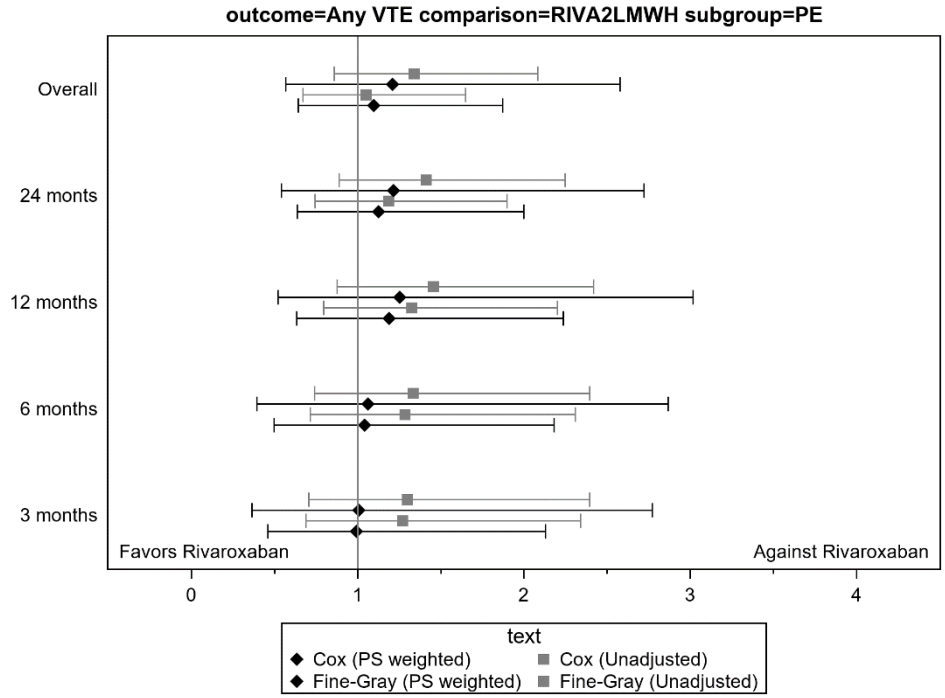

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Figure 10: Crude and adjusted hazard ratios from Cox regression, crude and adjusted sub-hazard ratios from Fine-Gray regression for major bleeding; DOAC vs LMWH under ITT exposure in the subgroup of patients with index CAT = PE.

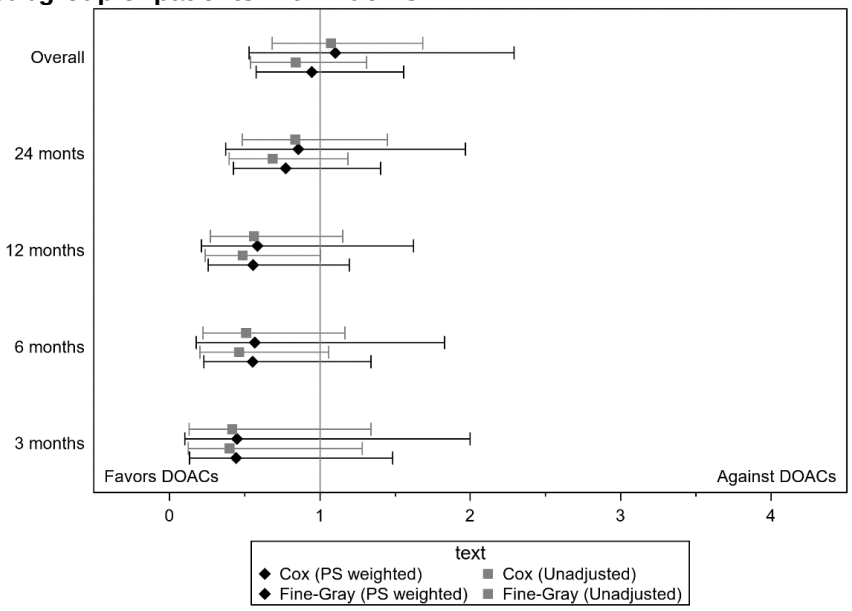


Figure 11: Crude and adjusted hazard ratios from Cox regression for major bleeding; RIVA vs LMWH under ITT exposure in the subgroup of patients with index CAT = PE

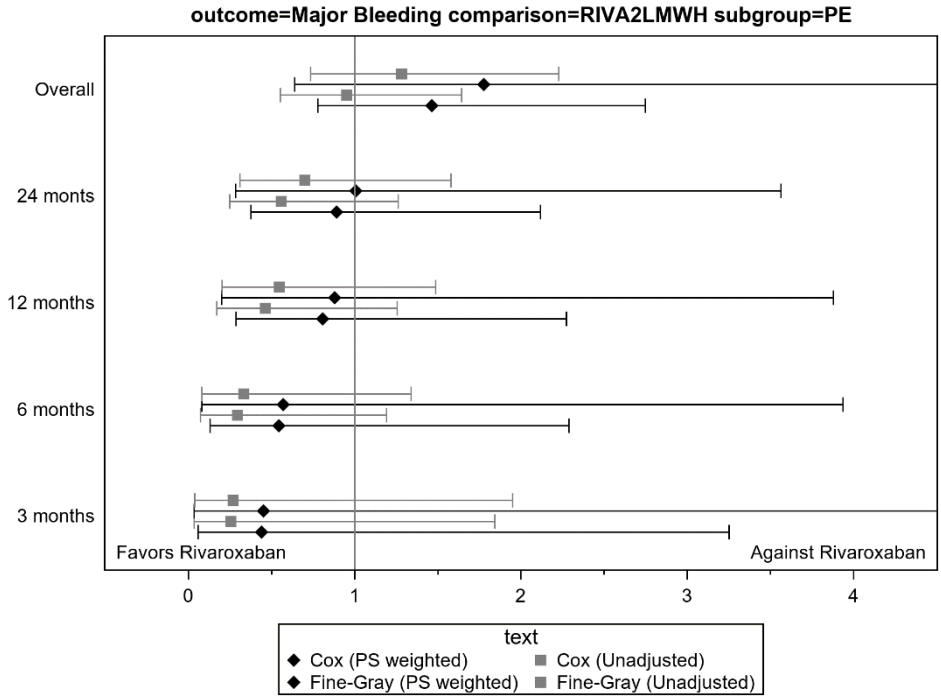


Figure 12: Crude and adjusted hazard ratios from Cox regression for all-cause mortality; DOAC vs LMWH under ITT exposure in the subgroup of patients with index CAT = PE.

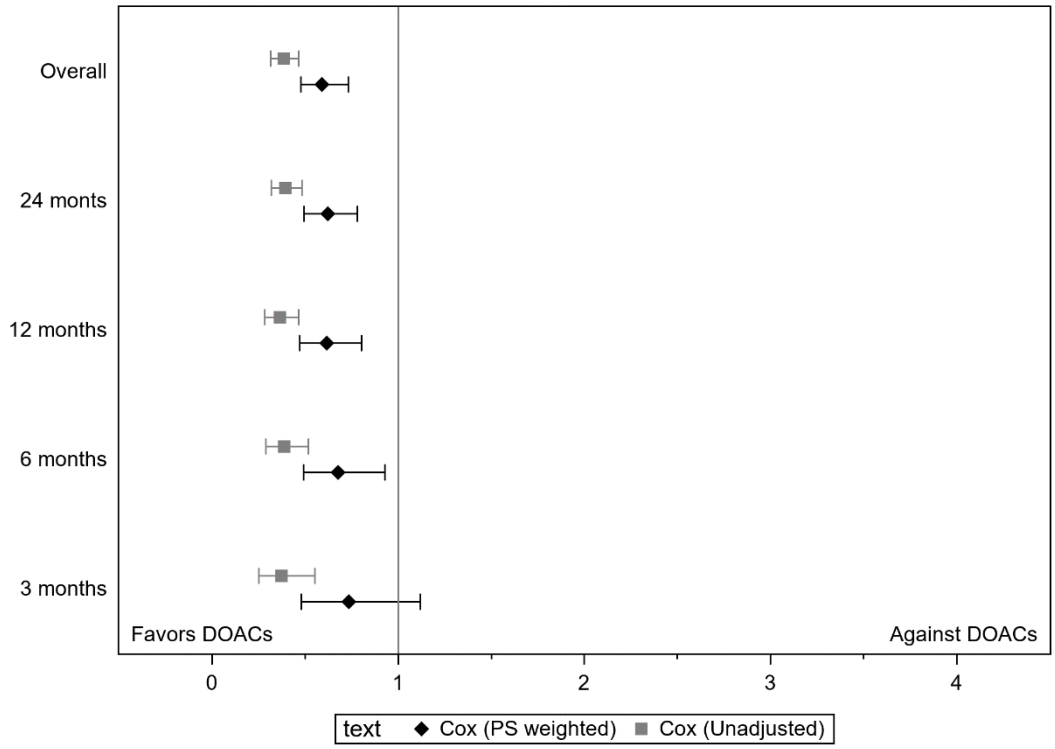
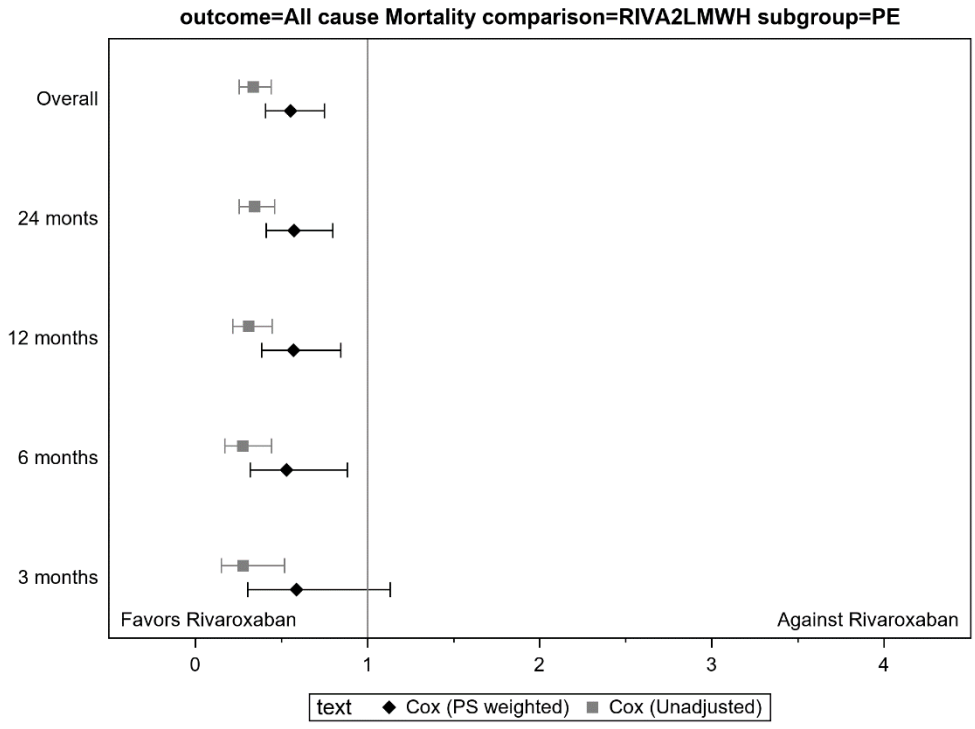


Figure 13: Crude and adjusted hazard ratios from Cox regression for all-cause mortality; RIVA vs LMWH under ITT exposure in the subgroup of patients with index CAT = PE.



Subgroup analysis according to cancer type (lung, breast, prostate) and type of index CAT (PE only, DVT only) using ITT and OT definitions for the comparison of DOACs versus LMWH and rivaroxaban versus LMWH are presented in the Appendix 3, Result Tables 22 to 31. Tables 22 and 23 in Appendix 3 present the HR from Cox regression and sub-HR from Fine-Gray regression respectively for lung cancer individuals only. Breast cancer only individuals are presented in tables 24 and 25. Prostate cancer only individuals are presented in tables 26 and 27. PE only individuals are presented in tables 28 and 29. DVT only individuals are presented in tables 30 and 31.

10.5 Safety data (Adverse events/adverse reactions)

N/A

11. Discussion

11.1 Key results

This study report is based on data from 8,058 adult individuals with a diagnosis of CAT during 2013 and 2019 based on data from available health registries in Sweden and followed up until December 2020.

We observed a predominance of main treatment indication for patients with CAT, including LMWH as the more frequent treatment. Combined treatments and use of VKA were also observed, but with lower frequency as expected considering updates of treatment guidelines, possible contraindications and the limitations related to exposure definition using dispensation in outpatients pharmacies records.

LMWH use was 88.2% at time 0 (initial treatment), decreasing to 81.9% and 77.3% at time 3 and 6 months respectively, and 64.3% at 12 months (extended treatment). DOACs use was 9.4% at time 0 (initial treatment), increasing to 11% and 14.7% at time 3 and 6 months respectively, and finally to 24.8% at 12 months (extended treatment). Rivaroxaban represented approximately half of DOACs for each time period. Recommendations for VTE treatment are divided into different stages: 1. initial treatment (within first weeks), 2. short-term treatment (initial 3-6 month) and 3. long-term treatment >6 months [10]. This estimates provide some indirect information about the proportion of different treatments use at different timepoints since index CAT.

Recurrent VTE

Recurrent VTE cumulative incidence proportions and cumulative incident functions have consistent results. Overall recurrent VTE cumulative incidence ranged from 4.5% in the 0 to 3 months period to 7.7% in the 0 to 24 months period. Overall recurrent VTE cumulative incidence function ranged from 4.6% in the 0 to 3 months period to 9.8% in the 0 to 24 months period. Overall recurrent VTE incidence rates ranged from 206.4 per 1000 PY in the 0 to 3 months period to 64.9 per 1000 PY in the 0 to 24 months period. Both patterns were consistent within subgroups of age strata, sex and type of CAT episode at index date.

For the comparison of recurrent VTE between DOACs and LMWH no hazard ratios' 95% confidence intervals excluded 1, and all hazard ratios were close to 1. For the comparison of recurrent VTE between rivaroxaban and LMWH no results were statistically significant, and all hazard ratios were close to 1. When considering death as a competing risk, all sub-hazard ratios were consistent, but slightly higher (closer to 1 in general) than the corresponding hazard ratio. Crude and weighted adjusted HR were similar.

Major bleeding

Major bleeding was consistently around half the risk of recurrent VTE for all categories and timeframes. Major bleeding cumulative incidence proportions and cumulative incident functions have consistent results. Overall major bleeding cumulative incidence ranged from 1.9% in the 0 to 3 months period to 5.7% in the 0 to 24 months period. Overall major bleeding cumulative incidence function ranged from 4.6% in the 0 to 3 months period to 9.8% in the 0 to 24 months period. Overall recurrent VTE incidence rates ranged from 76.9 per 1000 PY in the 0 to 3 months period to 34.6 per 1000 PY in the 0 to 24 months period. Both patterns were consistent within subgroups of age strata, sex and type of CAT episode at index date.

For the comparison of major bleeding between DOACs and LMWH no results were statistically significant, but all hazard ratios favored DOACs. The comparison of major bleeding between rivaroxaban and LMWH no results were statistically significant, but all HR favored rivaroxaban, with smaller effect size for longer follow-up times. When considering death as a competing risk, all sub-hazard ratios were consistent but slightly higher (closer to 1 in general) than the corresponding hazard ratio, still favoring DOACs or rivaroxaban for short follow-up times, but moving towards no difference for longer follow-up times. Crude and weighted adjusted HR were similar.

All-cause mortality

All-cause mortality cumulative incidence proportions and cumulative incident functions have consistent results. Overall all-cause mortality cumulative incidence ranged from 17.1% in the 0 to 3 months period to 47.4% in the 0 to 24 months period. Overall all-cause mortality cumulative incidence function ranged from 17.1% in the 0 to 3 months period to 48.3% in the 0 to 24 months period. Overall all-cause mortality incidence rates ranged from 756.0 per 1000 PY in the 0 to 3 months period to 380.2 per 1000 PY in the 0 to 24 months period. Both patterns were consistent within subgroups of sex and type of CAT episode at index date. Over 65 years age strata (>=65 years) shown consistent higher mortality that age strata under 65 years, as expected.

For the comparison of all-cause mortality between DOACs and LMWH all results were statistically significant favoring DOACs. For the comparison of all-cause mortality between rivaroxaban and LMWH all results were statistically significant favoring rivaroxaban. Weighted adjusted HR had smaller effect size than crude HRs.

11.2 Strengths

All persons diagnosed with incident CAT episodes in the entire Sweden during the study period were included in the study, thus the risk of selection bias was minimized.

Through the person identification number, almost no patients was lost during the follow-up period. All prescribed drugs in out-patient settings are dispensed through pharmacies in Sweden with direct electronic reporting to the Prescribed Drug Register.

11.3 Limitations

Only patients with a VTE diagnosis after the cancer diagnosis were included in this study. Around 25% of all VTE events are attributed to cancer, and up to 20% of individuals with cancer experience VTE at some stage of their evolution, with a higher incidence during the initial period after cancer diagnosis [30, 31]. In 5 to 10% of VTE patients, cancer is occult at the time of the VTE episode [30, 32]. In individuals with unprovoked VTE, the incidence of new diagnosis of cancer is about 4.5%-5%, being particularly higher in the first six months after the VTE episode [30, 33]. Since VTE can

be the first manifestation of an underlying occult cancer that is discovered during initial approach to VTE, the inclusion method in this study could have decreased the number of available individuals to be included.

Drugs administered during hospitalizations through requisition were not captured in this study, unless they were dispensed to the patient after discharge from hospital. Although the main analysis was based on the ITT approach that ignores the duration of use, there may be some amount of misclassification on the duration of use of a specific drug since it is an estimation from available information on drug dispensation, including dispensation dates, and number of pills/doses and boxes dispensed for outpatients. Since combined treatment in steps may be difficult to capture using out hospital dispensing drugs, there might be some degree of misclassification between VKA and LMWH exposure groups. Patients with VTE associated to cancer require extended anticoagulation treatment as long as cancer is active [10, 31], so different duration of treatments may indicate differences in underlaying cancer or comorbidities between exposure groups. Additionally, for those patients that discontinue anticoagulation, it is possible that the definition of exposure used in this study cannot distinguish between VTE therapeutic and prophylactic treatment doses.

The NPR records diagnoses at hospitals (in-patients and open care specialist visits). Sudden or acute diseases with a high probability of a health care contact (MI, stroke, major bleedings) are generally well recorded. Diseases will less clear onset and not in acute state (hypertension, diabetes mellitus) are sometimes not captured due to treatment in primary care. Such conditions are most likely under-recorded and is probably correct if they are recorded. Also, no visits to primary care units was captured. We anticipate some misclassification of VTE, most likely an under-reporting of VTE events, and in particular DVT since these patients are often managed by primary care. Moreover, when applying for data to the National Board of Health and Welfare (NBHW), the application is assessed and requested to be minimized. In the current data it was decided by the NBHW to truncate ICD-10 diagnosis codes to 3 positions for some codes in Chapter XI Diseases of the digestive system (K00-K93), therefore no distinction between bleeding and non-bleeding gastric ulcer could be made.

For the comparative element of the study, we are aware that all potential confounders such as systemic treatment for cancer, severity of cancer, lifestyle factors, family history of VTE, and reasons for prescriptions are not captured. Thus, one should bear in mind that residual confounding somewhat limits interpretability of the results. Although general principles are known for how unadjusted confounders will impact results given associations are known, in most real-life situations these associations remain unknown a priori. Therefore, the magnitude and direction of unadjusted confounders may differ on a case by case basis and is difficult to predict. Another bias more likely to influence results in a systematic way is channeling. As an example, if hypothetically physicians preferentially prescribe LMWH rather than DOACs to patients with a high bleeding risk, the resulting relative risk estimate comparing DOACs vs LMWH could potentially be markedly underestimated, i.e. biased in direction toward zero. Though, the comparison groups were balanced by propensity score overlap weighting including all identified available potential confounders before analysis.

A variety of scenarios were explored in the sample size study for an expected cohort size around 15,000 individuals. Included individuals were 8,058 from 12,685 with a record of cancer and VTE registered between 2013 and 2019, but only 6,449 (692 DOAC and 5,757 LMWH) were included in the comparative study. This low numbers and the imbalanced between groups influenced the precision of the effect measures estimation and the IRs. An example are the wide CI for the IR of recurrent VTE, bleeding and all-cause mortality in the DOAC and rivaroxaban exposure group. Caution should

be exercised when interpreting the hazard ratios for those outcomes with wide CIs, since this may represent a lack of power to explored the association between exposure and outcomes. This wide CIs indicate less precision and greater potential for random error, that affect even more shorter time frames and subgroup analysis based on small number of patients.

11.4 Interpretation

Observed frequency of recurrent VTE, major bleeding and all-cause mortality differed from previous publications. A recent systematic review and meta-analysis including 6 randomized controlled trials with 3 to 6 months of DOACs versus LMWH for the treatment of cancer associated VTE, explored recurrent VTE, major bleeding and all-cause mortality [34]. Recurrent VTE was significantly higher in individuals receiving LMWH: 99 of 1850 (cumulative incidence 5.3%) at 6 month follow-up in individuals receiving DOACs versus 152 of 1840 (8.3%) individuals receiving LMWHs. Major bleeding was higher in patients receiving DOACs, but without statistical significance: 80 of 1850 (4.3%) individuals receiving DOACs versus 68 of 1840 (3.7%) individuals receiving LMWHs. All-cause mortality did not differ between the 2 treatments: 23.3% in individuals receiving DOACs versus 23.5% in individuals receiving LMWHs. All these cumulative incidence proportions are higher than the cumulative incidence proportions in this study within 6 months follow-up, with the only exception of recurrent VTE in the DOAC group which is similar and the mortality in the LMWH treated individuals which is lower in our study. One may speculate about the reasons for differences between the results of our study and the RCT meta-analysis: One reason for a bit higher cumulative incidence proportions in RCTs may be because those patients have undergone a closer examination for outcomes as compared to our observational study. For example, for VTE only clinically manifest diagnosis leading to an hospitalization was recorded while in RCTs even a subclinical VTE may be detected.

Haas et al published an observational study using the Global Anticoagulant Register in the FIELD - VTE (GARFIELD-VTE), with the aim to compare the effectiveness of DOACs and VKAs on 12-month outcomes in VTE patients using an on-treatment approach [35]. In 264 individuals with VTE and cancer, the incidence rate of recurrent VTE was 34.0 per 1000 person years, major bleeding was 41.0 per 1000 person years, and all-cause mortality 265.2 per 1000 person years. In our particular study, the IR for recurrent VTE in the 0-12 follow-up period was higher (IR 75.2), and lower for major bleeding (IR 29.0) and all-cause mortality (IR 191.9). In all cases this estimators has broad and overlapping confidence intervals.

In our study, for cumulative incidence and cumulative function estimators, the lower incidences were consistently observed between 0-3 months and the higher in the 0-24 months, as expected because the denominator is the same but more cases are observed with longer follow-up. The opposite pattern was observed for incidence rates (higher incidences rates were consistently observed between 0-3 months and the lower in the 0-24 months), this higher incidence during first 3 months as compared to more long-time follow-up is likely explained by the fact that some outcomes, especially bleeding is frontloaded, i.e. most cases happen early after start of treatment. This differences can also be related to how the denominator is considered in this two different approaches to measure incidence, since in incidence rates the denominator increases with time since time 0. The observed differences between both approaches can be interpret as an artifact of the overlapping time frames.

In our study, the risk of recurrent VTE appears to be similar in patients treated with DOACs or rivaroxaban as compared to those treated with LMWH, the HRs were consistently close to 1 in all analysis. This is in concordance with current treatment recommendation for VTE treatment in patients with cancer which recommend the use of DOACs or LMWH for initial treatment (within first week),

since compared with LMWH, DOACs may reduce the risk of recurrent VTE but this effect may be small and the evidence may be uncertain [10]. For short term treatment (3 to 6 months), current recommendation favors DOACs since compared with LMWH, DOACs may reduce recurrent VTE [10]. With more long-term treatment, persistence is likely to be higher with DOACs versus LMWH, because of easier administration and treatment adherence [20, 36]. The sample size in this study may be small to detect small effect sizes considering recurrent VTE in the different exposure groups.

The results for major bleeding appeared similar to those of recurrent VTE, the HRs were close to one, if anything favored DOACs and rivaroxaban consistently, but with confidence intervals including 1. Recommendations from the American Society of Hematology 2021 guidelines for management of venous thromboembolism - prevention and treatment in patients with cancer, states that compared with LMWH, DOACs may reduce the risk of major bleeding within the first week of treatment, but this effect may be small and the evidence may be uncertain [10]. One potential reason why we found a slight reduction in risk of bleeding associated with DOACs and rivaroxaban as compared to LMWH, may be that the ICD codes for gastric ulcer were truncated meaning we could not clearly define if a bleeding occurred or not, we could not distinguish between a bleeding and a perforation. Consequently, if hypothetically a true higher incidence rate of gastrointestinal bleeding associated with DOACs existed, this would somehow have been masked by the present analysis meaning the true relative risk to be closer to unity than actually observed. This misclassification, however, would only marginally affect the overall bleeding results in this study. In a previous study short term treatment (3 to 6 months), DOACs was associated with a higher risk of bleeding which was in contrast to HR observed in this study [35], this may be related to the exclusion of cancers with higher risk of bleeding like GI cancers or due residual confounding in our particular study. Since the number of events of major bleedings is smaller than the number of events for recurrent VTE, the power in this study may be even smaller to detect small effect sizes considering major bleeding compared to recurrent VTE.

In a retrospective study in more than 26,000 patients with cancer associated VTE, a consistent effect was observed for bleeding-related hospitalization in crude and adjusted analysis [37]. The HR was 0.86 for DOACs versus LMWH (incidence rate 4.9 in DOACs treated individuals and 5.2 per patient year in LMWH). The HR was 0.86 for rivaroxaban versus LMWH.

A protective effect for all-cause mortality for DOACs or rivaroxaban compared to LMWH was observed for all follow up times. The OSCAR-US was an observational study by Coleman et al, that compared rivaroxaban with LMWH in patients with cancer associated VTE. The OSCAR-US study showed a HR for recurrent VTE of 0.69 (95%CI 0.51 - 0.92), without differences in major bleeding 0.79 (95%CI 0.55 - 1.13) and all-cause mortality HR 1.07 (95%CI 0.85 - 1.35), in contrast to the mortality results in this report [38]. Despite of adjusting for confounders, there are many unmeasured relevant additional confounders like systemic treatment for cancer, severity of cancer, lifestyle factors, family history of VTE, and indications for prescriptions. Also physicians' choice of treatment in the terminal phase of life may have an influence which we could not account for. The change from unadjusted to adjusted results likely demonstrates a possible additional confounding in the data. For this reason, interpretation specifically of mortality results should be taken with caution.

A systematic review and meta-analysis including 8 randomized controlled trials with 3 to 6 months of DOACs versus LMWH for the treatment of cancer explored the same outcomes, with a follow-up period between 3 and 12 months [39]. The results showed that DOACs significantly reduced the risk of recurrent VTE compared to LMWH or VKA (HR 0.62), and there were no statistically significant results for DOACs versus LMWH for major bleeding (HR 0.86), or all-cause mortality (HR 0.98). These results were consistent with the results in Frere et al meta-analysis and different from the results

presented in this particular study [34]. In the 12 months follow-up analysis, weighted adjusted HR in this study were 0.91 for recurrent VTE and 0.65 for major bleeding, both closer to unity and were not statistically significant, and all-cause mortality had a significant HR of 0.57. Main differences may be related to the design, included population and definition of exposure and/or outcomes between RCT and observational studies using secondary databases for a whole country.

Comparison between DOACs versus LMWH and between rivaroxaban versus LMWH produced similar results in this study. This is expected since LMWH is the same comparator group in both comparisons and rivaroxaban represents around 50% of all DOACs exposed individuals in this study. As expected, the last comparison had lower precision with wider CI for all comparisons.

11.5 Generalizability

This study utilized nationwide data from Swedish national registers which collects complete information from all residents in Sweden. Most relevant patients characteristics and comorbidities were considered and follow up was almost complete for the study cohort. The study findings are likely to be generalizable to adult patients diagnosed with cancer and VTE treated with DOACs or LMWH in Sweden, and in settings with similar populations and health care systems. Based on biological plausibility, there is no reason to suspect non-generalizability of these results to other similar populations.

12. Other information

None

13. Conclusion

DOACs including rivaroxaban and LMWH performed equal regarding recurrent VTE and major bleeding in the treatment of adult patients with CAT. DOACs and rivaroxaban showed a protective effect for all-cause mortality as compared to LMWH.

Because of potential residual confounding effects, results for all-cause mortality related to both DOACs and rivaroxaban versus LMWH should be interpreted with caution.

14. References

The current template uses the Vancouver style. References need to be added via the EndNote software.

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Appendices

Annex 1: List of stand-alone documents

Table 16: List of stand-alone documents

Document Name	Final version and date (if available)*
Appendix 1 Detailed list of variables	*21616 APPENDIX 1 OSCAR-SE Definitions V0.4 2022-10-19* 19 OCT 2022
Appendix 2 SAP	*21616 APPENDIX 2 OSCAR-SE Statistical Analysis Plan V0.4 2022-10-19* 19 OCT 2022
Appendix 3 Result tables and graphs	*21616 APPENDIX 3 OSCAR-SE TablesGraphs V1.0 2023-04-12* 12 APR 2023

Annex 2: Additional information

Protocol: Observational Studies in Cancer Associated Thrombosis for Rivaroxaban in SwEden (OSCAR-SE) v 1.0, 30 August 2021

Reference Number: RD-SOP-1216
Supplement Version: 3

Annex 3: Signature Pages

Signature Page - Study Conduct Responsible

Title	Observational Study of Cancer Associated Thrombosis for Rivaroxaban in SwEden (OSCAR-SE)
Report version and date	V 1.0 12 APR 2023
IMPACT study number	21616
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS43355
Medicinal product / Active substance / Medical Device / Combination Product	Rivaroxaban
Comparator / Reference therapy	Apixaban, dabigatran, edoxaban, warfarin, heparins
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that 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.

Print Name: PPD

Date, Signature: 4 MAY 2023, _____

Signature Page for VV-169555 v1.0

Reason for signing: Approved	Name: PPD Role: PPD Date of signature: 05-May-2023 08:58:05 GMT+0000

Signature Page for VV-169555 v1.0