Leibniz Institute for Prevention Research and Epidemiology – BIPS

Final Report (Version 1.0)

Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)

Funded by Bayer Pharma AG

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PASS information

Acronym/Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
Study type / Study phase	Observational post-authorization safety study (PASS) Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS11145
Active substance	B01AF01 Antithrombotic agents, direct factor Xa Inhibitors, Rivaroxaban
Medicinal product	Xarelto®
Product reference	EU/1/08/472/001-049
Procedure number	EMEA/H/C/00944
Comparator / Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany
Research question and objectives	This post-authorization study was designed to assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of rivaroxaban compared with new users of standard of care (SOC) in routine clinical practice in Germany. The primary objectives were: • to provide a description of patients who are dispensed oral rivaroxaban for the first time in comparison with those who are dispensed SOC for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration), • to determine time-trends in the characteristics of first-time use of rivaroxaban, • to study the occurrence of hospitalization for three bleeding events (primary safety outcomes): (a)

	intracranial hemorrhage, (b) gastrointestinal bleeding and (c) urogenital bleeding among users of rivaroxaban (for the treatment of DVT/PE and prevention of recurrent DVT and PE, SPAF and prevention of atherothrombotic events in patients with ACS) in comparison with users of SOC. The secondary objectives were: • to study the occurrence of hospitalization for bleeding events not specified as primary safety outcomes ("other bleeding") among first-time users of rivaroxaban, in comparison with individuals receiving current SOC (secondary safety outcome), • to study the occurrence of noninfective liver disease (secondary safety outcome), • to study outcomes related to effectiveness (DVT/PE, ischemic stroke, myocardial infarction), • to study all-cause mortality, • to conduct subgroup analysis of safety and effectiveness outcomes in populations of special interest, including patients with decreased renal function, elderly patients, and patients with cardiovascular comorbidities (e.g. hypertension, diabetes).
Country(-ies) of study	Germany
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Marketing authorization holder

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1. Abstract

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Report version and date	V1.0 26 NOV 2020
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IMPACT study number	16159
Keywords	Germany, rivaroxaban, vitamin K antagonists, phenprocoumon, safety, effectiveness, atrial fibrillation, venous thromboembolism, acute coronary syndrome
Rationale and background	Rivaroxaban (RVX) is an oral, direct factor Xa inhibitor with multiple indications, including but not limited to: prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery (TKR/THR); treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism (VTE-T); stroke prevention in atrial fibrillation (SPAF); and prevention of atherothrombotic events following an acute coronary syndrome (ACS). As anticoagulant use is associated with bleeding risk, monitoring of the safety profile and patterns of rivaroxaban use in routine care is required. This study forms part of the overall rivaroxaban post-authorization safety monitoring activities in four European countries.
Research question and objectives	To assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in first-time users of rivaroxaban compared with first-time users of phenprocoumon (PPC), which is the standard of care in Germany for the two main indications.
Study design	This study used a cohort design to assess patterns of rivaroxaban utilization and patient characteristics, and to estimate unadjusted incidence rates of safety and effectiveness outcomes during the first episode of treatment. Bleeding outcomes occurring during complete follow-up were also analyzed using a nested case-control design.

Setting	German Pharmacoepidemiological Research Database (GePaRD) which consists of claims data from four German statutory health insurance providers covering over 25 million individuals throughout Germany.
Subjects and study size, including dropouts	All patients with incident exposure to RVX or SOC during the enrollment period. After application of the inclusion and exclusion criteria, the following first-time users of RVX/SOC were identified: SPAF 127,743/88,655, VTE-T without a recent history of caner 25,914/20,502, VTE-T with a recent history of cancer 5198/-, TKR/THR 30,079/-, ACS 546/-.
Variables and data sources	Baseline covariates included medical history, comorbidity and co-medication. Additionally, for patients with nonvalvular atrial fibrillation, the risks of stroke and bleeding were estimated using the CHA_2DS_2VASc score and the HAS-BLED score, respectively. Potential indications were assessed by diagnoses and procedures. For the indications prevention of stroke in patients with atrial fibrillation (SPAF), treatment and secondary prevention of deep vein thrombosis or pulmonary embolism (VTE-T) and prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS), unadjusted incidence rates were estimated for all primary and secondary outcomes. Additionally, a nested case-control was performed to estimate confounder-adjusted odds ratios (ORs) of the four bleeding events (intracranial hemorrhage, gastrointestinal bleeding, urogenital bleeding, and other bleeding) in current users of RVX and PPC compared to past nonusers in the past year.
Results	For SPAF and VTE-T, unadjusted incidence rates of gastrointestinal and urogenital bleeding observed in first-time RVX users were higher than those observed in first-time PPC users. Unadjusted incidence rates of IC bleeding were similar in both cohorts and unadjusted incidence rates of other bleedings were lower in first-time RVX users. In the nested case-control analysis, current use of rivaroxaban was associated with a higher risk of intracranial, gastrointestinal, urogenital, and other bleeding relative to nonuse, both in the SPAF and VTE indication.
Discussion	As rivaroxaban and SOC are likely to be prescribed to groups of patients with different characteristics that cannot be fully adjusted for in the analyses, no comparative statistical analyses were conducted. Furthermore, informal comparisons of unadjusted incidence rates of bleeding outcomes between the rivaroxaban and SOC cohorts should be interpreted with caution because a greater proportion of the time at risk in the

	rivaroxaban cohort accumulated in the early high-risk period than in the SOC cohort and risk of bleedings is higher. The safety and effectiveness profile of rivaroxaban for SPAF and VTE-T in this real-world population is consistent with its expected profile, based on knowledge from randomized controlled trials and other studies. Limited conclusions can be made regarding the efficacy and safety of rivaroxaban for ACS, owing to very low uptake for this indication over the time period studied. No new safety concerns have been identified.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany

2. List of abbreviations

Abbreviation	Explanation
ACEi	Angiotensin-converting-enzyme inhibitor
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AOK	"Allgemeine Ortskrankenkasse" (German statutory health insurance provider)
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical (Classification System)
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPR	Central pharmaceutical reference database
CYP3A4	Cytochrome P450 3A4
DDD	Defined daily dose
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
eGFR	Estimated glomerular filtration rate
EBM	"Einheitlicher Bewertungsmaßstab"
EMA	European Medicine Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS	European Union Post-Authorisation Studies
EU RMP	European Union Risk Management Plan
GePaRD	German Pharmacoepidemiological Research Database
GEP	Good Epidemiological Practice
GI	Gastrointestinal
GPP	Good Pharmacoepidemiological Practice
GPS	Good Practice of Secondary Data Analysis
IC	Intracranial
ICB	Intracranial bleeding
ICD-10-GM	International Classification of Diseases 10th revision - German Modification
INR	International Normalized Ratio
IR	Incidence rate
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
NOAC	Non-VKA oral anticoagulant

NSAID	Nonsteroidal anti-inflammatory drug
OPS	"Operationen- und Prozedurenschlüssel" (Operation- and Procedure Code)
OR	Odds ratio
OTC	Over-the-counter
PAD	Peripheral artery disease
PASS	Post-authorization safety study
PE	Pulmonary embolism
P-GP	P-glycoprotein
PPC	Phenprocoumon
PPI	Proton pump inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PZN	"Pharmazentralnummer" (Central Pharmaceutical Number)
Q	Quarter
RVX	Rivaroxaban
SES	Socioeconomic status (SES)
Std	Standard deviation
SGB	"Sozialgesetzbuch" (German Social Security Statute Book)
SHI	Statutory health insurance provider
SOC	Standard of care
SPAF	Stroke prevention in nonvalvular atrial fibrillation
SPC	Summary of products characteristics
SSRI	Selective serotonin reuptake inhibitors
THR	Total Hip Replacement
TIA	Transient ischemic attack
TKR	Total knee replacement
UG	Urogenital
VKA	Vitamin K antagonists
VTE	Venous thromboembolism
VTE-T	Treatment and secondary prevention of VTE

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5. Milestones

Table 5–1: Milestones

Milestone	Planned date	Actual Date
Start of data collection	Q2 2015	Q2 2015
End of data collection	Q2 2020	Q3 2020
Registration in the EU PAS register	After PRAC approval	30 SEP 2018
Study progress reports	NOV 2014-2019	NOV 2014-2019
Interim report 1	Q4 2015	Q4 2015
Interim report 2	Q4 2017	Q4 2017
Final report of study results	Q4 2020	Q4 2020

EU PAS, European Union Post-Authorisation Studies; PRAC, Pharmacovigilance Risk Assessment Committee; Q, quarter

6. Rationale and background

Rivaroxaban (RVX), a direct factor Xa inhibitor, is licensed for multiple indications:

- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective (total) knee or hip replacement surgery (TKR/THR indication). This indication is not in the focus of this PASS program. The recommended dose is 10 mg once daily (od) for 35 days following hip replacement surgery and 14 days following knee replacement surgery.
- The treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients (VTE-T indication). The recommended dose is 15 mg twice daily (bid) for 3 weeks followed by 20 mg od for six months and, if indicated for extended prevention of DVT/PE, 20 mg od or 10 mg od thereafter depending on the risk of recurrent VTE. For individuals with moderate or severe renal impairment (creatinine clearance, 15–49 mL/min), a reduction of the dose

from 20 mg od to 15 mg od (after the initial three weeks at 15 mg bid) should be considered. When the recommended dose is 10 mg od, no dose adjustment from the recommended dose is necessary.

- The prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack (stroke prevention in atrial fibrillation, SPAF indication). The recommended dose is 20 mg od, with a dose adjustment of 15 mg od for individuals with moderate or severe renal impairment (creatinine clearance, 15–49 mL/min).
- Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (ACS indication). The recommended dose is 2.5 mg bid.
- Co-administered with ASA for the prevention of atherothrombotic events in adult patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischemic events; hereafter referred to as CAD/PAD. The recommended dose is 2.5 mg bid. This indication was approved by the EU Commission in August 2018 and is therefore outside the enrollment period of this study.

As is the case with other anticoagulants, clinical studies of rivaroxaban identified hemorrhage as an important safety outcome (1, 2). A post-authorization pharmacoepidemiological safety study program was initiated shortly after rivaroxaban launch to monitor patterns of rivaroxaban utilization and to determine the occurrence of bleeding events in first-time users of rivaroxaban and first-time users of standard of care anticoagulants (hereafter referred to as SOC) in routine clinical practice in the UK, Germany, the Netherlands and Sweden. The program included the four established indications for rivaroxaban at the time of study commencement (TKR/THR, VTE-T, SPAF and ACS), although TKR/THR was not within the scope of the safety and effectiveness objectives. The CAD/PAD indication was out of the scope of the program as it was approved for use after recruitment to this study had been completed.

This report summarizes the results from the study conducted in Germany.

7. Research questions and objectives

This study aimed to assess patterns of rivaroxaban utilization for SPAF, VTE-T, TKR/THR and ACS and to examine outcomes related to safety and effectiveness in first-time users of rivaroxaban for SPAF, VTE-T and ACS in routine clinical care.

7.1 Primary objectives

- To provide a description of patients who are dispensed oral rivaroxaban for the first time in comparison with those who are dispensed SOC for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration).
- To determine time-trends in the characteristics of first-time use of rivaroxaban.
- To study the occurrence of hospitalization for three types of bleeding events: (a) intracranial (IC) hemorrhage, (b) gastrointestinal (GI) bleeding and (c) urogenital (UG) bleeding among users of rivaroxaban (for the treatment of DVT/PE and

prevention of recurrent DVT and PE, SPAF and prevention of atherothrombotic events in patients with ACS) in comparison with users of SOC.

7.2 Secondary objectives

- To study the occurrence of hospitalization for bleeding events not specified as primary safety outcomes ("other bleeding") among first-time users of rivaroxaban, in comparison with individuals receiving current SOC (secondary safety outcome).
- To study the occurrence of noninfective liver disease (secondary safety outcome).
- To study outcomes related to effectiveness (DVT/PE, ischemic stroke, myocardial infarction).
- To study all-cause mortality.
- To conduct subgroup analysis of safety and effectiveness outcomes in populations of special interest, including patients with decreased renal function, elderly patients, and patients with cardiovascular comorbidities (e.g. hypertension, diabetes).

8. Amendments and updates

Table 8–1: Protocol updates

Number	Date	Section of study protocol	Amendment	Reason
5	NOV 2014	8.2 9.3.1 9.7.1	Additional variables for patient characterization and analyses thereof; strengthened analyses of renal impairment. Version 5.1	Response to PRAC review
4	MAY 2014	General	Extension of study timelines. Comparator updated for acute coronary syndromes. Added secondary safety outcome: "other bleeding" Transfer to European Medicines Agency (EMA) protocol template. Label wording updated. Version 5.0.	PRAC request
3	MAR 2012		Inclusion of additional indication, treatment of pulmonary embolism. V4.0 of protocol.	Label expansion
2	DEC 2011		Inclusion of additional indication, acute coronary syndrome. Version 3.0 of protocol submitted with EU RMP V 7.1	Label expansion
1	APR 2011		Inclusion of additional indication, stroke prevention in atrial fibrillation. Version 2.0 of protocol submitted with EU RMP V 6.1.	Label expansion

EU RMP, European Union Risk Management Plan; PRAC, Pharmacovigilance Risk Assessment Committee

9. Research methods

9.1 Study design and study period

A retrospective cohort study based on data from the German Pharmacoepidemiological Research Database (GePaRD) was conducted to assess patterns of drug utilization and to provide unadjusted incidence rates (IRs) of primary and secondary outcomes during the first treatment episode in first-time users of RVX and first-time users of phenprocoumon (PPC), the SOC in Germany for the two main approved indications SPAF and VTE in patients with no recent history of cancer (see 9.4.1). Additionally, a case-control study nested in the cohorts of first-time users of RVX and first-time users of PPC was performed to estimate confounder-adjusted odds ratios (ORs) of the four bleeding events (IC hemorrhage, GI bleeding, UG bleeding, and other bleeding) during the complete follow-up in current users of RVX and PPC compared nonusers in the past year.

The study period started December 9, 2011 (market authorization date of RVX) and ended December 31, 2017. To allow a minimum follow-up of 12 months, the enrollment period ended 31 December of 2016, the last available data year within this database.

9.2 Setting

The study was based on German statutory health insurance claims data included in GePaRD which is described in 9.5.

9.3 Subjects

The source population of this study was the GePaRD (see 9.5). The study population was composed of first-time users of either RVX or PPC as defined below.

9.3.1 Inclusion Criteria

The study was based on a cohort of first-time users of either RVX or PPC. All individuals enrolled in GePaRD during the study period were eligible for the cohort if they fulfilled all of the following inclusion criteria:

- at least one outpatient dispensing of a study drug, i.e. either RVX or PPC in the enrollment period, i.e. between December 9, 2011 and December 31, 2016,
- at least 365 days of continuous active insurance before the first RVX or PPC dispensing (start dispensing),
- no dispensing of the respective study drug any time before the start dispensing,
- no simultaneous dispensing of PPC and RVX at the time of the start dispensing,
- no simultaneous dispensing of the study drug from two or more physicians at the date of the start dispensing,
- at least two years and not older than 100 years of age at the date of the start dispensing,
- no missing values regarding sex (see 9.9.3), and
- residence in Germany.

9.3.2 Cohort Entry

Cohort entry was defined as the date of the first dispensing of one of the study drugs during the enrollment period fulfilling all inclusion criteria.

9.3.3 Cohort Exit

Cohort exit was defined as the first of the following dates:

- interruption of insurance of more than three days or end of continuous insurance (incl. death),
- end of available follow-up, or
- end of study period (i.e. 31 DEC 2017).

Patients were censored – separately for each outcome – at the first occurrence of the respective event and for the cohort analysis also at treatment switch or discontinuation (see 9.4.3.3).

9.4 Variables

9.4.1 Indication

9.4.1.1 SPAF

SPAF was defined as an in- or outpatient diagnosis of atrial fibrillation or atrial flutter (see Annex 2.1 Code lists) any time before cohort entry without a diagnosis of mitral stenosis or a code indicating an artificial heart valve any time before cohort entry (nonvalvular atrial fibrillation [AF]).

9.4.1.2 VTE-T

VTE-T was defined as an inpatient diagnosis of PE, an inpatient diagnosis of DVT, or an outpatient diagnosis of DVT with at least one outpatient dispensing of an anticoagulant in the same quarter (see Annex 2.1 Code lists) in the 90 days before cohort entry.

The VTE-T cohort was stratified into patients with or without recent history of cancer based on a diagnosis of cancer from 3 years before the cohort entry to up to 1 month after as characteristics and treatment recommendations of patients with cancer differ from those of patients without a recent history of cancer.

9.4.1.3 ACS

ACS was defined as an inpatient diagnosis of acute myocardial infarction, unstable angina or other acute ischemic diseases (see Annex 2.1 Code lists) in the 30 days before the start date. The I24.0 and I24.1 codes were added as a combination of I20.0, I21 and I24 had the best performance to identify occurrence of ACS in the French hospitalization database (3).

9.4.1.4 TKR/THR

TKR/THR was defined as an in- or outpatient procedure code for elective knee or hip replacement surgery (see Annex 2.1 Code lists) 60 days before cohort entry to up to 15 days after cohort entry.

9.4.1.5 Other indication

The category other indication comprised several potential other indications:

- A diagnosis of atrial fibrillation or flutter with a diagnosis of mitral stenosis or an indication of an artificial heart valve (valvular atrial fibrillation);
- A diagnosis of VTE as defined above, in lower limbs not coded as "deep vein" or in upper limbs in the 365 days to 90 days before cohort entry;
- An inpatient diagnosis of ACS as defined above in the 365 days to 30 days before cohort entry;
- A procedure code indicating other orthopedic surgery of lower limbs or upper limbs in the 60 days before cohort entry to up to 15 days after cohort entry;
- An in- or outpatient diagnosis of peripheral artery disease (PAD) or coronary artery disease (CAD) in the 365 days before cohort entry;

9.4.1.6 Assignment of indication

If a patient had more than one potential indication, priority was given to the diagnosis of the physician who prescribed the study drug and a hierarchy (atrial fibrillation – VTE – orthopedic surgery – ACS – other) was applied if the prescribing physician coded more than one potential indication, was not identifiable or coded no indication. Prescribed dose and duration are not available in GePaRD and the tablet strength was not used as it is not unequivocal.

9.4.2 Outcomes

The primary safety outcomes were the three types of bleeding events IC hemorrhage, GI bleeding, and UG bleeding leading to hospitalization. The secondary safety outcomes were other bleedings, noninfective liver disease and all-cause mortality and the effectiveness outcomes were VTE, ischemic stroke and myocardial infarction.

For all outcomes, only hospitalizations were taken into account as the analyses focused on acute and serious cases. The main discharge diagnosis was used to identify these events since this code indicates the reason for hospitalization. The time of the event was set to the admission date of the hospitalization.

9.4.2.1 IC hemorrhage

IC hemorrhage was defined as a hospitalization with a main discharge diagnosis of intracerebral hemorrhage, subarachnoid hemorrhage or subdural hematoma; irrespective of coding as traumatic or nontraumatic (see Annex 2.1 Code lists). Intracranial hemorrhage was additionally stratified into intracerebral, subarachnoid and subdural/extradural bleedings.

9.4.2.2 GI bleeding

GI bleeding was defined as a hospitalization with a main discharge diagnosis of gastrointestinal bleeding, i.e. a bleeding originating in the upper or lower gastrointestinal tract or, more specifically, in the esophagus, stomach, duodenum, jejunum, ileum, colon or rectum (see Annex 2.1 Code lists) and for upper gastrointestinal bleeding the lesion type being erosion, gastritis, duodenitis or peptic (gastric or duodenal) ulcer.

9.4.2.3 UG bleeding

UG bleeding was defined as a hospitalization with a main discharge diagnosis of urogenital bleeding (see Annex 2.1 Code lists).

9.4.2.4 Other bleeding

Other bleeding was defined as a hospitalization with a main discharge diagnosis of a bleeding other than IC, GI or UG (see Annex 2.1 Code lists).

9.4.2.5 Noninfective liver disease

Noninfective liver disease was defined as a hospitalization with a main discharge diagnosis of noninfective liver disease (see Annex 2.1 Code lists).

9.4.2.6 DVT/PE

DVT/PE was defined as a hospitalization with a main discharge diagnosis of DVT or PE (see Annex 2.1 Code lists). In sensitivity analyses, outpatient diagnoses of DVT with at least one outpatient dispensing of an anticoagulant in the same quarter were also taken into account.

9.4.2.7 Ischemic stroke

Ischemic stroke was defined as a hospitalization with a main discharge diagnosis of ischemic stroke (see Annex 2.1 Code lists). In a sensitivity analyses we also considered diagnoses coded as I64 “Stroke not specified as hemorrhagic or ischemic”.

9.4.2.8 Myocardial infarction

Myocardial infarction was defined as a hospitalization with a main discharge diagnosis of acute myocardial infarction (see Annex 2.1 Code lists).

9.4.2.9 All-cause mortality

Death was identified by an established algorithm based on the reason for ending the insurance or discharge from hospital (4, 5).

9.4.3 Exposure

The most widely used vitamin K antagonist in Germany, PPC, was used as SOC for the two main indications: SPAF and VTE in patients with no recent history of cancer. No SOC was defined for the indications ACS, TKR/THR and VTE with recent history of cancer, as patients with ACS are very heterogenic and standard treatment included multiple options and treatment of VTE in patients with cancer depends on the cancer type and grading which together with the respective treatment have substantial impact outcomes under study.

For all patients in the cohort, all dispensings of RVX and PPC were assessed. The start of a dispensing was defined as the dispensing date, or – if not available – the prescription date. GePaRD does not include information on the prescribed dose or duration, so the duration of supply with RVX and PPC had to be estimated from the data.

9.4.3.1 First treatment episode of RVX

For RVX the duration of supply was calculated based on the corresponding indication, i.e. the total number of mg of the respective dispensing was divided by the following amounts to calculate the duration of supply:

- SPAF: 20 mg (15 mg in case of renal impairment)
- DVT/PE: 30 mg for the first 21 days and 20 mg (15 mg in case of renal impairment) thereafter
- Knee/Hip replacement: 10 mg
- ACS: 5 mg

The end of a dispensing was then calculated as the start date + duration of supply - 1.

For the calculation of the first treatment episode of RVX, the following algorithm was applied: All dispensings of RVX were selected and the durations were calculated. Overlapping dispensings were shifted, i.e. the beginning of the $(i+1)^{th}$ dispensing was set to the day after the end of the i^{th} dispensing to account for stockpiling. Dispensings with a maximum of 30 days in-between were concatenated, i.e. the treatment episode started at the start of the first dispensing and ended at the end of the second dispensing. If less than 30 days of follow-up were available after the end of the last dispensing, the remaining follow-up time was added to the first treatment episode ("prospective gap filling") to avoid bias (6).

9.4.3.2 First treatment episode of PPC

The defined daily dose (DDD) of PPC is 3 mg, but patients usually receive 1.5 to 4 mg depending on their international normalized ratio (INR). Preliminary analyses showed that exposure periods were underestimated if a dose of 3 mg was used. We therefore assumed that all days between two dispensings were on treatment if the distance between them was shorter or equal to four times the number of DDDs of the first dispensing and applied the following algorithm:

The first treatment episode started with the date of the first dispensing and continued as long as there were further dispensings of PPC within four times the number of DDDs after the start of the previous dispensing. If there was no further dispensing within this time interval the treatment was assumed to be discontinued and the end of the first treatment episode was set to the start date of the last dispensing before discontinuation plus the number of DDDs of the last dispensing.

9.4.3.3 Discontinuation and switching

Discontinuation was defined as a gap greater than 30 days between the end of one dispensing and the beginning of the subsequent one (RVX) or greater than four times the number of DDDs of the current dispensing (PPC).

Switching was defined as a dispensing of the other study drug or any other oral anticoagulant during the first treatment episode.

9.4.4 Confounders and effect modifiers

9.4.4.1 Comorbidity and risk factors

Medical history of outcomes, risk factors, as well as data on other chronic diseases were obtained from in- and outpatient diagnoses (see Annex 2.1 Code lists) and procedures and were assessed any time prior to cohort entry (depending on the available data for the respective patient) and on the day of cohort entry.

9.4.4.2 Medications of interest

Medication of interest included antiplatelets, nonsteroidal anti-inflammatory drugs (NSAIDs), antiarrhythmic agents, antihypertensive agents, diuretics, statins, antidiabetic agents, oral steroids, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), and antibiotics as well as medication not recommended for concomitant use with RVX such as cytochrome P450 3A4 (CYP3A4) inhibitors/inducers and as P-glycoprotein (P-GP) inhibitors (see Annex 2.1 Code lists). Dispensings of medication of interest were assessed in the 90 days before and on cohort entry date.

Additionally, we assessed previous dispensings of oral anticoagulants (vitamin K antagonists [VKAs, B01AE]), direct thrombin inhibitors (B01AE), and direct factor Xa inhibitors (B01AF) any time before cohort entry and defined patients without such history of use as naive. Naive status was not assessed in the ACS cohort, as patients usually receive a combination of acetylsalicylic acid (ASA) plus clopidogrel or ticlopidine.

9.4.4.3 Renal function

Renal function was assessed based on the diagnoses of chronic kidney disease (CKD) and procedure codes for dialysis.

The International Classification of Diseases 10th revision - German Modification (ICD-10-GM) classification includes codes for the different stages of CKD and more general codes that do not specify the stage. As CKD is a chronic progressive disease, we used the maximum stage coded as the CKD stage.

Renal impairment was defined as CKD stage ≥ 3 or dialysis.

9.4.4.4 Risk scores

Two risk scores describing (i) the risk of stroke (CHA_2DS_2-VASc) and (ii) the risk of bleeding (HAS-BLED) were calculated for all patients with SPAF. Chronic comorbid

conditions such as hypertension and diabetes and prior history of events such as stroke or bleeding were assessed at any time prior to cohort entry (depending on the available data for the respective patient) and on the day of cohort entry as described in 9.4.4.1. Co-medication was assessed in the 12 months preceding cohort entry as described in 9.4.4.2.

9.4.4.4.1 CHA_2DS_2-Vasc score

The CHA_2DS_2-VASc score includes the most common stroke risk factors in everyday clinical practice and assigns one or two risk points for each of the following items: congestive heart failure (one point), hypertension (one point), age ≥75 (two points), age 65-74 (one point), diabetes (one point), ischemic stroke/transient ischemic attack (two points), vascular disease (one point), and female sex (one point). If no other risk factors were present, female sex scores was set to zero. The accumulated evidence shows that CHA_2DS_2-VASc is better at identifying 'truly low-risk' patients with atrial fibrillation and is as good as, and possibly better than, scores such as $CHADS_2$ in identifying patients who develop stroke and thromboembolism (7).

9.4.4.4.2 HAS-BLED score

The HAS-BLED score assigns one or two risk points for several risk factors for bleedings and has been validated in several independent cohorts (7). Since laboratory values are not part of GePaRD, 'labile INRs' were not included in the calculation and some minor adaptions to GePaRD were made: hypertension (one point), renal impairment (one point), liver impairment (one point), previous history of stroke (one point), bleeding history (one point), elderly (> 65 years) (one point), use of antiplatelet agents or NSAIDs (one point), and alcohol abuse (one point) (8).

9.4.4.5 Pregnancy and pregnancy outcomes

Pregnancies in women of childbearing age (i.e. 11 ≤ age ≤ 50) at cohort entry and during follow-up were identified and dated by an established algorithm (9, 10).

9.4.4.6 Healthcare utilization

The number of hospitalizations in the 12 months before or on cohort entry and the number of hospitalizations in the 12 months after cohort entry were assessed as proxies for overall health status and access to medical care.

The number of outpatient visits or contacts is not assessable in GePaRD as not all visits or contacts are coded and there is no meaningful proxy as number of contacts/visits that have a service code (see 9.5) and number of different physicians depend largely on other factors than overall health status of the patient.

9.5 Data sources and measurement

The source of data for this study was the GePaRD, which is based on claims data from four statutory health insurance providers (SHIs) in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 17 million individuals, which is approximately 20% of the German population of about 83 million inhabitants.

All geographical regions of the country are represented and the data has been shown to be representative with respect to drug prescriptions (11, 12).

GePaRD contains demographic information such as year of birth, sex, and region of residence as well as information on hospitalizations, outpatient visits, and outpatient drug prescriptions.

Information on hospitalizations includes the date of admission, the admission diagnosis, diagnostic and surgical/medical procedures during the hospital stay, the discharge date, main and secondary discharge diagnoses, and the reason for discharge (incl. death).

Outpatient data include diagnoses as well as outpatient diagnostic and therapeutic procedures and services. It is mandatory in the outpatient setting to code the diagnostic certainty. This coding differentiates between “confirmed”, “suspected”, “status post”, and “excluded” diagnoses. Physicians in the outpatient setting are expected to code the disease(s) for which they treat their patients once per quarter (13, 14). Outpatient diagnosis codes are thus available on a quarterly basis only. However, given that an exact date is available for outpatient visits, the diagnosis can be assigned to the date of the visit if there was only one outpatient visit in the respective quarter, i.e., the exact date of diagnosis can partly be determined indirectly.

Hospital and outpatient diagnoses are coded using the ICD-10-GM with at least four digits; diagnostic and surgical/medical procedures are coded using the Operations and Procedures Coding System (OPS) and outpatient treatment/diagnostic procedures as well as immunizations are coded using claim codes for outpatient services and procedures (Einheitlicher Bewertungsmaßstab, EBM).

GePaRD contains information on all drugs prescribed by physicians that were dispensed in a pharmacy and were reimbursed by the health insurance provider. Information on drugs is coded based on the German modification of the Anatomical Therapeutic Chemical (ATC) Classification System. Information on drugs that are purchased over the counter (OTC) is not available in the database. Furthermore, there is no information on medication administered in the hospital, but there are a few exceptions regarding expensive drugs (e.g., monoclonal antibodies). Outpatient drug data include the dates of the prescription and dispensing, the number of prescribed packages, the specialty of the prescribing physician, and the central pharmaceutical number of the drug. Based on the central pharmaceutical number, information on the generic and brand name of the drug, packaging size, strength, the DDD, and further pharmaceutical information (e.g., route of administration) is linked to GePaRD.

If lab tests and physical exams were performed, the related information including the date is available in the database provided that they are reimbursable. The results of these examinations or lab tests are not available, but can partly be derived indirectly if specific ICD-10-GM diagnoses or treatments are coded subsequently to the test or the exam.

There is no lifestyle information in GePaRD. Certain subgroups that have developed diseases due to an unhealthy lifestyle may be identified through diagnostic codes (e.g., obesity, liver diseases due to alcohol abuse) or specific treatments. There is also an ICD-10-GM code for heavy smoking but it is expected that this information is only in the database if the person was treated for this condition. The socioeconomic status (SES) can be approximated through information on the educational level or the deprivation index of the place of residence for the majority of persons in GePaRD.

A major strength of the GePaRD database is its large sample size allowing, for example, investigation of rare exposures and outcomes. In addition, millions of individuals can be followed up over a long period of time given that only a minority of people in Germany switch between health insurance providers. In the outpatient setting, the data cover the care provided by general practitioners and specialists. While in databases recording only the prescription of drugs it is uncertain whether prescriptions were actually filled, GePaRD only contains information on drugs that were actually dispensed, i.e., this part of primary nonadherence is not an issue in GePaRD. In terms of drug safety in pregnancy, it is advantageous that the beginning of pregnancy can be estimated very precisely and that the majority of newborns can be followed up for many years, i.e., outcomes occurring later in life can also be studied.

There are limitations inherent to the use of claims data. This includes the lack of information on lifestyle factors, lab values, and other measurements (e.g., lung function), overall frailty, the severity of diseases, cause of death, and OTC medication. Particularly in the outpatient setting, miscoding or unspecific coding of diseases may occur, i.e., algorithms combining different types of information are typically applied to define cases. Furthermore, information on the prescribed daily dose is not available in GePaRD; the dose and intended duration have to be estimated and sensitivity analyses have to be performed to check the robustness of the results.

The GePaRD has been used successfully to study hemorrhagic complications of drug treatment (15–18) and also evaluated use of rivaroxaban during a time when it was only approved for the orthopedic indication (19).

9.6 Bias

As this study was performed using secondary data, recall bias was not of concern. This is especially true for the assessment of drug exposure information based on pharmacy dispensing claims, which is – for reimbursable drugs – considered to be the gold standard of drug exposure information compared with self-reported information or prescribing records in outpatient medical records (20). However, as neither the prescribed dose nor the actually used dose are available in GePaRD, the exposure periods had to be estimated. This might lead to falsely classifying exposed time as unexposed and vice versa. This misclassification is probably not random as actual exposure depends on the compliance and health status of the patient. Additionally, the estimation of the exposure period differed between RVX and PPC because RVX has a fixed dose regimen whereas PPC is up- or down-titrated according to the INR. This is one of the reasons why no direct comparison between first-time RVX and first-time PPC users was made.

Outcome misclassification is assumed to be small as hospital discharge diagnoses have a high validity and especially a high specificity (21). However, patients dying due to the bleeding event before they reach the hospital will not be captured, which might lead to bias if the short-term mortality of bleedings differs between the drugs. It is also possible that patients might have prodromal symptoms and stop using RVX or PPC before the occurrence of a severe bleeding.

As in all observational studies, control of potential confounders is essential. The assessment of reimbursable co-medication is assumed to be complete, but OTC drugs, including the use of aspirin, are not captured in the database. Most comorbidities were probably identified based on the in- and outpatient diagnoses, but some misclassification is expected. As lifestyle related factors such as smoking, alcohol consumption and obesity are not directly included in GePaRD, proxies (e.g. alcohol-related diseases) were used to reduce the amount of unmeasured confounding.

To avoid bias from depletion of susceptibles, only first-time users of RVX and PPC were examined. This also reduced the amount of confounding by indication. However, it is likely that the decision to prescribe either RVX or PPC depends on the characteristics of the patient and the physician (e.g. specialty, localization and characteristics of practice, physician's preference). Not all of these characteristics are assessable, especially with claims data. This might result in residual confounding and biased comparisons between RVX and PPC. Therefore, no direct comparison between first-time RVX and first-time PPC users was made.

9.7 Study size

This final report was based on all data available at the time of the final analysis (last update of GePaRD in May 2020) and was based on all first-time users of RVX or PPC as defined in 9.3. Since only descriptive analyses were planned, no prior sample size calculation was conducted.

9.8 Data transformation

De-identified patient-level data from GePaRD was transformed to create the analysis data sets including the demographic, exposure, comorbidity, co-medication, and outcome variables necessary for the analysis as described in 9.4.

9.9 Statistical methods

9.9.1 Main summary measures

9.9.1.1 Drug utilization

Characteristics of the start dispensing were examined by indication and included strength and duration of the first treatment episode. For SPAF, we also examined the pattern of RVX use during the first year of treatment.

The analysis of the characteristics of users was examined by indication and included demographics (sex, age, socioeconomic status), comorbidity, medication dispensed in the 90 days before cohort entry, risk scores, renal impairment, and lifestyle factors. For RVX descriptive analyses were stratified by calendar year of cohort entry.

Continuous variables and score values were described by mean, standard deviation, median, minimum, maximum, 1st and 3rd quartile. For dichotomous variables such as comorbidity or concomitant medication, frequencies and percentages were presented.

9.9.1.2 Safety outcomes

The primary safety outcomes were the three types of bleeding events IC hemorrhage, GI bleeding, and UG bleeding leading to hospitalization. The secondary safety outcomes were other bleedings, noninfective liver disease and all-cause mortality and the effectiveness outcomes were VTE, ischemic stroke and myocardial infarction.

Unadjusted incidence rates of primary and secondary safety outcomes were calculated for first-time users of RVX for all indications (excluding TKR/THR) and for-first-time users of PPC for the two main indications where PPC is SOC in Germany: SPAF and VTE in patients with no recent history of cancer.

9.9.2 Main statistical methods

9.9.2.1 Cohort analysis

In the cohort analysis, unadjusted incidence rates were calculated for all patients with the respective indication and stratified by sex, age at cohort entry, renal function at cohort entry, and history of diabetes at cohort entry. Unadjusted incidence rates per 100 person-years were calculated by dividing the number of events in the respective stratum by the total person-time of the respective stratum. Patients were censored at the first of the following: end of the first treatment episode (switching, discontinuation), occurrence of the outcome of interest, or end of follow-up (death, end of available data). 95% confidence intervals (CIs) were calculated using the relationship between the Poisson distribution and chi-square distribution (22).

9.9.2.2 Nested case-control analysis

The nested case-control analysis was based on all cases of four bleeding events (IC hemorrhage, GI bleeding, UG bleeding, and other bleeding) occurring during total follow-up (i.e., irrespective of treatment episode). The index date was set to the admission date of the respective hospitalization.

Up to 10 controls were matched to each case by indication, sex, age at index date (± 1 year), calendar year of index date, and SHI, using risk set sampling with time in cohort as the time axis. Eligible patients hospitalized for any reason at the index date of the case were excluded from the set of potential controls. Cases were eligible to be selected as a control before their index day and controls could be selected for more than one case.

Use status at index date with respect to RVX and with respect to PPC was categorized as:

- current use, if supply of RVX/PPC ended less than 31 days before the index date
- nonuse in the past year, if the supply of RVX/PPC ended more than 365 days before the index date, and
- recent use, if the supply of RVX/PPC ended in-between.

In the analyses, current users of RVX and PPC were compared to nonusers in the past year, i.e. RVX and PPC were not directly compared.

Conditional logistic regression analyses were used to estimate confounder-adjusted ORs of the four bleeding events (IC hemorrhage, GI bleeding, UG bleeding, and other bleeding) to compare current users of RVX/PPC with nonusers of RVX/PPC in the past year. Potential confounders included in the models were lifestyle factors, medical history, risk scores, and current use of medication of interest. Under the study design of incidence density sampling, the OR is an unbiased estimator of the incidence rate ratio (RR) (23).

9.9.3 Missing values

In GePaRD, missing data can only occur for core demographic variables (e.g. sex or age) though missings of these variables are very rare. Diagnoses or dispensings can only be identified in the database if they were coded. Thus, all patients for whom a certain diagnosis/dispensing was found in the database were considered as having the respective disease/being exposed to the respective drug. All others were considered as not having the disease/not being exposed to the drug. Therefore, uncoded diagnoses/dispensings resulted in misclassification and not in missing values.

9.9.4 Sensitivity analyses

9.9.4.1 Outpatient diagnoses of DVT

In order to avoid overestimation and increase the specificity of detection of DVT events, only events requiring hospitalization were used in the main analysis. In a sensitivity analysis, outpatient diagnoses for DVT were also taken into account.

9.9.4.2 Ischemic stroke

Usually ischemic strokes are coded with the ICD-10-GM code I63 (“cerebral infarction”). In a sensitivity analysis, events coded as I64 (“stroke not specified as hemorrhagic or ischemic”) were also included.

9.9.5 Amendments to the statistical analysis plan

9.9.5.1 Deviations from initially planned analytical approaches

Some details of the final analysis strategy deviate from the protocol-specified objectives.

- No SOC group was defined for the ACS indication; all analyses focused on first-time users of rivaroxaban due to the difficulties in identifying patients with ACS, low numbers of patients in the ACS cohorts, and high heterogeneity of SOC. These factors resulted in a small, heterogeneous cohort of patients who are not well defined, making it difficult to interpret any comparative analyses.
- Safety and effectiveness outcomes were not directly compared between first-time users of rivaroxaban and first-time users of SOC because residual confounding, which results from selective prescribing of rivaroxaban and SOC to different groups of patients, could not be fully eliminated during statistical analyses.
- Additionally, a nested case-control analysis examining confounder-adjusted risks of outcomes among rivaroxaban and SOC users was performed.

9.9.5.2 GePaRD-specific amendments to the common Data Strategy Document

The following GePaRD-specific amendments to the common Data Strategy Document for the pharmacoepidemiological studies in Germany, Netherlands UK and Sweden were made:

- Case-control matching: Up to 10 controls were matched to each case by indication, sex, age at index date (± 1 year), calendar year of index date, and SHI, using risk set sampling with time in cohort as the time axis. Eligible patients hospitalized for any reason at the index date of the case were excluded from the set of potential controls. Cases were eligible to be selected as a control before their index day and controls could be selected for more than one case.

9.10 Quality control

BIPS adheres to high standards throughout the research process based on robust methodologies, transparency and scientific independence and conducts studies in accordance with the Guidelines for Good Pharmacoepidemiology Practice (GPP) (24), Good Practice of Secondary Data Analysis (GPS) (25), Good Epidemiological Practice (GEP) (26), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (27), and the ENCePP Code of Conduct (28).

Standard operating procedures, work instructions and checklists are used to guide the conduct of a study. These procedures and documents include rules for secure and confidential data storage, methods to maintain and archive project documents, rules and procedures for writing, execution and quality control of SAS programming, standards for writing protocols and reports, and requirements for senior scientific review of key study documents.

GePaRD is based on deterministically linked claims data. The linkage of outpatient, hospital and dispensation data is performed at each SHI based on insurance member identifiers. The SHIs deliver the data to a third-party trust center where the data are pseudonymized and delivered to BIPS according to the data protection concept. Comprehensive plausibility checks are performed before pseudonymization, as well as before inclusion of new data into GePaRD.

10. Results

10.1 Participants

Overall, 277,954 persons received at least one dispensing of RVX and 474,225 persons received at least one dispensing of PPC during the enrollment period (see Figure 10–1).

Of the 277,954 persons who received at least one dispensing of RVX, 9836 (3.5%) were excluded because they had less than a year of baseline data and 1376 (0.5%) were excluded because they received RVX any time prior to cohort entry. Additionally, 644 persons (0.2%) were excluded because they were dispensed both study drugs, RVX and another direct oral anticoagulant (DOAC) or VKA, or RVX from two or more physicians at the date of the start dispensing. Finally, 50 persons who did not fulfill the age criteria (2-100 years), 1 person with no valid sex, and 463 (0.2%) with no valid place of residence in Germany were excluded. Thus, 265,584 patients (95.5%) fulfilled all inclusion criteria and were eligible for the cohort of first-time users of RVX.

Of the 474,225 persons who received at least one dispensing of PPC, 35,938 (7.6%) were excluded because they had less than a year of baseline data and 264,770 (55.8%) were excluded because they received PPC any time prior to cohort entry. Additionally, 523 persons (0.1%) were excluded because they were dispensed both study drugs, PPC and another VKA or DOAC, or PPC from two or more physicians at the date of the start dispensing. Finally, 13 persons who did not fulfil the age criteria (2-100 years), 1 person with no valid sex, and 253 (0.1%) with no valid place of residence in Germany were excluded. Thus, 172,727 patients (36.4%) fulfilled all inclusion criteria and were eligible for the cohort of first-time users of PPC.

The most common indication in first-time users of RVX was SPAF (48.1%), followed by TKR/THR (11.3%) and VTE-T without recent history of cancer (9.8%, see Annex 2.2 Table 1). In only 546 (0.2%) first-time users of RVX ACS was identified as indication. Use of RVX in the ACS indication, however, was only approved in May 2013 and the respective dose became available in Germany only in June 2014.

17.2% of first-time users of RVX were assigned the indication “other”, which included patients only fulfilling less stringent criteria of SPAF, VTE-T, TKR/THR, or ACS, patients with a diagnosis of PAD, patients with a diagnosis of CAD, or patients with an orthopedic surgery of upper limbs (see 9.4.1). In about 11.4% of the first-time users of RVX, no indication could be identified.

For first-time users of PPC, indication was only assessed with regard to SPAF and VTE-T without a history of cancer, where PPC is the SOC in Germany. The majority of patients (51.3%) received PPC for the SPAF indication, 11.9% received PPC for the indication VTE-T without a recent history of cancer.

About half (53.3%) of the first-time RVX users were women. Of these 141,676 women 14,953 were of childbearing age (11-50 years) and 778 pregnancies were identified, of which 15 pregnancies overlapped the date of the start dispensing. Most of these pregnancies (88.9%) resulted in live births; 52 pregnancies (6.7%) ended in terminations, 23 (3.0%) were ectopic pregnancies, 10 (1.3%) ended in miscarriages and 1 (0.1%) ended in a stillbirth (see Annex 2.2 Table 45). As pregnancies and pregnancy outcomes were ascertained during the entire follow-up period, not all fetuses were exposed to RVX.

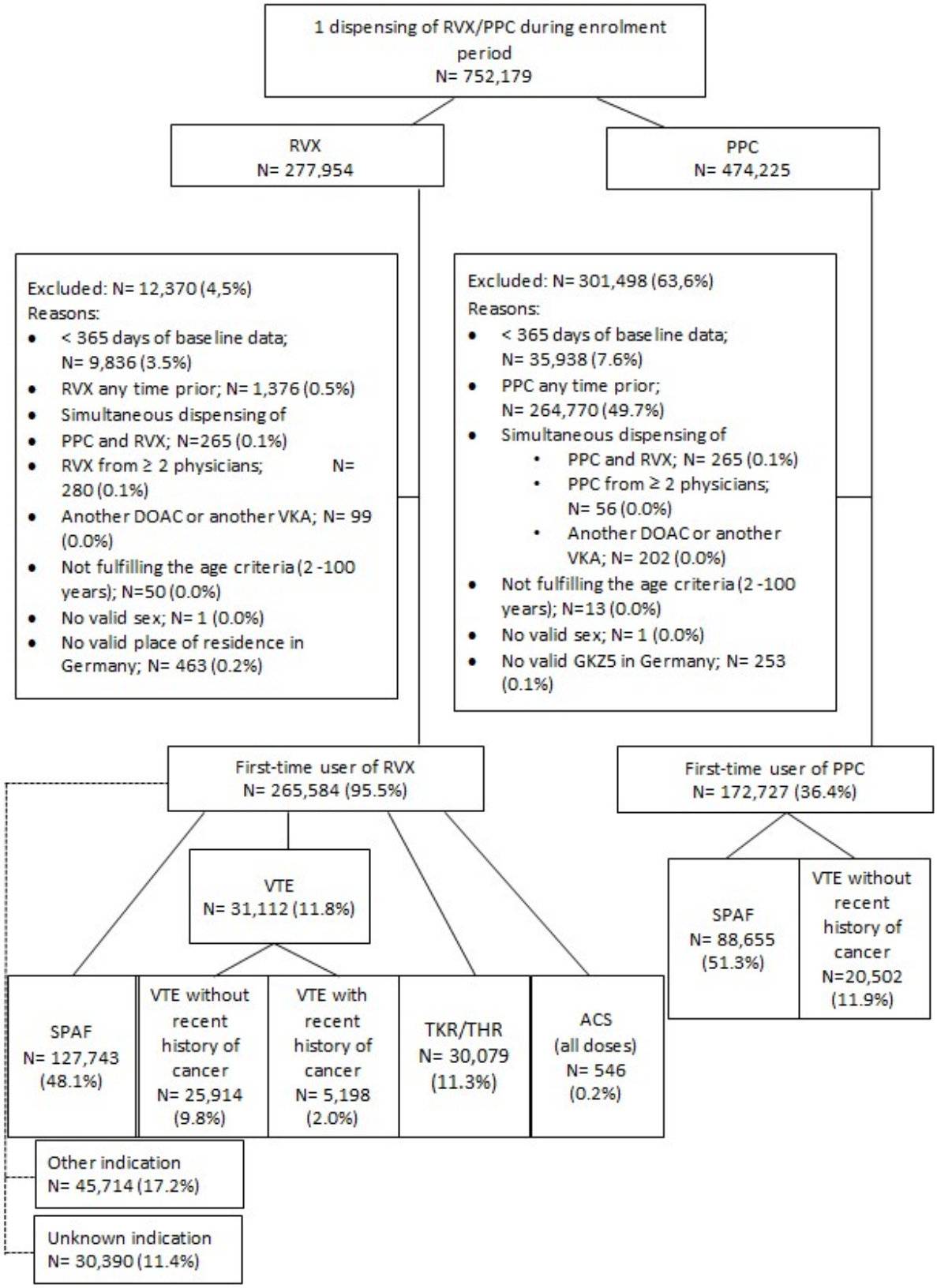

Figure 10–1: Flowchart of users of rivaroxaban (RVX) and phenprocoumon (PPC)

10.2 Descriptive data and drug utilization

10.2.1 SPAF

The majority (65.8%) of the first-time RVX users with the SPAF indication had a start dispensing of 20 mg and 28.2% an index dispensing of 15 mg which is indicated in patients with renal impairment (see Annex 2.2 Table 3).

For the majority of patients (61.3%) the first treatment episode was longer than 180 days, for 46.4% of patients longer than 365 days. In only 12.8% the first treatment episode was 30 days or less (see Annex 2.2 Table 3).

Patterns of RVX use were examined in patients with at least one year of follow-up and at least two dispensations of RVX (n = 98,682). More than half (60.0%) used RVX continuously in the first year of treatment (see Annex 2.2 Table 8). Of the 39,425 users who discontinued, 5,939 (15.1%) switched directly to a different NOAC (3,230) or a VKA (2705). The majority of the patients who discontinued RVX (56.3%) reinitiated oral anticoagulation in the first year of treatment, 88.2% of them with RVX. About 28.6% of the patients who discontinued RVX did not reinitiate oral anticoagulation in the first year of treatment.

About half of the patients with the SPAF indication were male; 51.5% of the first-time RVX users and 52.6% of the first-time PPC users (see Annex 2.2 Table 9). The median age was 75 years in both groups. However, more patients in the RVX group than the PPC group (10.0% vs.7.7%) were younger than 60 or older than 80 years (30.3% vs. 27.5%).

The vast majority of first-time PPC users (95.1%) had not used oral anticoagulants before cohort entry; in comparison, considerably fewer first-time RVX users were naive to oral anticoagulation (67.6%, see Annex 2.2 Table 9).

About 30% of the first-time PPC users entered the cohort between December 2011 and December 2012, whereas only 13.8% of first-time RVX users entered the cohort during these 13 months (see Annex 2.2 Table 9). About a quarter of the first-time RVX users entered in 2013. After this year, numbers declined over the years to 16.8% in 2016.

In early adopters, i.e. first-time RVX users in 2011, the proportion of males was higher (54.3% vs. 51.5% overall), more patients were between 60 and 70 years of age (26.1% vs. 18.3% overall) and less were 80 years or older (26.1% vs. 30.3% overall, see Annex 2.2 Table 10) compared with the overall cohort. Between 2012 and 2016, the proportion of males increased from 50.8% to 52.7%, the proportion of patients below 60 years of age increased from 7.6% to 11.7% and the proportion of patients aged 80 years or older decreased from 31.1% to 29.8%. During the entire enrollment period, the proportion of non-naive users decreased from 65.2% in 2011 to 24.0% in 2016.

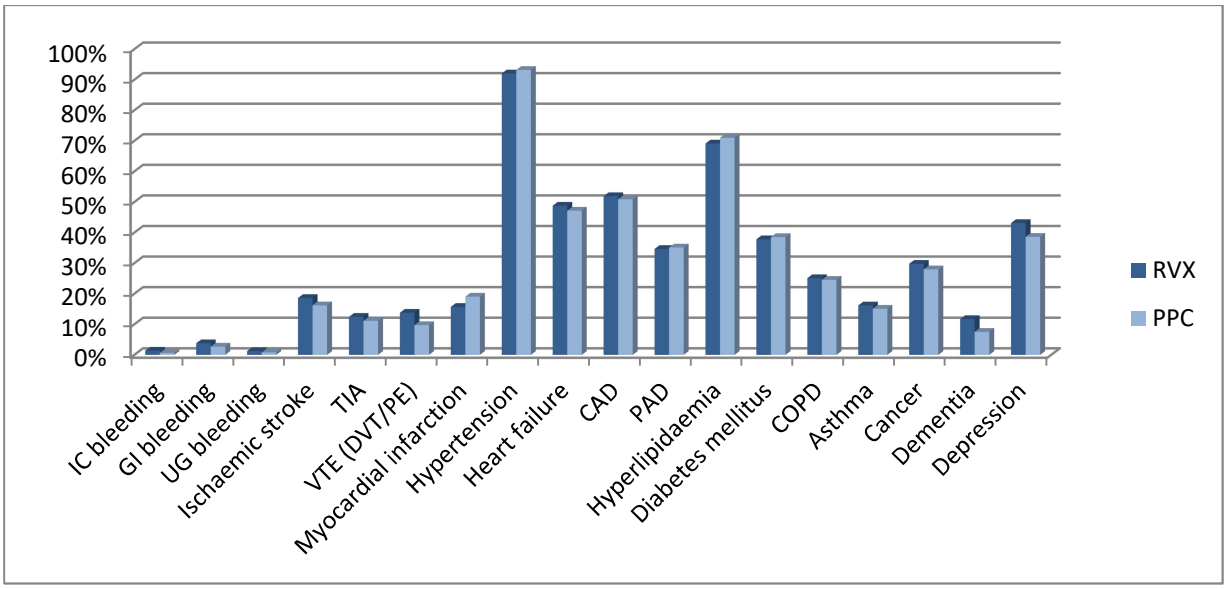

Figure 10–2: Medical history prior to cohort entry date in first-timer users (RVX vs PPC) with SPAF indication

First-time users of RVX more often had a history of IC, GI bleeding or UG bleeding compared to first-time users of PPC (1.3% vs. 0.6%, 3.8% vs. 2.7%, 1.2% vs. 0.8%, see Annex 2.2 Table 35). A previous diagnosis of ischemic stroke (18.6% vs. 16.2%), transient ischemic attack (TIA, 12.4% vs. 11.1%) or VTE (13.8% vs. 9.7%) was also more common in first-time users of RVX. Compared with first-time users of RVX, first-time users of PPC more often had a previous diagnosis of myocardial infarction (19.0% vs. 15.7%), hypertension (93.2% vs. 92.0%), PAD (35.1% vs. 34.6%), hyperlipidemia (71.0% vs. 69.1%), and diabetes mellitus (38.5% vs. 37.8%, see Annex 2.2 Table 35).

Accordingly, a dispensing of antiplatelets (19.6% vs. 12.1%), antihypertensive agents (89.1% vs. 87.0%) and especially angiotensin-converting-enzyme inhibitors (ACEis) (45.6% vs. 39.8%), diuretics (37.1% vs. 35.0%) statins (30.5% vs. 26.4%), and antidiabetic agents (16.4% vs. 15.1%) were more common among first-time users of RVX in the 90 days before cohort entry (see Annex 2.2 Table 27). First-time users of RVX more often had a previous diagnosis of heart failure (48.8% vs. 47.3%), CAD (51.9% vs. 50.9%), chronic obstructive pulmonary disease (COPD, 25.1% vs. 24.5%), asthma (16.2% vs. 15.1%), cancer (29.8% vs. 28.0 %), dementia (11.7% vs. 7.5%), and depression (43.1% vs. 38.6%)) than first-time users of PPC. They also more often had a dispensing of angiotensin receptor blockers (ARBs, 26.2% vs. 25.1%) and SSRIs (3.5% vs. 2.9%).

Polypharmacy was more frequent in first-time users of RVX: 11.1% of them received dispensings of 10 or more different ATC codes in the year before cohort entry, compared with 9.7% of PPC users (see Annex 2.2 Table 27). Similarly, first-time users of RVX more often had a dispensing of NSAIDs (16.2% vs. 15.2%), antiarrhythmic agents (10.1% vs. 9.1%), oral steroids (7.6% vs. 7.2%), PPIs (33.0 % vs. 31.8%), and antibiotics (17.9% vs. 16.7%) than first-time users of PPC in the 90 days before cohort entry.

In both cohorts, patients received medication with a special warning or precaution in the 90 days before cohort entry (see Annex 2.2 Table 27). The frequency of dispensings of CYP3A4 or P-GP inhibitors was higher in first-time users of PPC than in first-time users of RVX (9.2% vs. 8.4%). The frequency of dispensing of CYP3A4 inducers was low in both cohorts (07% vs. 0.6%).

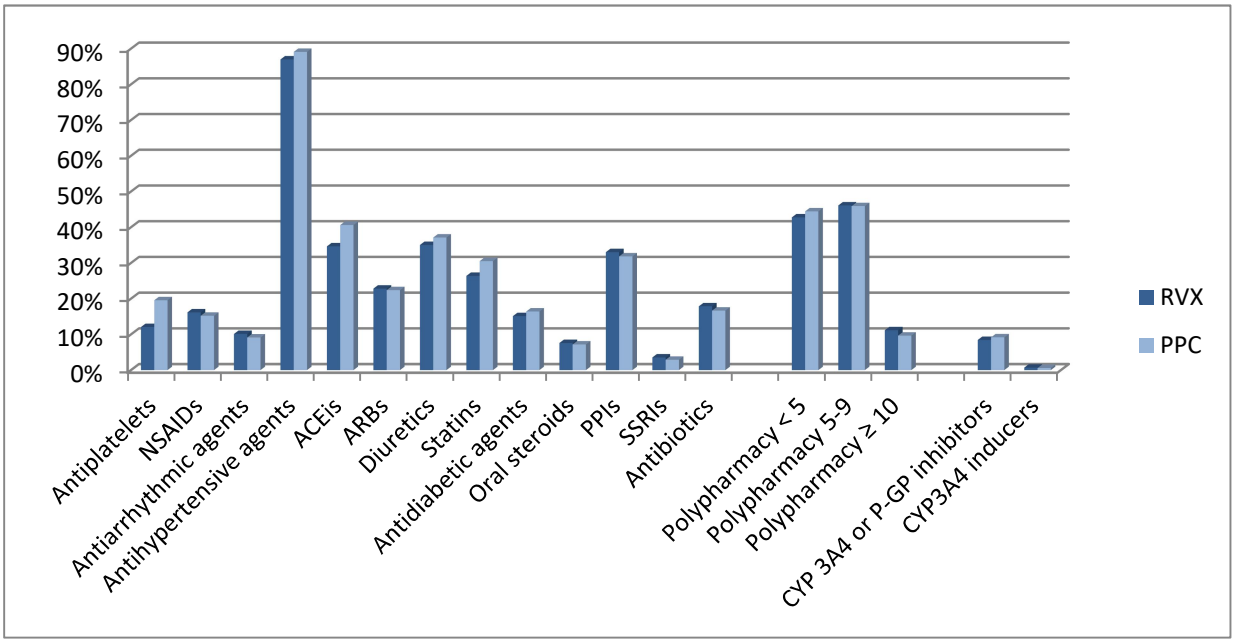

Figure 10–3: Medications of interest in the 90 days before or on start date in first-time users (RVX vs PPC) with SPAF indication

In both cohorts, the median CHA_2DS_2VASc score was 5 (see Annex 2.2 Table 39). More patients in the RVX than in the PPC cohort had a CHA_2DS_2VASc score below 2 (6.6% vs. 4.2%) or above 5 (33.5% vs. 30.6%). Similarly, the median HAS-BLED score was 3 in both cohorts, but more first-time users of RVX than of PPC had a value of 1 (9.6% vs. 8.0%) or above 3 (35.9% vs. 34.5%, see Annex 2.2 Table 40).

22.6% of first-time RVX users and 24.5% of first-time PPC users had been diagnosed with severe or moderate renal impairment (i.e. CKD stage 3-5 or a code indicating dialysis) at cohort entry (see Annex 2.2 Table 41). In both cohorts, the majority of patients with a diagnosis of CKD were in stage 3 (12.5% RVX and 11.9% PPC). More first-time users of PPC than RVX (3.3% vs. 2.4%) with a diagnosis of CKD were in stage 4 (severe renal impairment) and stage 5 (= kidney failure, 2.1% vs. 0.6%).

In both cohorts, about a quarter of patients were not hospitalized in the 12 months before or on the date of cohort entry (26.2% RVX vs. 26.6% PPC, see Annex 2.2 Table 19). First-time users of RVX, however, were more frequently hospitalized two or more times than first-time users of PPC (30.9 vs. 29.2).

Slightly more than a third of the first-time RVX (38.5%) and PPC (39.3%) users had a diagnosis of obesity (see Annex 2.2 Table 23). 6.5% of first-time RVX users and 6.0% of first-time PPC users had a diagnosis indicating alcohol abuse.

Regarding SES, first-time RVX users were more often living in regions with the lowest deprivation/highest SES (27.2% vs. 20.8%) or highest deprivation/lowest SES (14.2% vs. 13.7%, see Annex 2.2 Table 23) than first-time PPC users.

The median duration of the first treatment episode was 303 days (25%-percentile 98 days - 5%-percentile 788 days) in first-time RVX users and 670 days (192 - 1320) in first-time PPC users. Median total follow-up was 1077 days (661-1520) for first-time RVX users and 1321 days (815-1791) for first-time PPC users.

10.2.2 VTE-T without recent history of cancer

The majority (56.1%) of the first-time RVX users with the indication VTE-T without recent history of cancer had an index dispensing of 15 mg, which corresponds to the recommended initial dose of 15 mg twice per day (see Annex 2.2 Table 4). 17.0% of patients received multiple tablet strengths at start date and 24.6% received a dispensing of 20 mg, which is the recommended dose after the first 21 days. No patient received the combination package of 15 and 20 mg because the marketing authorization in Germany was granted in April 2017.

For about half of first-time RVX users (54.6%) the first treatment episode was longer than 180 days, which is the recommended minimum duration (see Annex 2.2 Table 4). For about a quarter (28.7%) of patients the first treatment episode was longer than 365 days and in only 10.7% the first treatment episode was 30 days or fewer.

More than 50% of the patients with indication VTE-T without recent history of cancer were female, 54.2% of the first-time RVX users and 54.7% of the first-time PPC users (see Annex 2.2 Table 11). The median age was 62 years in the RVX group and 65 years in the PPC group. More first-time users in the RVX group than the PPC group (26% vs. 23.2%) were younger than 50 years and more PPC users than RVX users were older than 80 years (14.6% vs. 14.0%).

The vast majority of first-time PPC users (99.1%) had not used oral anticoagulants before cohort entry; less first-time RVX users than PPC users were naive (88.0%, see Annex 2.2 Table 11).

More than a third (36.6%) of the first-time PPC users entered the cohort between December 2011 and 2012, whereas only 7.9% of the first-time RVX users entered the cohort during this time period (see Annex 2.2 Table 11). The proportion of first-time users of RVX entering the cohort increased from 20.7% in 2013 to 24.3% in 2015.

In early adopters, i.e. first-time RVX users in 2011, the proportion of males was higher (57.1% vs. 45.8% overall), more patients were under the age of 60 (57.1% vs. 44.7% overall) and fewer were 80 years or older (7.1% vs. 14.0% overall, see Annex 2.2 Table 12) compared with the overall cohort. Between 2012 and 2016, the proportion of males increased from 44.6% to 47.0%, the proportion of patients below 60 years of age increased from 42.5% to 45.1% and the proportion of patients aged 80 years or older decreased from 17.8% to 13.4%. During the entire enrollment period, the proportion of naive patients increased from 64.3% in 2011 to 90.1% in 2016.

A previous history of VTE was more frequent in first-time users of RVX (28.1%) than in first-time users of PPC (21.4%, see Annex 2.2 Table 36). First-time users of RVX more often had a history of IC, GI bleeding or UG bleeding than first-time users of PPC (0.9% vs. 0.5%, 1.7% vs. 1.6%, 0.8% vs. 0.7%, respectively). They also had more often a previous diagnosis of ischemic stroke (7.0% vs. 6.5%), TIA (5.8% vs. 5.7%), asthma (17.6% vs. 17.0%), dementia (8.3% vs. 6.4%), and depression (42.9% vs. 41.3%). First-time users of PPC more often had a previous diagnosis of myocardial infarction (6.5% vs. 6.2%), hypertension (66.0% vs. 63.0%), heart failure (22.1% vs. 21.1%), CAD (24.6% vs. 23.3%), PAD (20.8% vs. 19.8%), hyperlipidemia (52.6% vs. 50.2%), diabetes mellitus (23.1% vs. 21.5%), and COPD

(19.3% vs. 17.6%). The proportion of patients with liver disease and cancer was similar between both groups.

Accordingly, first-time PPC users more often had a dispensing of antiplatelets (5.5% vs. 5.0%, see Annex 2.2 Table 28), antihypertensive agents (48.1% vs. 44.4%), diuretics (18.0% vs. 15.9%), statins (11.3% vs. 10.5%), and antidiabetic agents (7.9% vs. 7.1%) than first-time users of RVX in the 90 days before cohort entry. First-time users of RVX more often had a dispensing of NSAIDs (26.1% vs. 25.1%), SSRIs (4.2% vs. 3.5%), and antibiotics (23.8% vs. 23.5%) than first-time users of PPC in the 90 days before cohort entry.

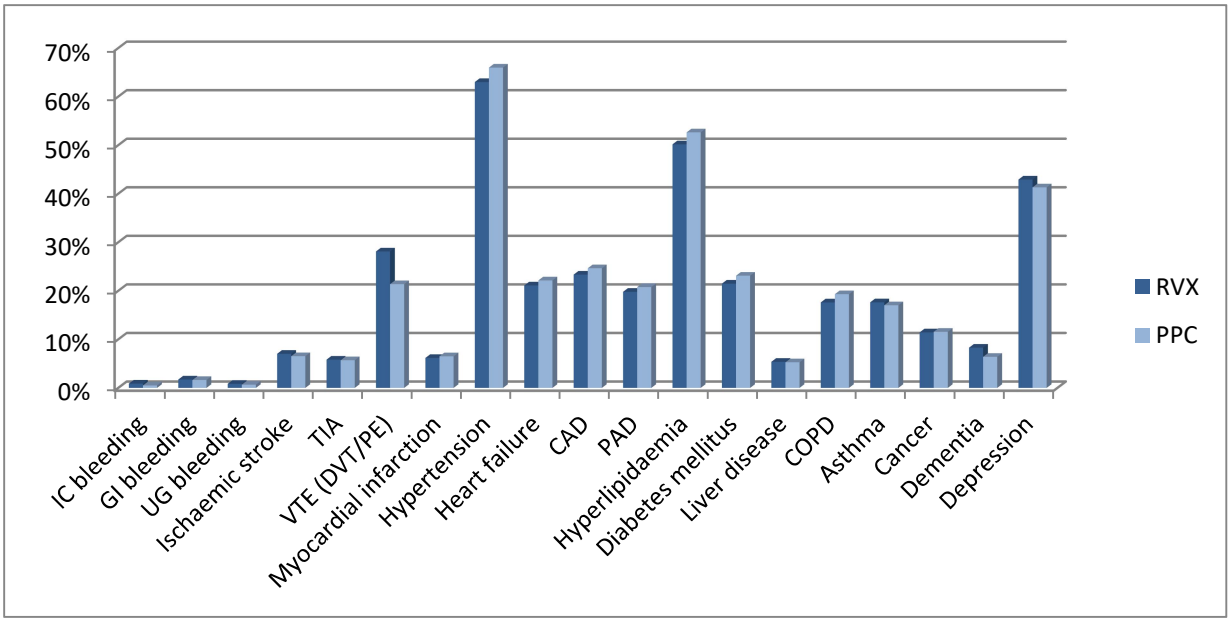

Figure 10–4: Medical history prior to start date in first-timer users (RVX vs PPC) with VTE indication without recent history of cancer

Polypharmacy was more frequent in first-time users of PPC: 31.3% of them received dispensings of 4 or more different ATC codes in the year before cohort entry, compared with 28.7% of RVX users and 4.4% received dispensings of 10 or more different ATC codes compared with 3.7%.

In both cohorts, patients received medication with a special warning or precaution in the 90 days before cohort entry (see Annex 2.2 Table 28). The proportion of patients dispensed CYP3A4 or P-GP inhibitors was higher in first-time users of PPC than in first-time users of RVX (4.0% vs. 3.3%). In both groups, the frequency of dispensings of CYP3A4 was low (0.8%).

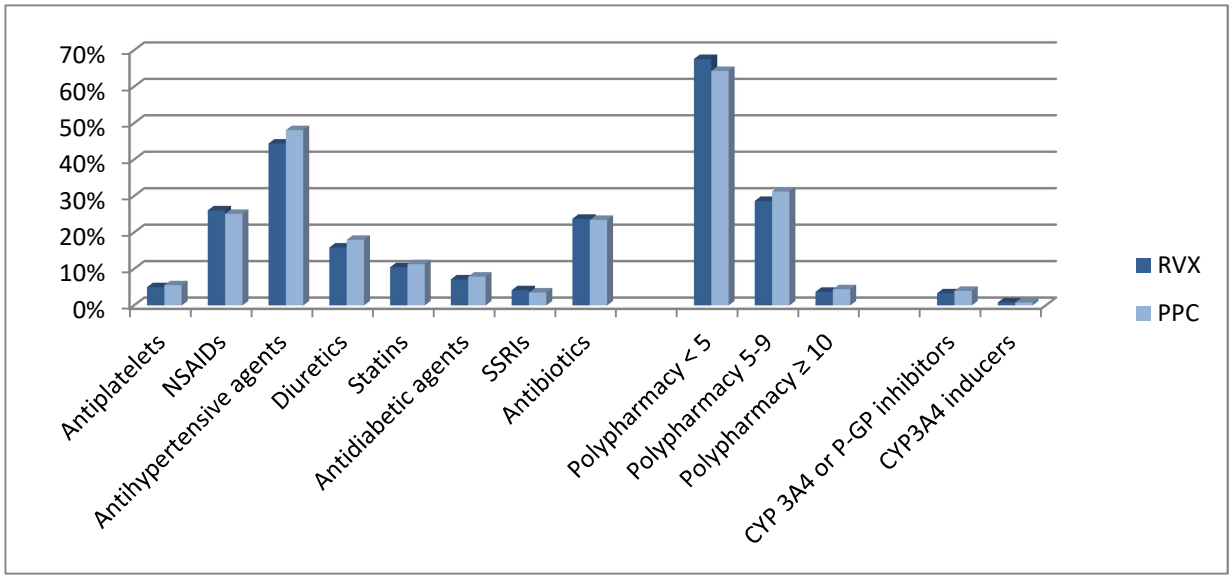

Figure 10–5: Medications of interest in the 90 days before or on start date in first-time users (RVX vs PPC) with VTE indication without recent history of cancer

11.6% of first-time users of RVX and 15.5% of first-time users of PPC had been diagnosed with severe or moderate renal impairment (i.e. CKD stage 3-5 or a code indicating dialysis) at cohort entry (see Annex 2.2 Table 42). In both cohorts, the majority of patients with a diagnosis of CKD were in stage 3 (6.0% RVX and 7.6% PPC). More first-time users of PPC than first-time users of RVX (2.0% vs. 0.9%) were in stage 4 (severe renal impairment) and stage 5 (= kidney failure, 1.0% vs. 0.3%).

Compared with first-time users of RVX, first-time users of PPC were more frequently hospitalized once (48.2% vs. 46.2%) in the 12 months before or on the date of cohort entry or two or more times (30.6% vs. 27.1%, see Annex 2.2 Table 20).

Slightly more than a third of the first-time RVX (35.5%) and PPC (36.5%) users had a diagnosis of obesity (see Annex 2.2 Table 24). 5.6% of first-time RVX users and 5.3% of first-time PPC users had a diagnosis indicating alcohol abuse.

Regarding SES, first-time RVX users were more often living in regions with the lowest deprivation/highest SES (27.6% vs. 22.2%) or highest deprivation/lowest SES (13.5% vs. 13.0%, see Annex 2.2 Table 24).

The median duration of the first treatment episode was 207 days (25%-percentile 102 days - 5%-percentile 412 days) in first-time RVX users and 260 days (100 - 623) in first-time PPC users. Median total follow-up was 1033 days (664-1434) for first-time RVX users and 1494 days (969-1896) for first-time PPC users (see Annex 2.2 Table 2).

10.2.3 VTE-T with recent history of cancer

The majority of first-time RVX users with the indication VTE-T with recent history of cancer had an index dispensing of 15 mg (53.8%), which corresponds to the recommended initial dose of 15 mg twice per day (see Annex 2.2 Table 5). 13.0% of patients received multiple tablet strengths at start date and 30.2% received a dispensing of 20 mg, which is the recommended dose after the first 21 days. No patient received the combination package of 15 and 20 mg because the marketing authorization was granted in April 2017 in Germany.

For the majority of first-time RVX users (53.9%) the first treatment episode was longer than 180 days, which is the recommended minimum duration (see Annex 2.2 Table 5). For 30.0% of patients the first treatment episode was longer than 365 days and in only 12.0% the first treatment episode was 30 days or fewer.

About half (54.1%) of first-time users of RVX with the indication VTE-T with recent history of cancer were female (see Annex 2.2 Table 13). The median age was 72 years and 64.0% of first-time users of RVX were in the age group of 60-79 years.

The vast majority (87.2%) of first-time RVX users with the indication VTE-T with recent history of cancer had not used oral anticoagulants before cohort entry and were classified as naive (see Annex 2.2 Table 13).

Only one first-time RVX user entered the cohort between December 2011 and 2012 (see Annex 2.2 Table 13). The proportion of first-time users of RVX entering the cohort increased from 20.9% in 2013 to 24.3% in 2015.

Between 2012 and 2016, the proportion of males fluctuated around 46%, the proportion of patients below 60 years of age around 17% and the proportion of patients aged 80 years around 19% (see Annex 2.2 Table 14). During the entire enrollment period, the proportion of naive users increased from 77.4% in 2012 to 90.4% in 2016.

A third (33.6%) of the patients had a previous history of VTE (see Annex 2.2 Table 37). Only few first-time users of RVX had a history of bleeding events (IC bleeding 0.8%, GI bleeding 2.6% and UG bleeding 1.9%). The most frequent comorbidities at baseline were hypertension (78.0%), hyperlipidemia (61.0%), history of depression (51.4%), CAD (31.6%), diabetes (30.4%), heart failure (28.0%), PAD (27.6%), and COPD (24.6%). The most frequent medications of interest were antihypertensive agents (53.1%), PPIs (43.4%), antibiotics (30.0%), diuretics (22.0%), oral steroids (22.1%), and NSAIDs (20.6%) (see Annex 2.2 Table 29).

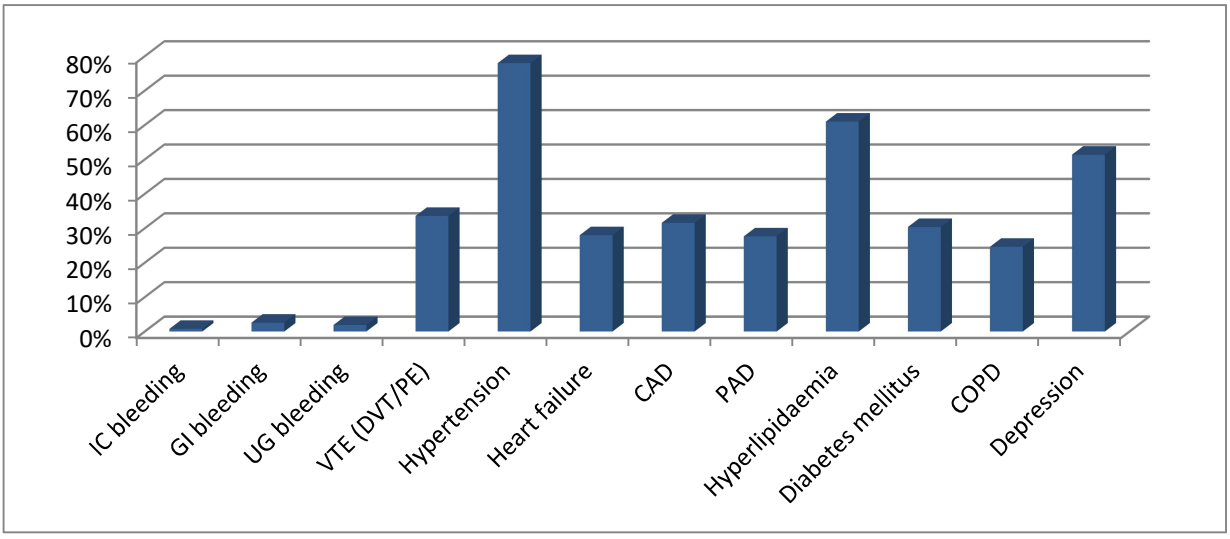

Figure 10–6: Medical history prior to start date in first-timer users of RVX with VTE indication with recent history of cancer

About half (51.6%) of first-time RVX users received dispensings of more than 4 different ATC codes in the year before cohort entry, 7.5% received dispensings of 10 or more different ATC codes (see Annex 2.2 Table 29).

Only few first-time users of RVX received medication with a special warning or precaution in the 90 days before cohort entry (see Annex 2.2 Table 29): 0.7% received CYP3A4 inducers and 2.9% received CYP3A4 or P-GP inhibitors.

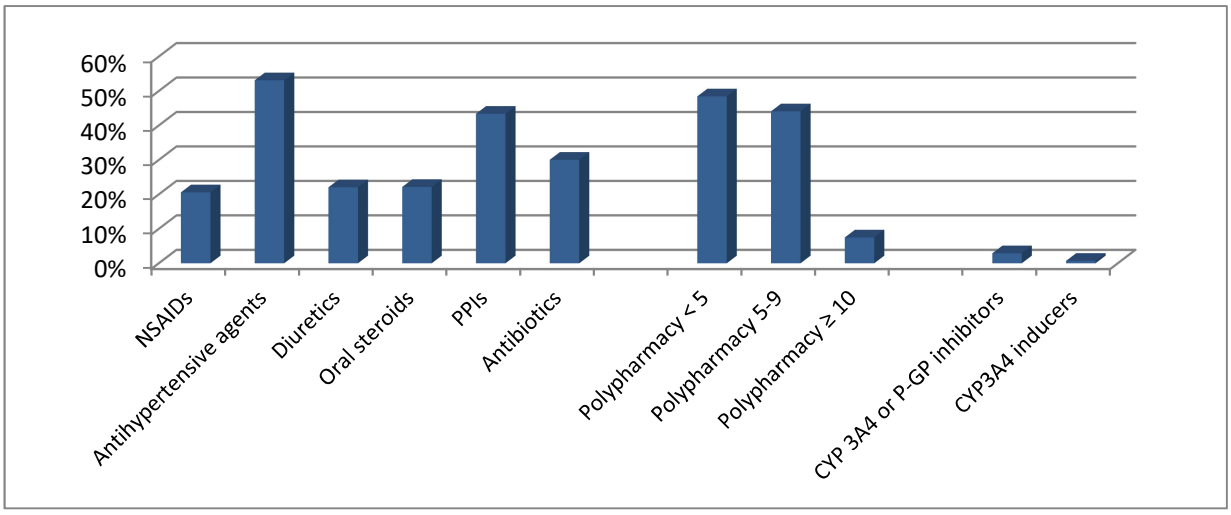

Figure 10–7: Medications of interest in the 90 days before or on start date in first-time users of RVX with VTE indication with recent history of cancer

About a fifth of VTE-T patients with a recent history of cancer (20.4%) had been diagnosed with severe or moderate renal impairment (i.e. CKD stage 3-5 or a code indicating dialysis) at cohort entry (see Annex 2.2 Table 43). The majority of patients with a diagnosis of CKD were in stage 3 (10.8%), 1.8% were in stage 4 (severe renal impairment) and only 0.4% in stage 5 (= kidney failure).

More than 80% of patients were hospitalized in the 12 months before or on the date of cohort entry (87.4%); 58.1% were hospitalized more than once (see Annex 2.2 Table 21).

About a third of the first-time RVX users (35.8%) had a diagnosis of obesity (see Annex 2.2 Table 25). 5.3% of RVX first-time users had a diagnosis indicating alcohol abuse.

Regarding SES, first-time RVX users were more often living in regions with the lower deprivation/higher SES: 48.3% lived in the upper two quintiles of SES and only 12.7% in the lowest quintile.

The median duration of the first treatment episode was 201 days (88 - 413) in first-time RVX users. Median total follow-up was 824 days (450 – 1286) for first-time RVX users (see Annex 2.2 Table 2).

10.2.4 THR/TKR

The vast majority of first-time RVX users with the THR/TKR indication had an index dispensing of 10 mg (92.5%), which is the recommended dose for 35 days following hip replacement surgery and 14 days following knee replacement surgery (see Annex 2.2 Table 6). 3.1% of the patients received 15 mg and 4.2% received 20 mg.

For the majority of first-time RVX users (75.7%) the first treatment episode was 60 days or fewer. In 24.3% of the patients the first treatment episode was longer than 60 days, in 4.9% even longer than 180 days (see Annex 2.2 Table 6).

The majority (65.4%) of first-time users of RVX who underwent THR/TKR were female (see Annex 2.2 Table 15). The median age was 68 years and more than a third of first-time users were in the age group of 70-79 years (36.5%).

The proportion of first-time users of RVX increased from 14.5% in 2012 to 22.8% in 2016 (see Annex 2.2 Table 15). Neither the age nor the male-to-female ratio of the cohort changed during this time (see Annex 2.2 Table 16).

10.2.5 ACS

Only 546 first-time users of RVX with ACS were identified (see Annex 2.2 Table 7). Of these, only 24 (4.4%) had an index dispensation of 2.5 mg which corresponds to the recommended dose of 2.5 mg twice daily.

More than 20% (23.1%) of the patients with the ACS indication entered the cohort before the ACS indication was approved in May 2013 (see Annex 2.2 Table 17). Based on an assumed daily dose of 5 mg (see 9.4.3.1), the first treatment episode was longer than 180 days for 70.0% of the first-time RVX users and for 57.7% longer than 365 days (see Annex 2.2 Table 7).

Owing to the likely misclassification of indication in patients who received RVX tablets with a strength of 10 mg or higher, presentation of results is focused on RVX first-time users with a start dispensing of 2.5 mg.

15 of the 24 first-time users of RVX with the ACS indication and start dispensing of 2.5 mg were male (62.5%) and the median age was 62.5 years (see Annex 2.2 Table 17).

No first-time user of RVX with the ACS indication and start dispensing of 2.5 mg had a history of bleeding (see Annex 2.2 Table 38). The most frequent comorbidities were a history of myocardial infarction excluding the event necessitating treatment (91.7%), hypertension (87.5%), hyperlipidemia (79.2%), history of depression (45.8%), asthma (33.3%), heart failure (29.2%), cancer (25.0%), and PAD (20.8%). The most frequent medications of interest were antiplatelets (95.8%), antihypertensive agents (91.7%), statins (87.5%), PPIs (54.2%), diuretics (37.5%), and antibiotics (20.8%).

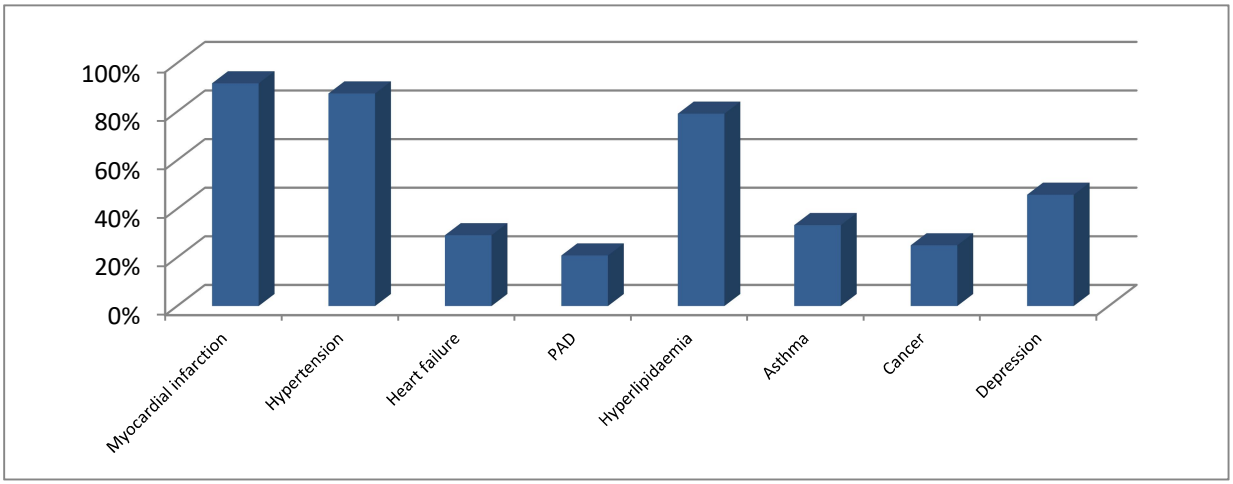

Figure 10–8: Medical history prior to start date in first-timer users of RVX with ACS indication

Half of first-time RVX users with the ACS indication and start dispensing of 2.5 mg received dispensings of more than 4 different ATC codes in the year before cohort entry and 1 patient (4.2%) received dispensings of 10 or more different ATC codes (see Annex 2.2 Table 30).

Four first-time RVX users with the ACS indication and start dispensing of 2.5 mg received medication with a special warning or precaution in the 90 days before cohort entry (see Annex 2.2 Table 30). All of them received CYP3A4 or P-GP inhibitors and no patient received CYP3A4 inducers.

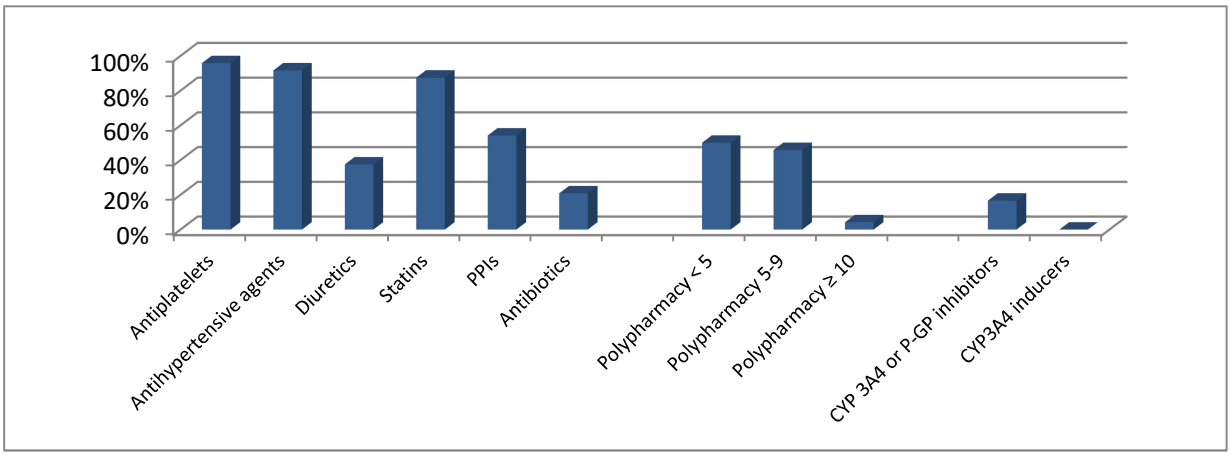

Figure 10–9: Medications of interest in the 90 days before or on start date in first-time users of RVX with ACS indication

Only 4 first-time users of 2.5 mg of RVX (16.7%) had severe or moderate renal impairment (i.e. CKD stage 3-5 or a code indicating dialysis) at cohort entry (see Annex 2.2 Table 44). Three of them were in stage 3 and one patient had unclassified CKD.

Owing to their indication, all 24 first-time RVX users with the ACS indication and start dispensing of 2.5 mg were hospitalized in the 12 months before or on the date of cohort entry, 12 of them even more than once (see Annex 2.2 Table 22).

A third of the first-time RVX users with the ACS indication and a start dispensing of 2.5 mg had a diagnosis of obesity (see Annex 2.2 Table 26). None of the first-time users of RVX had a diagnosis indicating alcohol abuse.

Regarding socioeconomic status, first-time RVX users with the ACS indication and a start dispensing of 2.5 mg were more often living in regions with the lowest deprivation/highest SES: 58.3% lived in the upper two quintiles of SES and only 8.3% in the lowest quintile (see Annex 2.2 Table 26). Based on an assumed daily dose of 5 mg, the median duration of the first treatment episode was 394 days (126 - 784) in first-time RVX users irrespective of tablet strength of start dispensing (see Annex 2.2 Table 2). Median total follow-up of start dispensing was 940.5 days (520 - 1462) irrespective of tablet strength.

10.3 Outcome data

10.3.1 SPAF

During total follow-up, a total of 21,462 bleeding events were observed in 127,743 first-time RVX users and 88,655 first-time PPC users (see Table 10–1:). Within both cohorts, GI bleedings were the most frequent bleeding event with 9,769 cases (42.7%), followed by other

bleedings with 4,924 cases (22.9%), IC bleedings with 3,995 cases (18.6%) and urogenital UG bleedings with 2,774 events (12.9%).

During the first RVX treatment episode, 5,980 bleeding events were observed in 127,743 first-time RVX users (see Table 10–1:). Among these first-time RVX users, GI bleedings were the most frequent bleeding event with 2,988 cases (49.9%) followed by other bleedings with 1,205 cases (20.2%), IC bleedings with 938 cases (15.7%) and urogenital UG bleedings with 849 cases (14.2%).

During the first PPC treatment episode, 5,549 bleeding events were observed in 88,655 first-time PPC users (see Table 10–1:). Overall, GI bleedings were the most frequent bleeding event with 2,219 cases (40%), followed by other bleedings with 1,719 cases (31%), IC bleedings with 946 cases (17.1%) and urogenital UG bleedings with 665 cases (11.9%).

Table 10–1: Number of bleeding events in first-time users of RVX and first-time users of PPC - SPAF cohort

		RVX	PPC
	N = 216,398	N = 127,743	N = 88,655
	total follow-up	first treatment episode	first treatment episode
Primary safety outcomes, n (%)			
Intracranial bleeding	3,995 (18.6)	938 (15.7)	946 (17.1)
Gastrointestinal bleeding	9,769 (45.5)	2,988 (49.9)	2,219 (40)
Urogenital bleeding	2,774 (12.9)	849 (14.2)	665 (11.9)
Secondary safety outcomes, n (%)			
Other bleeding	4,924 (22.9)	1,205 (20.2)	1,719 (31)
Any bleeding (total)	**21,462**	**5,980**	**5,549**

Source: Annex 2.2 Table 46, Annex 2.2 Table 49, Annex 2.2 Table 52, Annex 2.2 Table 55, Annex 2.2 Table 79, Annex 2.2 Table 87, Annex 2.2 Table 95 and Annex 2.2 Table 103
RVX, rivaroxaban; PPC, phenprocoumon; SPAF, stroke prevention in nonvalvular atrial fibrillation

10.3.2 VTE-T without recent history of cancer

During total follow-up, 2,425 bleeding events were observed in 25,914 first-time RVX users and 20,502 first-time PPC users (see Table 10–2).

During the first RVX treatment episode, 589 bleeding events were observed in 25,914 first-time RVX users (see Table 10–2). Overall, GI bleedings were the most frequent bleeding event with 264 cases (44.8%) followed by UG bleedings with 155 cases (26.3%), other bleedings with 103 cases (17.5%) and IC bleedings with 67 cases (11.4%).

During the first PPC treatment episode, 657 bleeding events were observed in 20,502 first-time PPC users (see Table 10–2). Overall, GI bleedings were the most frequent bleeding event with 263 cases (40.0%), followed by other bleedings with 204 cases (31.1%), UG bleedings with 102 cases(15.5%) and IC bleedings with 88 cases (13.4%). Within both cohorts, GI bleedings were the most frequent bleeding event with 1,080 cases (44.5%), followed by other bleedings with 520 cases (21.4%), UG bleedings with 465 events (19.2%) and IC bleedings with 360 cases (14.9%).

During the first RVX treatment episode, 589 bleeding events were observed in 25,914 first-time RVX users (see Table 10–2). Overall, GI bleedings were the most frequent bleeding event with 264 cases (44.8%) followed by UG bleedings with 155 cases (26.3%), other bleedings with 103 cases (17.5%) and IC bleedings with 67 cases (11.4%).

During the first PPC treatment episode, 657 bleeding events were observed in 20,502 first-time PPC users (see Table 10–2). Overall, GI bleedings were the most frequent bleeding event with 263 cases (40.0%), followed by other bleedings with 204 cases (31.1%), UG bleedings with 102 cases(15.5%) and IC bleedings with 88 cases (13.4%).

Table 10–2: Number of bleeding events in first-time users of RVX and first-time users of PPC - VTE-T without recent history of cancer cohort

	RVX N = 25,914		PPC N = 20,502	
	total follow-up	**first treatment episode**	**first treatment episode**	
Primary safety outcomes				
Intracranial bleeding, n (%)	360 (14.8)	67 (11.4)	88 (13.4)	
Intracerebral, n	-	*28*	*42*	
Subarachnoid, n	-	*14*	*15*	
Subdural/extradural, n	-	*25*	*31*	
Gastrointestinal bleeding, n (%)	1,080 (44.5)	264 (44.8)	263 (40.0)	
Urogenital bleeding, n (%)	465 (19.2)	155 (26.3)	102 (15.5)	
Secondary safety outcomes, n (%)				
Other bleeding	520 (21.4)	103 (17.5)	204 (31.1)	
Any bleeding (total)	**2,425**	**589**	**657**	

Source: Annex 2.2 Table 47, Annex 2.2 Table 50, Annex 2.2 Table 53, Annex 2.2 Table 56, Annex 2.2 Table 83, Annex 2.2 Table 91, Annex 2.2 Table 99 and Annex 2.2 Table 107

RVX, rivaroxaban; PPC, phenprocoumon; VTE-T, treatment and secondary prevention of venous thromboembolism

10.3.3 ACS indication

During the first treatment episode, 46 bleeding events were observed in 546 first-time RVX users. Overall, GI bleedings were the most frequent bleeding event with 29 cases (63.0%), followed by other bleedings with 9 cases (19.6%), UG bleedings with 6 events (13.0%), and IC bleedings with 2 cases (4.4%).

10.4 Main Results

10.4.1 Cohort Analysis

10.4.1.1 SPAF

10.4.1.1.1 IC hemorrhage

During the first treatment episode, 938 IC hemorrhages were observed in 175,578.2 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.53 (95% CI 0.50-0.57) per 100 person-years (see Annex 2.2 Table 46). Most (59%) of the IC hemorrhages were intracerebral with an incidence rate of 0.32 (0.29-0.34) per 100 person-years.

The incidence rate of IC hemorrhage in male first-time RVX users was 0.55 (0.50-0.60) per 100 person-years and 0.52 (0.48-0.57) per 100 person-years in female first-time RVX users.

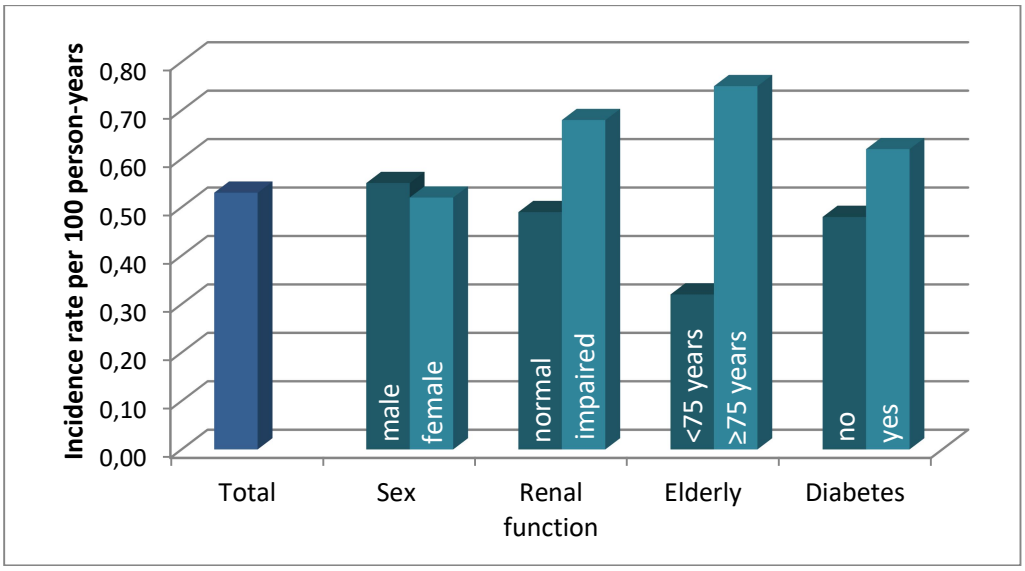

Figure 10–10: Incidence rate of IC bleeding associated with first use of RVX

The incidence rate increased with age from 0.08 (0.01-0.28) per 100 person-years in first-time RVX users younger than 50 years to 1.07 (0.81-1.40) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.75 (0.70-0.82) per 100 person-years, compared with 0.32 (0.28-0.36) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of IC hemorrhage was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.68 vs. 0.49 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.62 vs. 0.48 per 100 person-years).

During the first treatment episode, 946 IC hemorrhages were observed in 194,598.6 years of follow-up of first-time PPC users, resulting in an incidence rate of 0.49 (95% CI 0.46-0.52) per 100 person-years. Most (44.3%) of the IC hemorrhages were intracerebral with an incidence rate of 0.21 (0.19-0.24) per 100 person-years.

Incidence rate of IC hemorrhage in male first-time PPC users was 0.49 (0.45-0.53) per 100 person-years and 0.48 (0.44-0.53) per 100 person-years in female first-time PPC users.

The incidence rate increased with age from 0.23 (0.07-0.53) per 100 person-years in first-time PPC users younger than 50 years to 0.94 (0.63-1.35) per 100 person-years in first-time PPC users aged 90 years or older.

10.4.1.1.2 GI bleeding

During the first treatment episode, 2988 GI bleedings were observed in 173,832.2 years of follow-up of first-time RVX users, resulting in an incidence rate of 1.72 (95% CI 1.66-1.78) per 100 person-years (see Annex 2.2 Table 49).

The incidence rate of GI bleeding in male first-time RVX users was 1.66 (1.57-1.74) per 100 person-years and 1.78 (1.69-1.88) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.42 (0.21-0.76) per 100 person-years in first-time RVX users younger than 50 years to 3.83 (3.31-4.41) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older,

the incidence rate was 2.45 (2.35-2.56) per 100 person-years, compared to 1.01 (0.95-1.08) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of GI bleeding was higher in first-time RVX users with impaired renal function than in users with normal renal function (2.86 vs. 1.35 per 100 person-years) and in first-time RVX users with diabetes than in those without (2.14 vs. 1.46 per 100 person-years).

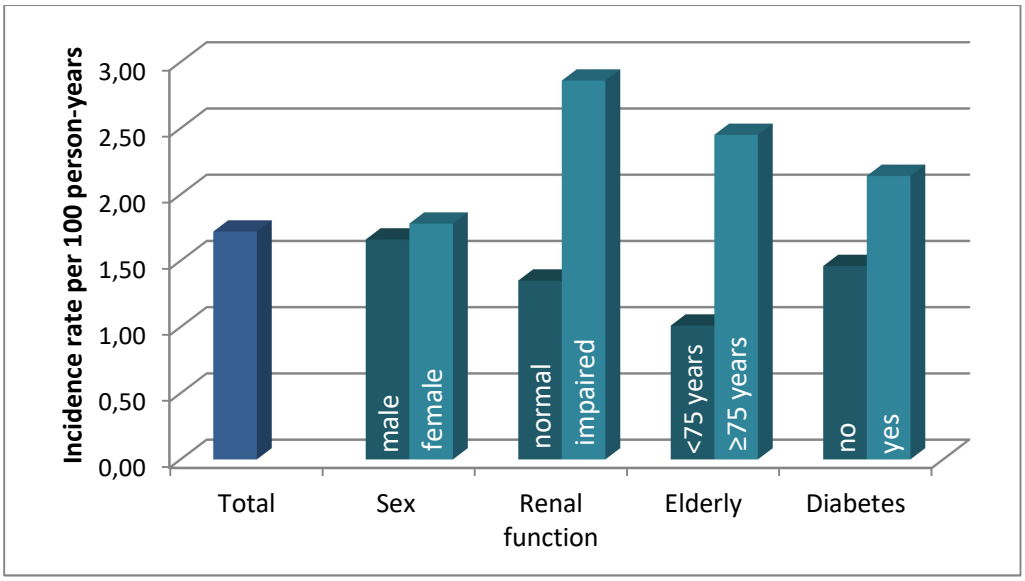

Figure 10–11: Incidence rate of GI bleeding associated with first use of RVX

During the first treatment episode, 2219 GI bleedings were observed in 192,655.8 years of follow-up of first-time PPC users, resulting in an incidence rate of 1.15 (95% CI 1.10-1.20) per 100 person-years.

The incidence rate of GI bleeding in male first-time PPC users was 1.14 (1.07-1.20) per 100 person-years and 1.17 (1.10-1.24) per 100 person-years in female first-time PPC users.

The incidence rate increased with age from 0.59 (0.32-1.01) per 100 person-years in patients younger than 50 years to 2.30 (1.80-2.91) per 100 person-years in patients aged 90 years or older.

10.4.1.1.3 Urogenital bleeding

During the first treatment episode, 849 UG bleedings were observed in 175,113.2 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.48 (95% CI 0.45-0.52) per 100 person-years (see Annex 2.2 Table 52).

The incidence rate of UG bleeding in male first-time RVX users was 0.57 (0.53-0.63) per 100 person-years and 0.39 (0.35-0.44) per 100 person-years in female first-time RVX users.

The incidence rate varied between age groups. It was highest in first-time RVX users younger than 50 years (0.78, 0.47-1.20) and lowest in first-time RVX users aged between 60 and 70 years (0.28, 0.23-0.34). In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.62 (0.57-0.67) per 100 person-years, compared with 0.36 (0.32-0.40) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of UG bleeding was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.69 vs. 0.42 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.57 vs. 0.43 per 100 person-years).

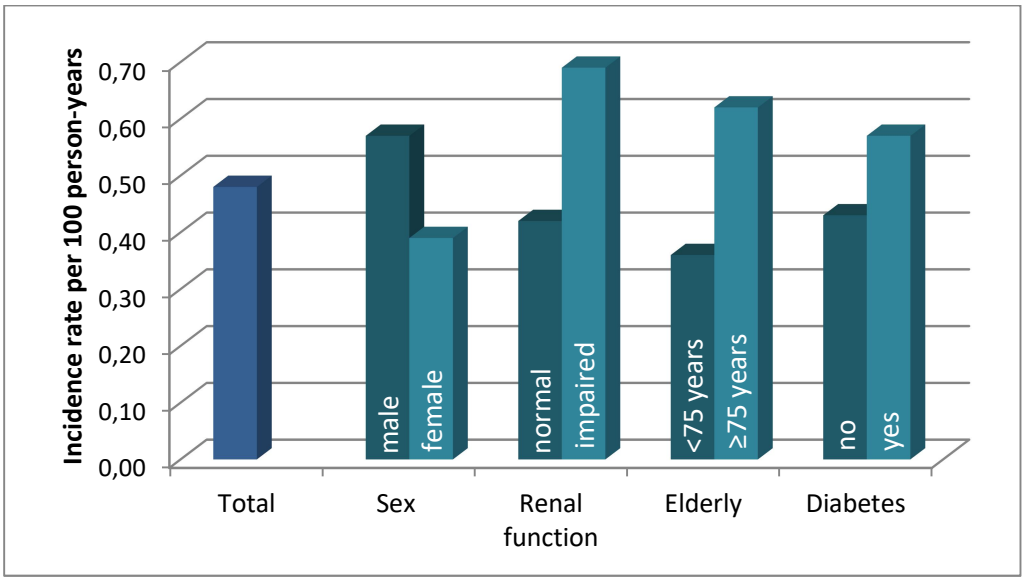

Figure 10–12: Incidence rate of UG bleeding associated with first use of RVX

During the first treatment episode, 665 UG bleeding events were observed in 194,178.4 years of follow-up of first-time PPC users, resulting in an incidence rate of 0.34 (95% CI 0.32-0.37) per 100 person-years.

The incidence rate of UG bleeding in male first-time PPC users was 0.39 (0.36-0.43) per 100 person-years and 0.29 (0.25-0.32) per 100 person-years in female first-time PPC users.

The incidence rate varied between age groups. It was highest in first-time PPC users aged 90 years or older (0.65, 0.40-1.01) and lowest in first-time PPC users aged between 50 and 60 years (0.27, 0.19-0.39).

10.4.1.1.4 Other bleeding

During the first treatment episode, 1205 other bleedings were observed in 174,797.0 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.69 (95% CI 0.65-0.73) per 100 person-years (see Annex 2.2 Table 55).

The incidence rate of other bleedings in male first-time RVX users was 0.72 (0.67-0.78) per 100 person-years and 0.65 (0.60-0.71) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.19 (0.06-0.45) per 100 person-years in first-time RVX users younger than 50 years to 1.06 (0.80-1.38) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.89 (0.83-0.96) per 100 person-years, compared with 0.49 (0.45-0.54) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of other bleedings was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.95 vs. 0.61 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.85 vs. 0.59 per 100 person-years).

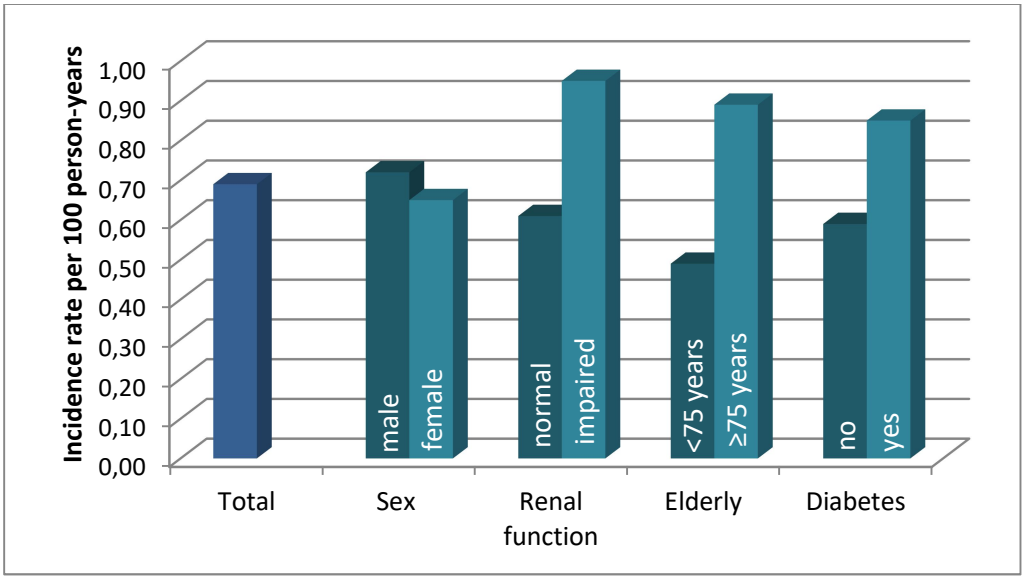

Figure 10–13: Incidence rate of other bleeding associated with first use of RVX

During the first treatment episode, 1719 other bleedings were observed in 192,833.7 years of follow-up of first-time PPC users, resulting in an incidence rate of 0.89 (95% CI 0.85-0.93) per 100 person-years.

The incidence rate of other bleedings in male first-time PPC users was 0.88 (0.83-0.94) per 100 person-years and 0.90 (0.84-0.97) per 100 person-years in female first-time PPC users.

The incidence rate varied between age groups. It was highest in first-time PPC users aged 90 years or older (1.51, 1.10-2.01) and lowest in first-time PPC users aged between 50 and 60 years (0.54, 0.41-0.69).

10.4.1.1.5 Noninfective liver disease

During the first treatment episode, 335 cases of noninfective liver disease were observed in 175,630.2 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.19 (95% CI 0.17-0.21) per 100 person-years (see Annex 2.2 Table 58).

The incidence rate of noninfective liver disease in male first-time RVX users was 0.19 (0.16-0.22) per 100 person-years and 0.20 (0.17-0.23) per 100 person-years in female first-time RVX users.

The incidence rate decreased with age from 0.23 (0.08-0.50) per 100 person-years in first-time RVX users younger than 50 years to 0.18 (0.08-0.33) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.18 (0.15-0.21) per 100 person-years, compared with 0.21 (0.18-0.24) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of noninfective liver diseases was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.26 vs. 0.17 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.26 vs. 0.15 per 100 person-years).

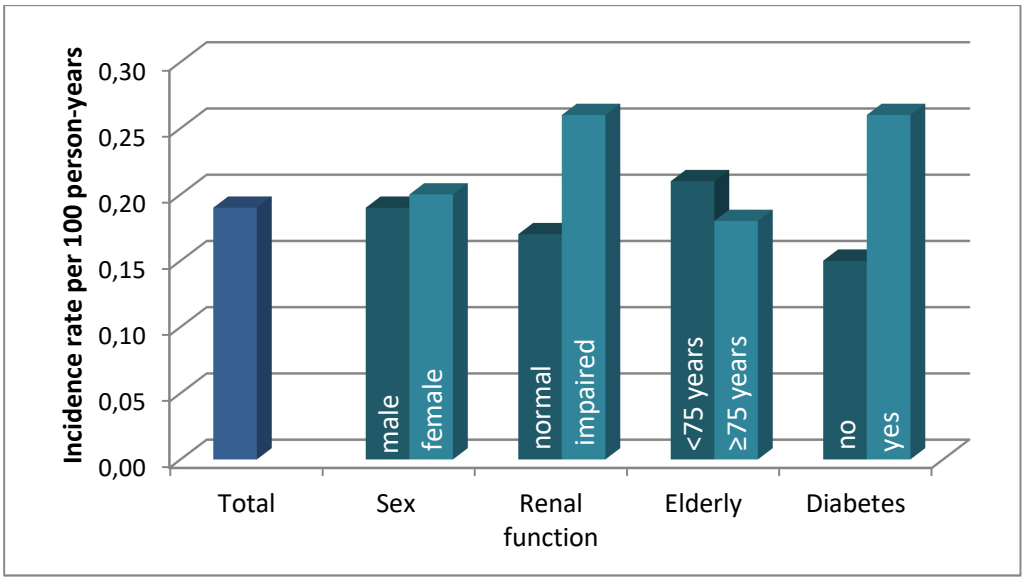

Figure 10–14: Incidence rate of noninfective liver disease associated with first use of RVX

10.4.1.1.6 VTE (DVT/PE)

During the first treatment episode, 268 hospitalized VTEs were observed in 175,660.0 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.15 (95% CI 0.13-0.17) per 100 person-years (see Annex 2.2 Table 61 and Annex 2.2 Table 62). Most of the VTE cases (190, 70.9%) were PEs with an incidence rate of 0.11 (0.09-0.12) per 100 person-years; 79 cases were hospitalized DVT events with an incidence rate of 0.04 (0.04-0.06) per 100 person-years.

The incidence rate of VTE in male first-time RVX users was 0.14 (0.12-0.17) per 100 person-years and 0.16 (0.14-0.19) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.12 (0.02-0.34) per 100 person-years in first-time RVX users younger than 50 years to 0.27 (0.15-0.46) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.17 (0.15-0.20) per 100 person-years, compared with 0.13 (0.11-0.16) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of VTEs was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.23 vs. 0.13 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.18 vs. 0.14 per 100 person-years).

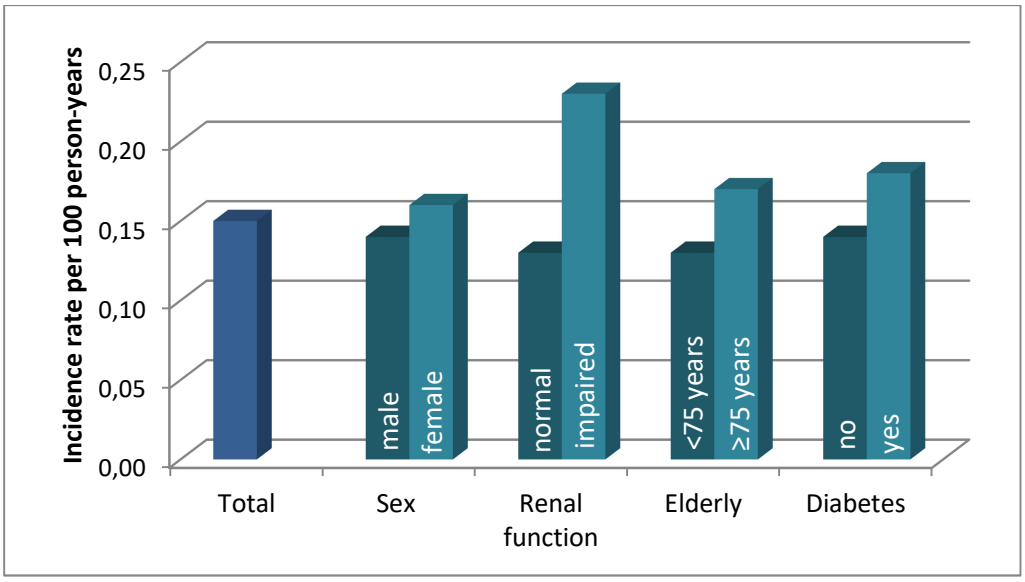

Figure 10–15: Incidence rate of DVT/PE associated with first use of RVX

When outpatient diagnoses of DVT were included in the analysis in addition to hospital diagnoses, the number of DVT events increased to 1330, resulting in an incidence rate of 0.86 (0.82-0.91) per 100 person-years for VTE and 0.76 (0.72-0.81) per 100 person-years for DVT. The incidence rate of VTE increased relative to the previous analysis to 0.82 (0.76-0.89) per 100 person-years in male first-time users of RVX and 0.91 (0.84-0.97) per 100 person-years in female first-time users of RVX.

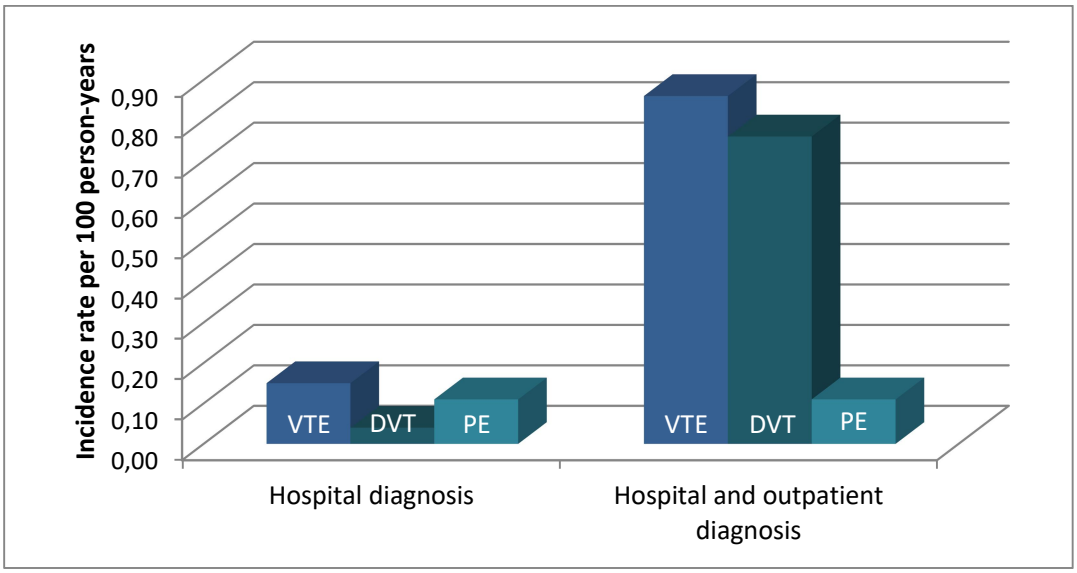

Figure 10–16: Incidence rates of DVT/PE with exclusion/inclusion of outpatient diagnosis

10.4.1.1.7 Ischemic stroke

During the first treatment episode, 1978 ischemic strokes were observed in 174,469.8 years of follow-up of first-time RVX users, resulting in an incidence rate of 1.13 (95% CI 1.08-1.18) per 100 person-years(see Annex 2.2 Table 67 and Annex 2.2 Table 68).

The incidence rate of ischemic stroke in male first-time RVX users was 1.07 (1.00-1.14) per 100 person-years and 1.20 (1.13-1.28) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.27 (0.11-0.56) per 100 person-years in first-time RVX users younger than 50 years to 2.23 (1.84-2.68) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 1.59 (1.51-1.68) per 100 person-years, compared to 0.69 (0.63-0.74) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of ischemic stroke was higher in first-time RVX users with impaired renal function than in users with normal renal function (1.62 vs. 0.97 per 100 person-years) and in first-time RVX users with diabetes than in those without (1.44 vs. 0.94 per 100 person-years).

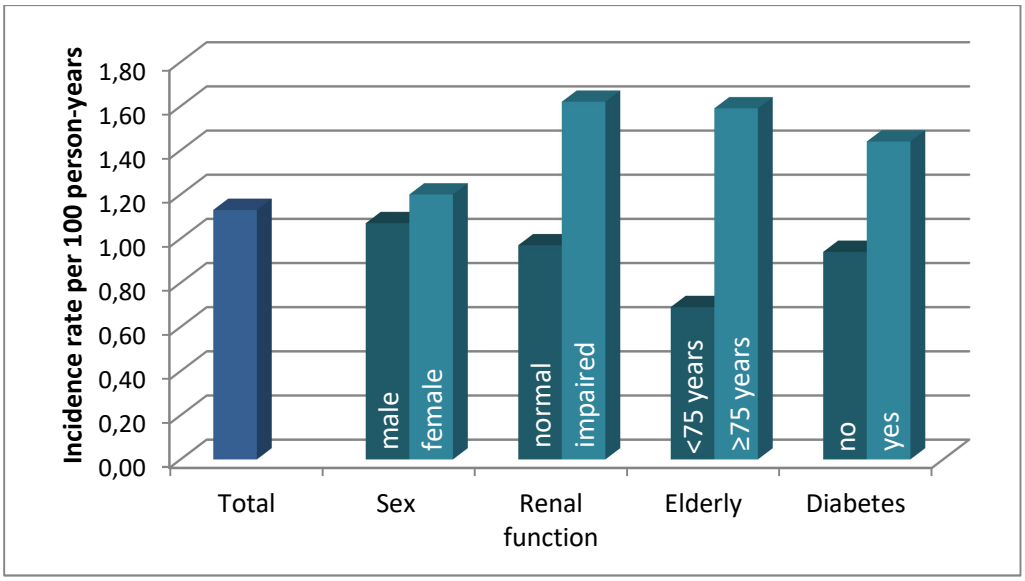

Figure 10–17: Incidence rate of ischemic stroke associated with first use of RVX

When the ICD-10-GM code I64 ("stroke not specified as hemorrhagic or ischemic") was included in the analysis in addition to the code I63, the number of (ischemic) stroke events increased by about 3% to 2034, resulting in an incidence rate of 1.17 (1.12-1.22) per 100 person-years.

10.4.1.1.8 Myocardial infarction

During the first treatment episode, 1376 myocardial infarctions were observed in 175,091.2 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.79 (95% CI 0.74-0.83) per 100 person-years (see Annex 2.2 Table 73).

The incidence rate of myocardial infarction (MI) in male first-time RVX users was 0.93 (0.87-0.99) per 100 person-years and 0.64 (0.59-0.69) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.15 (0.04-0.39) per 100 person-years in first-time RVX users younger than 50 years to 1.51 (1.19-1.89) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 1.04 (0.98-1.11) per 100 person-years, compared with 0.54 (0.49-0.59) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of myocardial infarction was higher in first-time RVX users with impaired renal function than in users with normal renal function (1.27 vs. 0.63 per 100 person-years) and in first-time RVX users with diabetes than in those without (1.06 vs. 0.62 per 100 person-years).

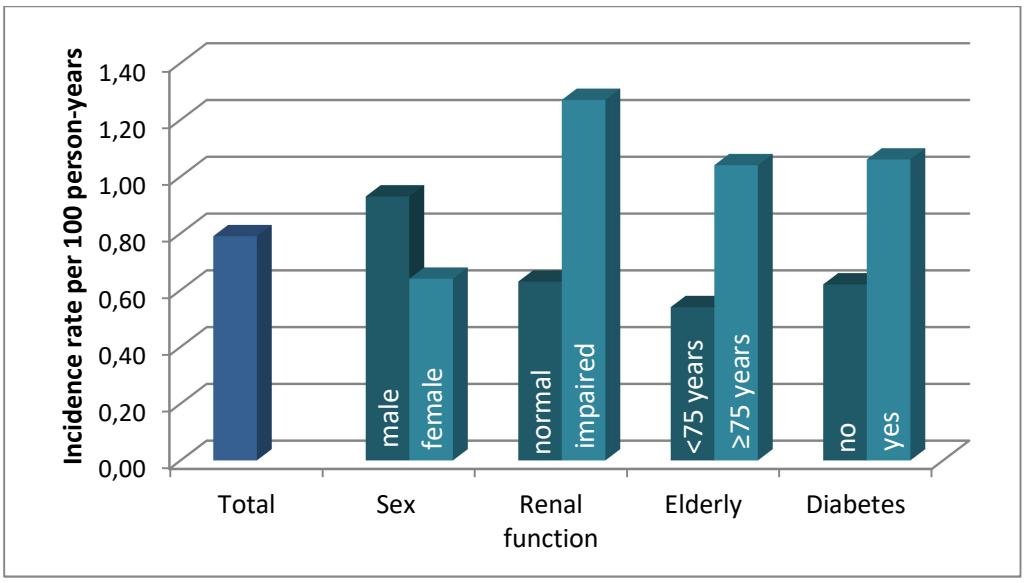

Figure 10–18: Incidence rate of myocardial infarction associated with first use of RVX

10.4.1.1.9 All-cause mortality

During the first treatment episode, 10,694 deaths were observed in 175,865.0 years of follow-up of first-time RVX users, resulting in an incidence rate of 6.08 (95% CI 5.97-6.20) per 100 person-years (see Annex 2.2 Table 76).

The incidence rate of death in male first-time RVX users was 5.76 (5.60-5.91) per 100 person-years and 6.42 (6.25-6.59) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 1.15 (0.78-1.65) per 100 person-years in first-time RVX users younger than 50 years to 29.65 (28.18-31.18) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 9.77 (9.56-9.98) per 100 person-years, compared with 2.48 (2.38-2.59) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of death was higher in first-time RVX users with impaired renal function than in users with normal renal function (11.97 vs. 4.15 per 100 person-years) and in first-time RVX users with diabetes than in those without (8.27 vs. 4.71 per 100 person-years).

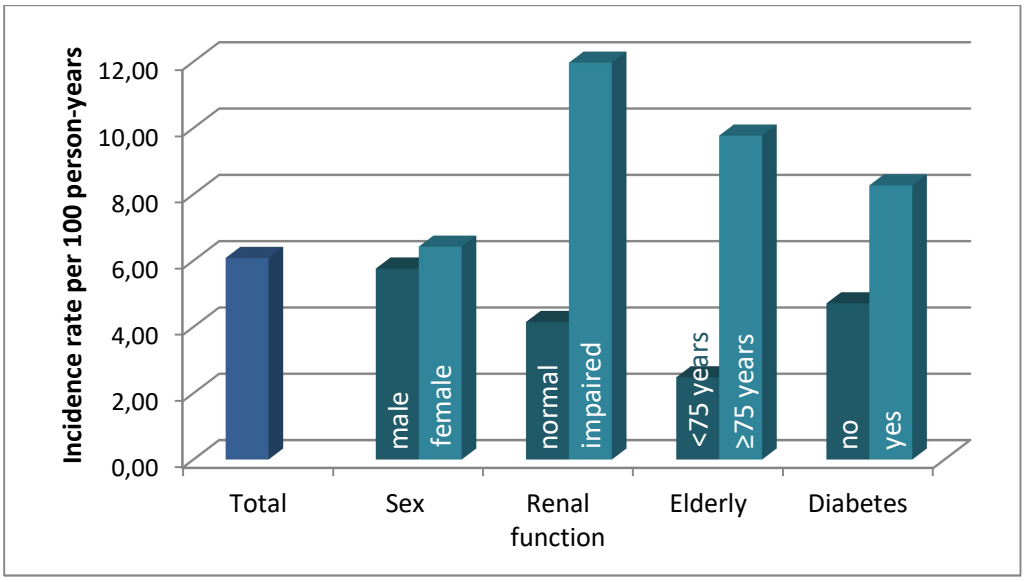

Figure 10–19: Incidence rate of all-cause mortality associated with first use of RVX

10.4.1.2 VTE

10.4.1.2.1 IC hemorrhage

During the first treatment episode, 67 IC hemorrhages were observed in 23,448.5 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.29 (95% CI 0.22-0.36) per 100 person-years (see Annex 2.2 Table 47). Most (41.8%) of the IC hemorrhages were intracerebral with an incidence rate of 0.12 (0.08-0.17) per 100 person-years.

The incidence rate of IC hemorrhage in male first-time RVX users was 0.24 (0.16-0.35) per 100 person-years and 0.33 (0.23-0.44) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.06 (0.01-0.18) per 100 person-years in first-time RVX users younger than 50 years to 0.84 (0.23-2.16) per 100 person-years in first-time RVX users aged 90 years or older, except for the age group of 60-69 years in which the incidence rate decreased to 0.07 (0.01-0.19) per 100 person-years. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.54 (0.38-0.75) per 100 person-years, compared with 0.18 (0.13-0.26) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of IC hemorrhage was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.38 vs. 0.27 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.33 vs. 0.27 per 100 person-years).

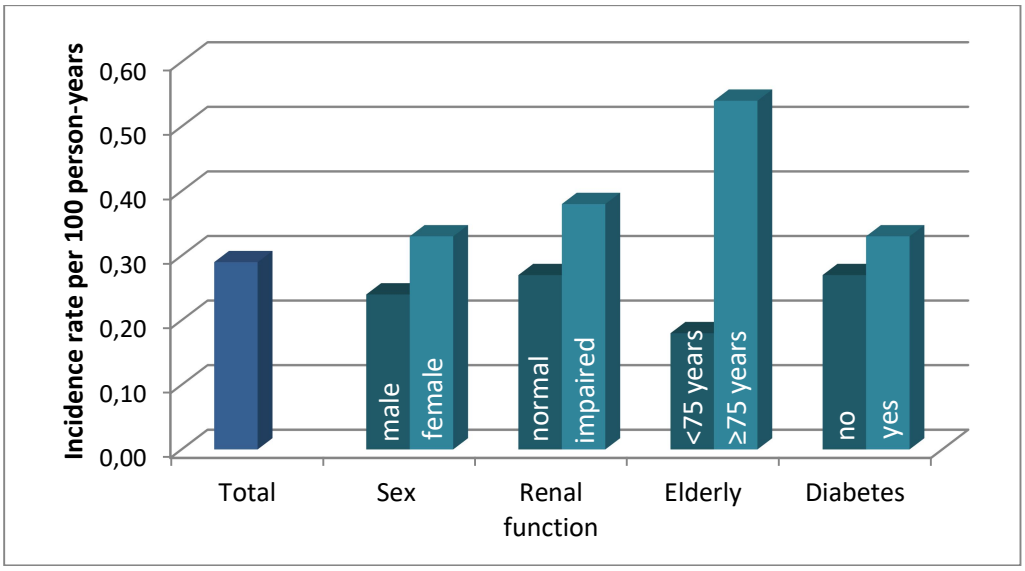

Figure 10–20: Incidence rate of IC bleeding associated with first use of RVX

During the first treatment episode, 88 IC hemorrhages were observed in 28,192.9 years of follow-up of first-time PPC users, resulting in an incidence rate of 0.31 (95% CI 0.25-0.38) per 100 person-years. Most (47.7%) of the IC hemorrhages were intracerebral with an incidence rate of 0.15 (0.11-0.20) per 100 person-years.

The incidence rate of IC hemorrhage in male first-time PPC users was 0.29 (0.20-0.39) per 100 person-years and 0.34 (0.25-0.45) per 100 person-years in female first-time PPC users.

The incidence rate increased with age from 0.09 (0.03-0.21) per 100 person-years in first-time PPC users younger than 50 years to 1.16 (0.32-2.97) per 100 person-years in first-time PPC users aged 90 years or older.

10.4.1.2.2 GI bleeding

During the first treatment episode, 264 GI bleedings were observed in 23,294.5 years of follow-up of first-time RVX users, resulting in an incidence rate of 1.13 (95% CI 1.00-1.28) per 100 person-years (see Annex 2.2 Table 50).

The incidence rate of GI bleeding in male first-time RVX users was 0.86 (0.70-1.06) per 100 person-years and 1.38 (1.18-1.60) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.40 (0.24-0.62) per 100 person-years in first-time RVX users younger than 50 years to 6.10 (4.05-8.81) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 2.41 (2.05-2.81) per 100 person-years, compared with 0.63 (0.52-0.77) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of GI bleeding was higher in first-time RVX users with impaired renal function than in users with normal renal function (2.41 vs. 0.90 per 100 person-years) and in first-time RVX users with diabetes than in those without (1.68 vs. 0.96 per 100 person-years).

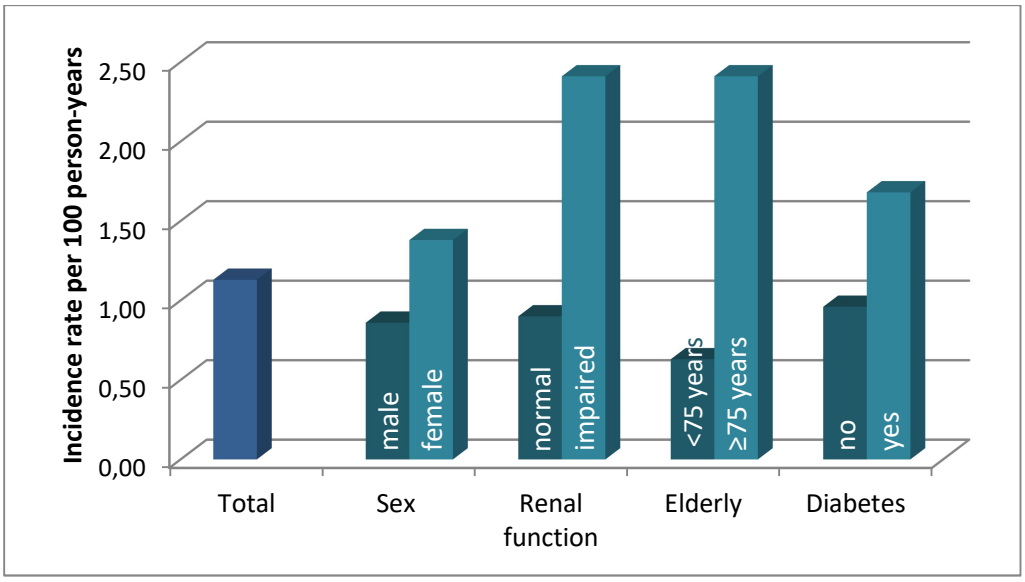

Figure 10–21: Incidence rate of GI bleeding associated with first use of RVX

During the first treatment episode, 263 GI bleedings were observed in 28,004.4 years of follow-up of first-time PPC users, resulting in an incidence rate of 0.94 (95% CI 0.83-1.06) per 100 person-years.

The incidence rate of GI bleeding in male first-time PPC users was 0.72 (0.59-0.88) per 100 person-years and 1.14 (0.98-1.33) per 100 person-years in female first-time PPC users.

The incidence rate increased with age from 0.28 (0.15-0.45) per 100 person-years in first-time RVX users younger than 50 years to 2.61 (1.19-4.96) per 100 person-years in first-time RVX users aged 90 years or older.

10.4.1.2.3 UG bleeding

During the first treatment episode, 155 UG bleedings were observed in 23,354.1 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.66 (95% CI 0.56-0.78) per 100 person-years (see Annex 2.2 Table 53).

The incidence rate of UG bleeding in male first-time RVX users was 0.19 (0.12-0.29) per 100 person-years and 1.10 (0.92-1.30) per 100 person-years in female first-time RVX users.

The incidence rate varied between age groups. It was highest in first-time RVX users younger than 50 (1.67, 1.32-2.08) and lowest in first-time RVX users aged between 60 and 70 years (0.25, 0.12-0.44). In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.47 (0.32-0.66) per 100 person-years, compared with 0.74 (0.62-0.88) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of UG bleeding was higher in first-time RVX users with normal renal function than in users with normal renal function (0.69 vs. 0.55 per 100 person-years) and in first-time RVX users without diabetes than in those without (0.69 vs. 0.57 per 100 person-years).

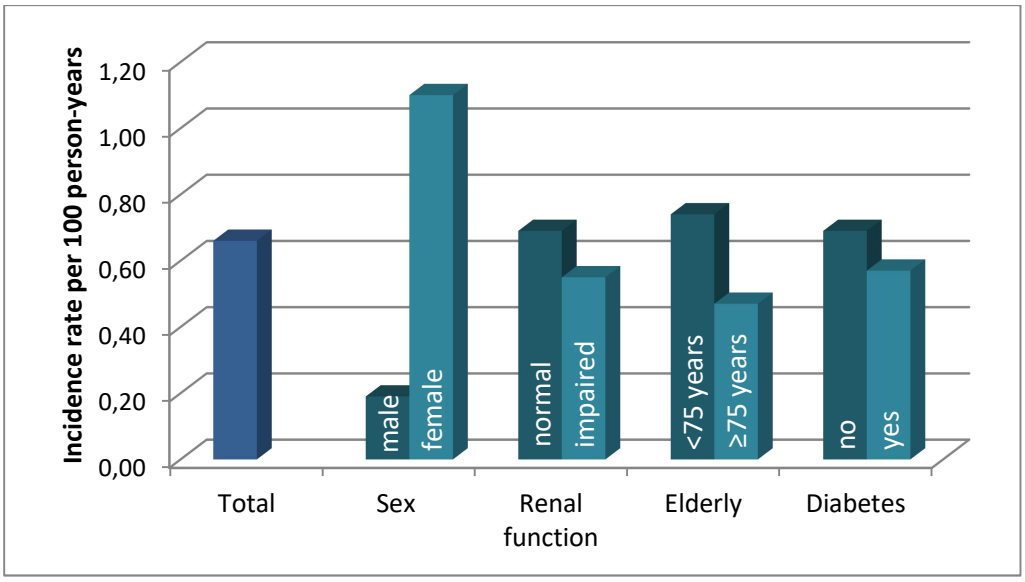

Figure 10–22: Incidence rate of UG bleeding associated with first use of RVX

During the first treatment episode, 102 UG bleeding were observed in 28,103.0 years of follow-up of first-time PPC users, resulting in an incidence rate of 0.36 (95% CI 0.30-0.44) per 100 person-years.

The incidence rate of UG bleeding in male first-time PPC users was 0.19 (0.12-0.28) per 100 person-years and 0.53 (0.41-0.66) per 100 person-years in female first-time PPC users.

The incidence rate varied between age groups. It was highest in first-time PPC users older than 90 years (0.87, 0.18-2.53) and lowest in first-time PPC users aged between 70 and 80.

10.4.1.2.4 Other bleeding

During the first treatment episode, 103 other bleeding events were observed in 23,402.7 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.44 (95% CI 0.36-0.53) per 100 person-years (see Annex 2.2 Table 56).

The incidence rate of other bleeding events in male first-time RVX users was 0.39 (0.28-0.52) per 100 person-years and 0.49 (0.37-0.63) per 100 person-years in female first-time RVX users.

The incidence rate varied between age groups. It was highest in first-time RVX users aged between 80 and 90 years (0.95, 0.63-1.38) and lowest in first-time RVX users between aged 50 and 60 years (0.18, 0.08-0.36).

In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 0.69 (0.51-0.93) per 100 person-years, compared with 0.34 (0.26-0.44) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of other bleedings was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.79 vs. 0.37 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.56 vs. 0.40 per 100 person-years).

During the first treatment episode, 204 other bleeding events were observed in 28,038.7 years of follow-up of first-time PPC users, resulting in an incidence rate of 0.73 (95% CI 0.63-0.83) per 100 person-years.

The incidence rate of other bleeding events in male first-time PPC users was 0.55 (0.43-0.69) per 100 person-years and 0.89 (0.75-1.06) per 100 person-years in female first-time PPC users.

The incidence rate increased with age from 0.18 (0.09-0.34) per 100 person-years in first-time RVX users younger than 50 years to 1.74 (0.64-3.78) per 100 person-years in first-time RVX users aged 90 years or older.

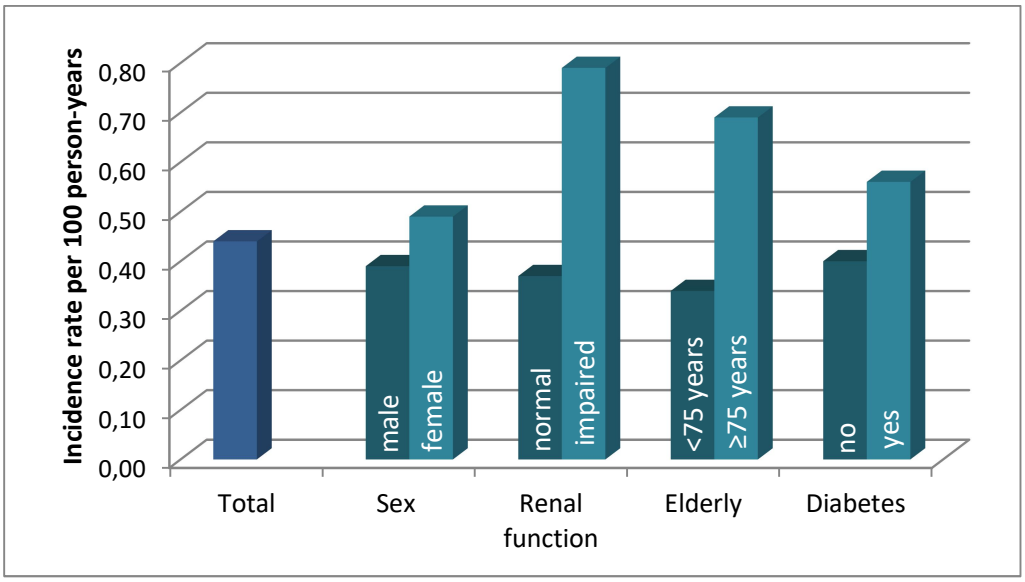

Figure 10–23: Incidence rate of other bleeding associated with first use of RVX

10.4.1.2.5 Noninfective liver disease

During the first treatment episode, 46 cases of noninfective liver disease were observed in 23,453.4 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.20 (95% CI 0.14-0.26 per 100 person-years) (see Annex 2.2 Table 59).

The incidence rate of noninfective liver disease cases in male first-time RVX users was 0.21 (0.13-0.31) per 100 person-years and 0.19 (0.12-0.28) per 100 person-years in female first-time RVX users.

The incidence varied between age groups. It was highest in first-time RVX users aged between 60 and 70 years (0.27, 0.14-0.47) and lowest in first-time RVX users aged between 70 and 80 years (0.14, 0.06-0.27).

The incidence rate of noninfective liver disease was higher in first-time RVX users with impaired renal function than in users with normal renal function (0.30 vs. 0.18 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.21 vs. 0.19 per 100 person-years).

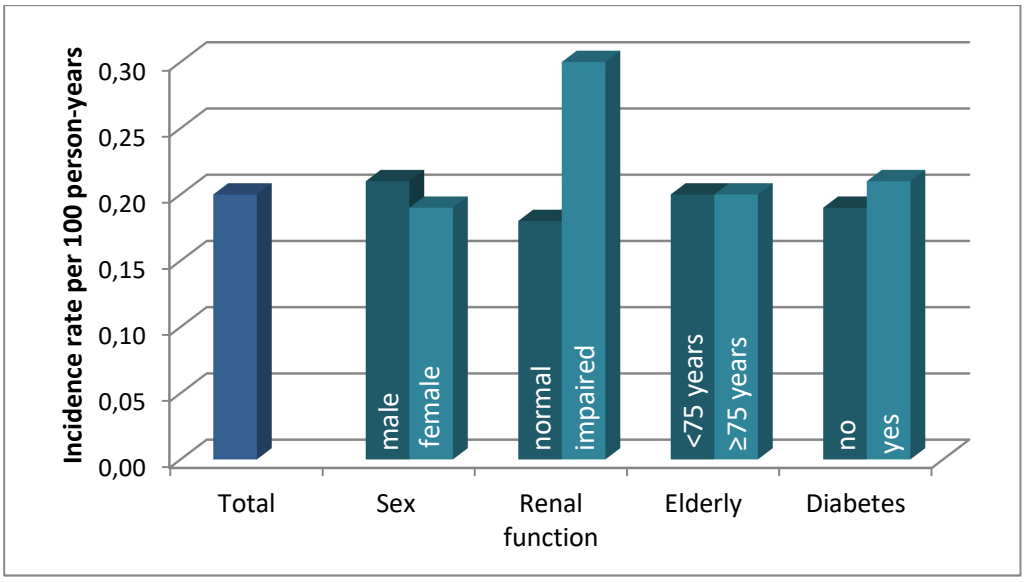

Figure 10–24: Incidence rate of noninfective liver disease associated with first use of RVX

10.4.1.2.6 VTE (DVT/PE)

During the first treatment episode, 529 hospitalized VTEs were observed in 22,984.7 years of follow-up of first-time RVX users, resulting in an incidence rate of recurrent VTE of 2.30 (95% CI 2.11-2.51) per 100 person-years (see Annex 2.2 Table 63 and Annex 2.2 Table 64). Most of the VTE cases (347, 65.6%) were PEs with an incidence rate of 1.50 (1.35-1.67); 188 cases were hospitalized DVT events with an incidence rate of 0.81 (0.69-0.93).

The incidence rate of VTE in male first-time RVX users was 2.39 (2.11-2.70) per 100 person-years and 2.22 (1.96-2.50) per 100 person-years in female first-time RVX users.

The incidence rate varied between age groups. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 1.80 (1.49-2.16) per 100 person-years, compared with 2.50 (2.27-2.76) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of VTEs was higher in first-time RVX users with normal renal function than in users with impaired renal function (2.31 vs. 2.26 per 100 person-years) and in first-time RVX users without diabetes than in those with diabetes (2.38 vs. 2.07 per 100 person-years).

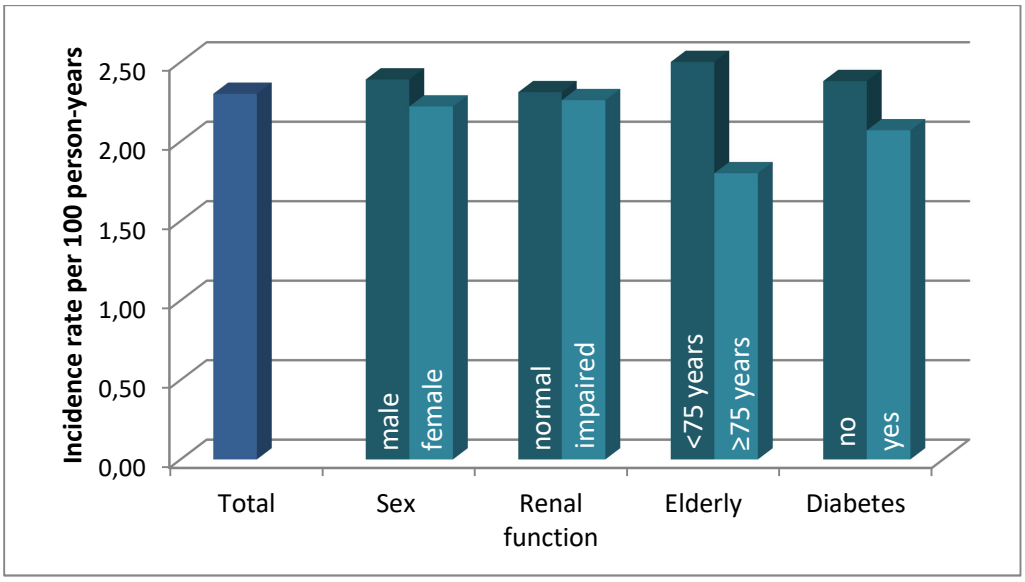

Figure 10–25: Incidence rate of DVT/PE associated with first use of RVX

When outpatient diagnoses of VTE were included in the analysis in addition to hospital diagnoses, the number of DVT events increased to 10,659, resulting in an incidence rate of 73.79 (72.41-75.19) per 100 person-years for VTE and 71.18 (69.83-72.54) per 100 person-years for DVT. The incidence rate of VTE increased relative to the previous analysis 76.25 (74.18-78.36) per 100 person-years in male first-time users of RVX and 71.71 (69.87-73.59) per 100 person-years in in female first-time users of RVX.

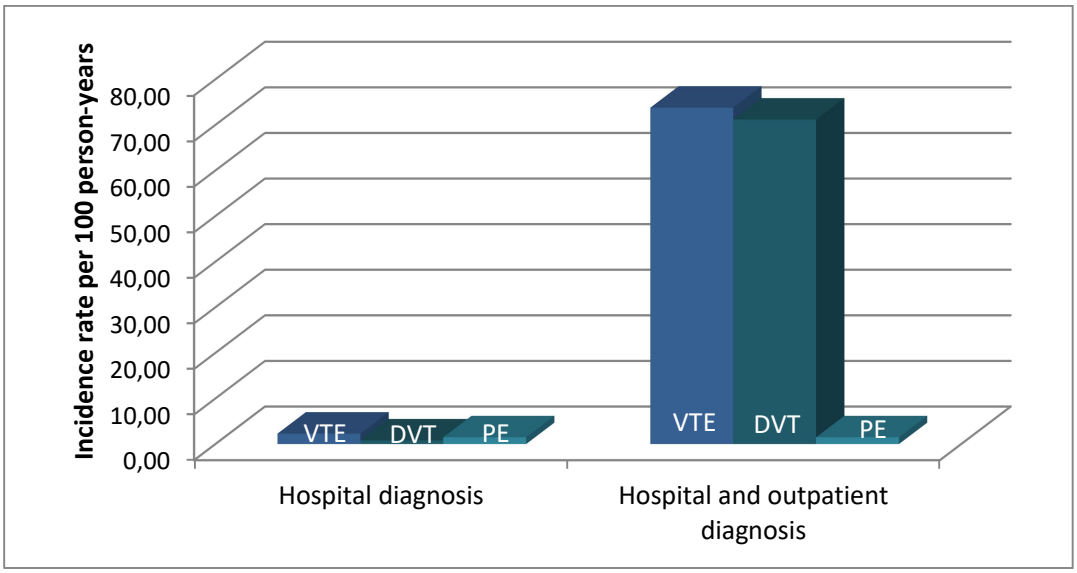

Figure 10–26: Incidence rates of DVT/PE with exclusion/inclusion of outpatient diagnosis

10.4.1.2.7 Ischemic stroke

During the first treatment episode, 150 ischemic strokes were observed in 23,383.2 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.64 (95% CI 0.54-0.75) per 100 person-years (see Annex 2.2 Table 69 and Annex 2.2 Table 70).

The incidence rate of ischemic strokes in male first-time RVX users was 0.61 (0.47-0.77) per 100 person-years and 0.67 (0.53-0.83) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.17 (0.07-0.33) per 100 person-years in first-time RVX users younger than 50 years to 1.27 (0.47-2.76) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 1.09 (0.85-1.37) per 100 person-years, compared with 0.47 (0.37-0.58) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of ischemic strokes was higher in first-time RVX users with impaired renal function than in users with normal renal function (1.04 vs. 0.57 per 100 person-years) and in first-time RVX users with diabetes than in those without (1.08 vs. 0.50 per 100 person-years).

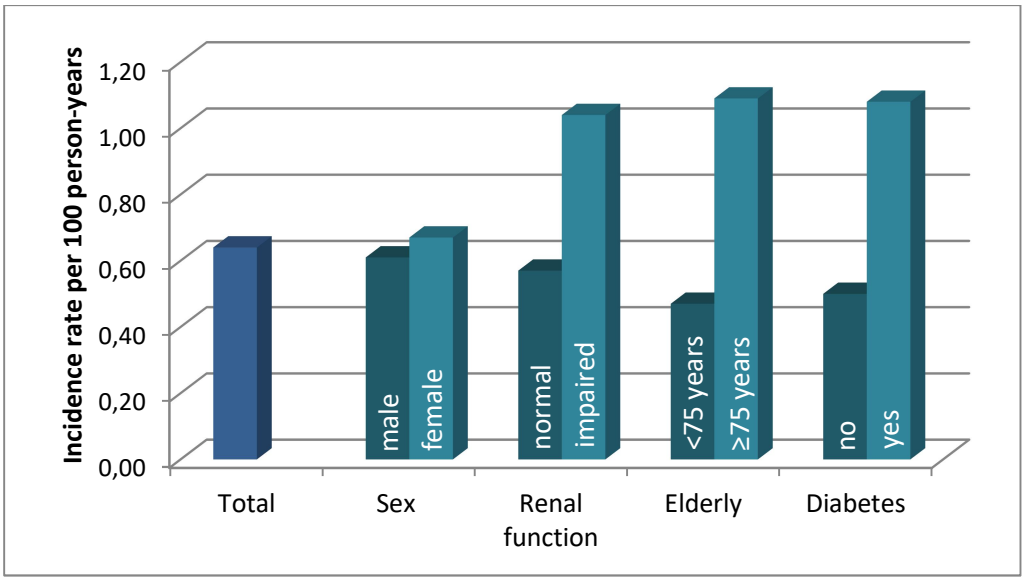

Figure 10–27: Incidence rate of ischemic stroke associated with first use of RVX

The number of ischemic stroke events did not change when the ICD-10-GM code I64 ("stroke not specified as hemorrhagic or ischemic") was included in the analysis, in addition to code I63.

10.4.1.2.8 Myocardial infarction

During the first treatment episode, 113 myocardial infarctions were observed in 23,416.3 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.48 (95% CI 0.40-0.58) per 100 person-years (see Annex 2.2 Table 74).

The incidence rate of myocardial infarctions in male first-time RVX users was 0.60 (0.47-0.76) per 100 person-years and 0.37 (0.27-0.50) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.06 (0.01-0.18) per 100 person-years in first-time RVX users younger than 50 years to 1.48 (0.60-3.05) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 1.07 (0.84-1.35) per 100 person-years, compared with 0.25 (0.18-0.34) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of ischemic strokes was higher in first-time RVX users with impaired renal function than in users with normal renal function (1.23 vs. 0.34 per 100 person-years) and in first-time RVX users with diabetes than in those without (0.75 vs. 0.40 per 100 person-years).

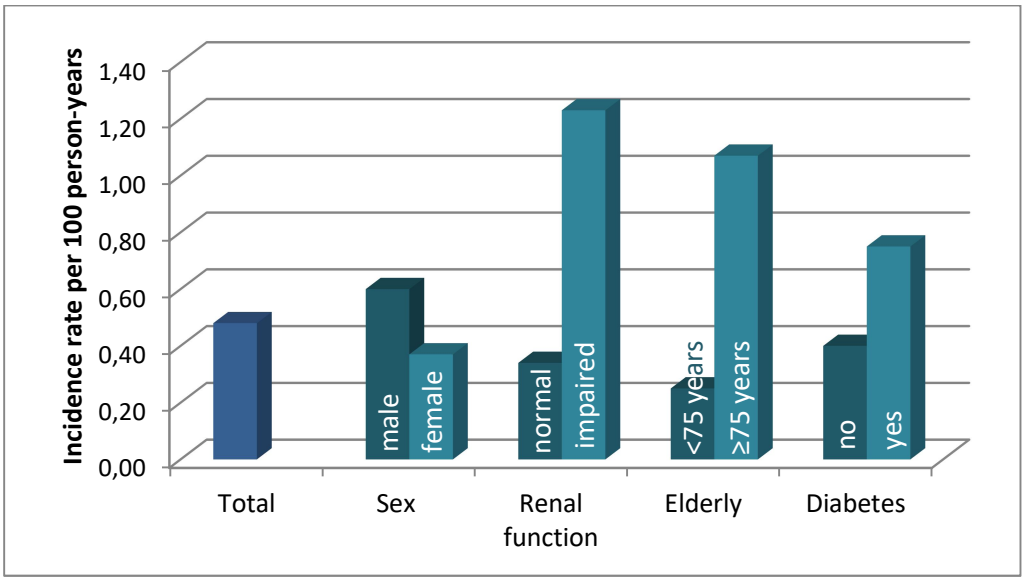

Figure 10–28: Incidence rate of myocardial infarction associated with first use of RVX

10.4.1.2.9 All-cause mortality

During the first treatment episode, 766 deaths were observed in 23,473.6 years of follow-up of first-time RVX users, resulting in an incidence rate of 3.26 (95% CI 3.04-3.50) per 100 person-years (see Annex 2.2 Table 77).

The incidence rate of death in male first-time RVX users was 2.40 (2.12-2.70) per 100 person-years and 4.05 (3.70-4.42) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 0.38 (0.22-0.59) per 100 person-years in first-time RVX users younger than 50 years to 26.06 (21.67-31.07) per 100 person-years in patients aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 8.51 (7.83-9.24) per 100 person-years, compared with 1.18 (1.02-1.36) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of death was higher in first-time RVX users with impaired renal function than in users with normal renal function (7.96 vs. 2.39 per 100 person-years) and in first-time RVX users with diabetes than in those without (5.12 vs. 2.66 per 100 person-years).

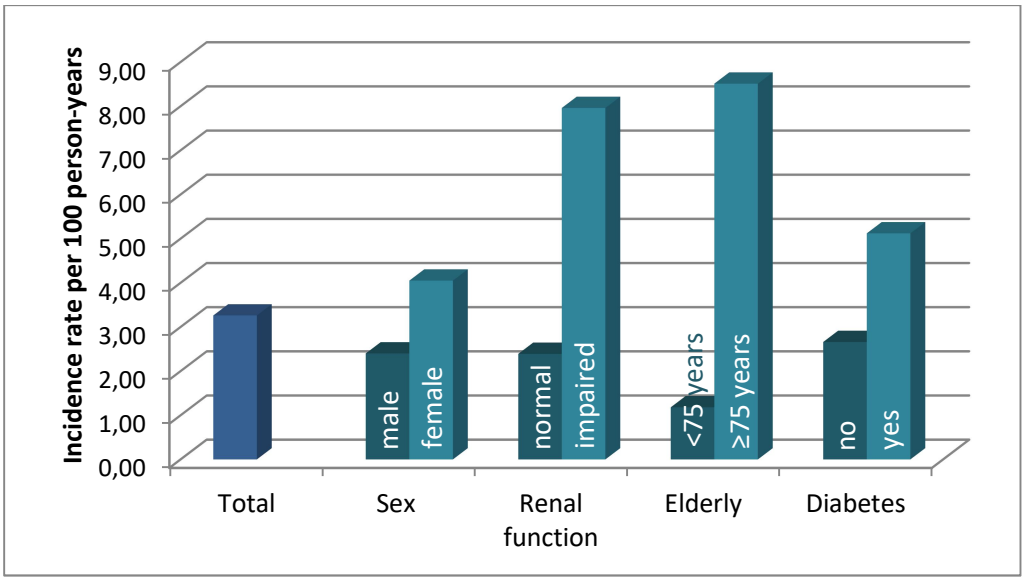

Figure 10–29: Incidence rate of all-cause mortality associated with first use of RVX

10.4.1.3 ACS

10.4.1.3.1 IC hemorrhage

During the first treatment episode, 2 IC hemorrhages were observed in 833.6 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.24 (95% CI 0.03-0.87) per 100 person-years (see Annex 2.2 Table 48). All IC hemorrhages were intracerebral with an incidence rate of 0.24 (0.03-0.87) per 100 person-years. No IC hemorrhage was observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

10.4.1.3.2 GI bleeding

During the first treatment episode, 29 GI bleedings were observed in 816.6 years of follow-up of first-time RVX users, resulting in an incidence rate of 3.55 (95% CI 2.38-5.10) per 100 person-years (see Annex 2.2 Table 51). No GI bleeding was observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

The incidence rate of GI bleeding in male first-time RVX users was 4.36 (2.63-6.81) per 100 person-years and 2.63 (1.26-4.83) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 1.80 (0.22-6.52) per 100 person-years in first-time RVX users aged between 60 and 69 years to 6.12 (0.74-22.10) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 4.82 (3.02-7.30) per 100 person-years, compared to 1.94 (0.78-4.00) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of GI bleeding was higher in first-time RVX users with impaired renal function than in users with normal renal function (4.67 vs. 2.97 per 100 person-years) and in first-time RVX users without diabetes than in those with (3.89 vs. 3.05 per 100 person-years).

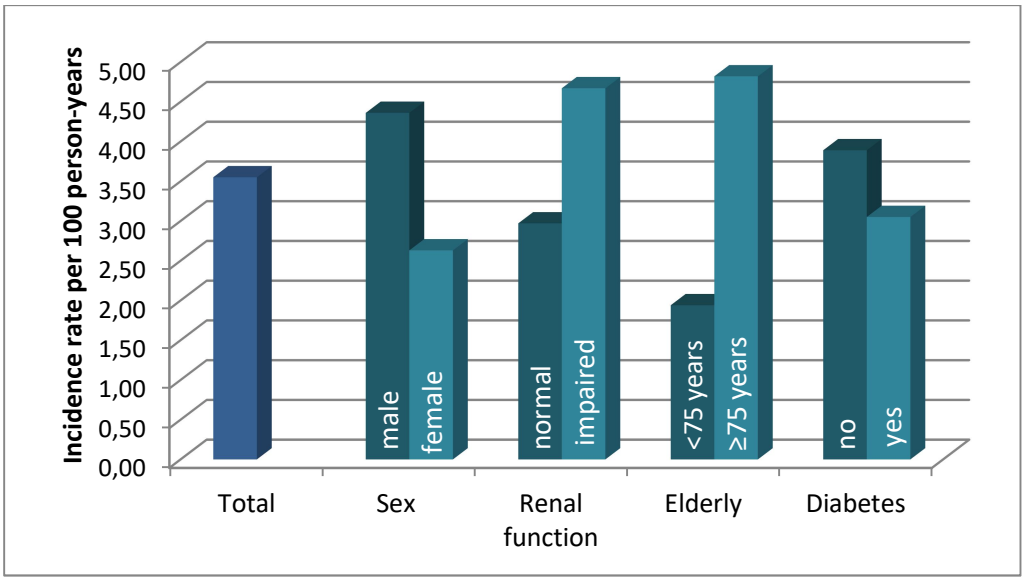

Figure 10–30: Incidence rate of GI bleeding associated with first use of RVX

10.4.1.3.3 UG bleeding

During the first treatment episode, 6 UG bleedings were observed in 826.9 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.73 (95% CI 0.27-1.58) per 100 person-years (see Annex 2.2 Table 54). No UG bleeding was observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

10.4.1.3.4 Other bleeding

During the first treatment episode, 9 other bleeding events were observed in 828.6 years of follow-up of first-time RVX users, resulting in an incidence rate of 1.09 (95% CI 0.50-2.06) per 100 person-years (see Annex 2.2 Table 57). No other bleeding was observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

10.4.1.3.5 Noninfective liver disease

During the first treatment episode, no noninfective liver disease cases were observed.

10.4.1.3.6 VTE (DVT/PE)

During the first treatment episode, 4 VTEs were observed in 828.0 years of follow-up of first-time RVX users, resulting in an incidence rate of 0.48 (95% CI 0.13-1.24) per 100 person-years (see Annex 2.2 Table 65 and Annex 2.2 Table 66). Two cases of PE and DVT were observed, resulting in an incidence rate of 0.24 (0.03-0.87) both. One VTE was observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

When outpatient diagnoses of VTE were included in the analysis in addition to hospital diagnoses, the number of DVT events increased to 11, resulting in an incidence rate of 1.59 (0.85-2.72) per 100 person-years for VTE and 1.34 (0.67-2.40) per 100 person-years for DVT.

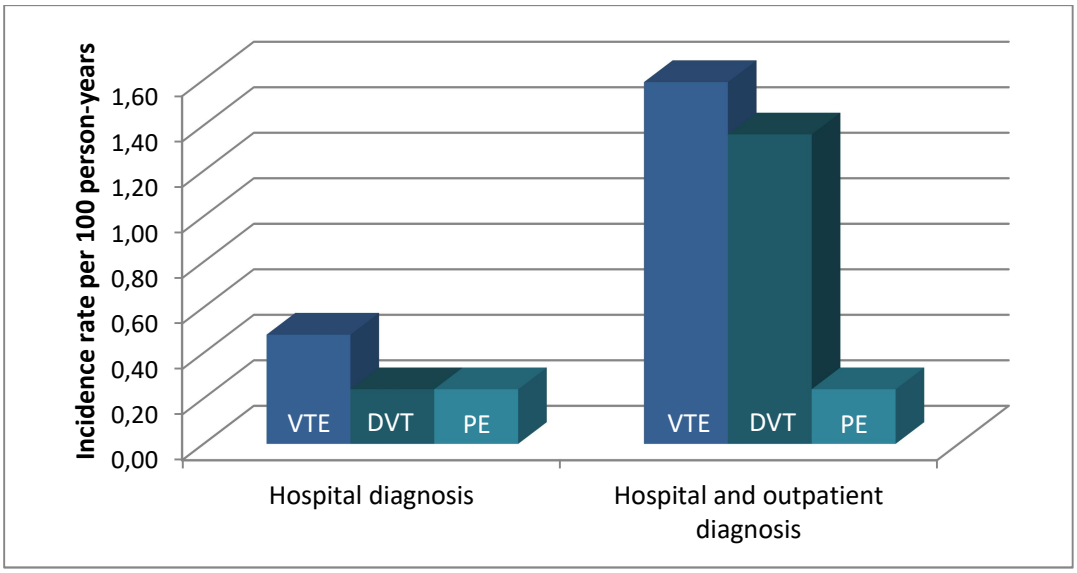

Figure 10–31: Incidence rates of DVT/PE with exclusion/inclusion of outpatient diagnosis

10.4.1.3.7 Ischemic stroke

During the first treatment episode, 12 ischemic strokes were observed in 825.9 years of follow-up of first-time RVX users, resulting in an incidence rate of 1.45 (95% CI 0.75-2.54) per 100 person-years (see Annex 2.2 Table 71 and Annex 2.2 Table 72). No cases of ischemic stroke were observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

The incidence rate of ischemic stroke in male first-time RVX users was 1.35 (0.49-2.93) per 100 person-years and 1.58 (0.58-3.44) per 100 person-years in female first-time RVX users.

In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 1.73 (0.75-3.40) per 100 person-years, compared with 1.10 (0.30-2.83) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of ischemic strokes was higher in first-time RVX users with impaired renal function than in users with normal renal function (2.15 vs. 1.10 per 100 person-years) and in first-time RVX users without diabetes than in those with (1.81 vs. 0.92 per 100 person-years).

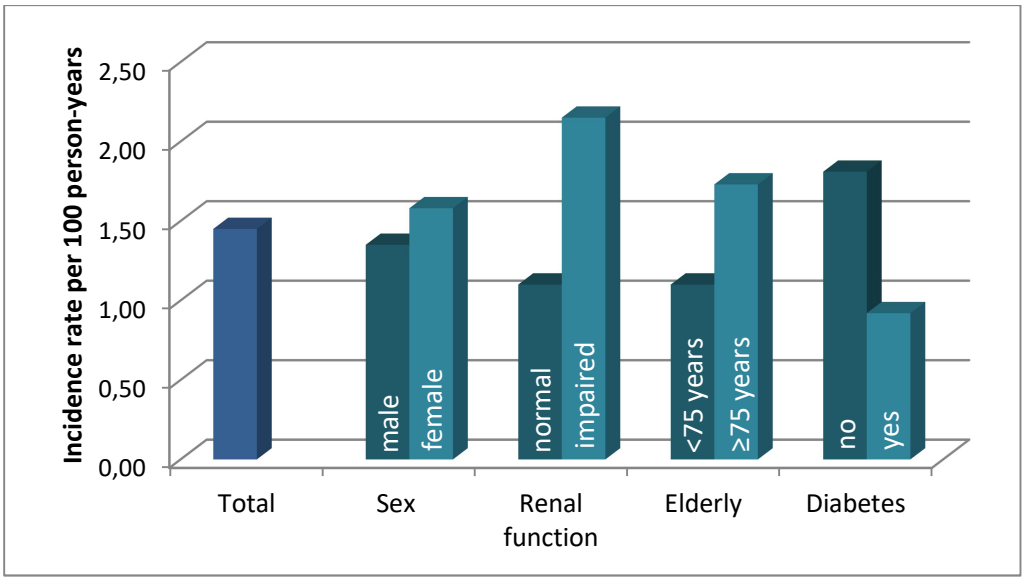

Figure 10–32: Incidence rate of ischemic stroke associated with first use RVX

When the ICD-10-GM code I64 ("stroke not specified as hemorrhagic or ischemic") was included in the analysis in addition to code I63, the number of ischemic stroke events increased by 1, resulting in an incidence rate of 1.57 (0.84-2.69) per 100 person-years.

10.4.1.3.8 Myocardial infarction

During the first treatment episode, 42 myocardial infarctions were observed in 796.0 years of follow-up of first-time RVX users, resulting in an incidence rate of 5.28 (95% CI 3.80-7.13) per 100 person-years (see Annex 2.2 Table 75). No myocardial infarction was observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

The incidence rate of myocardial infarction in male first-time RVX users was 5.57 (3.57-8.29) per 100 person-years and 4.93 (2.92-7.79) per 100 person-years in female first-time RVX users.

In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 6.95 (4.72-9.86) per 100 person-years, compared with 3.15 (1.57-5.63) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of MI was higher in first-time RVX users with impaired renal function than in users with normal renal function (7.55 vs. 4.14 per 100 person-years) and in first-time RVX users with diabetes than in those without (6.95 vs. 4.25 per 100 person-years).

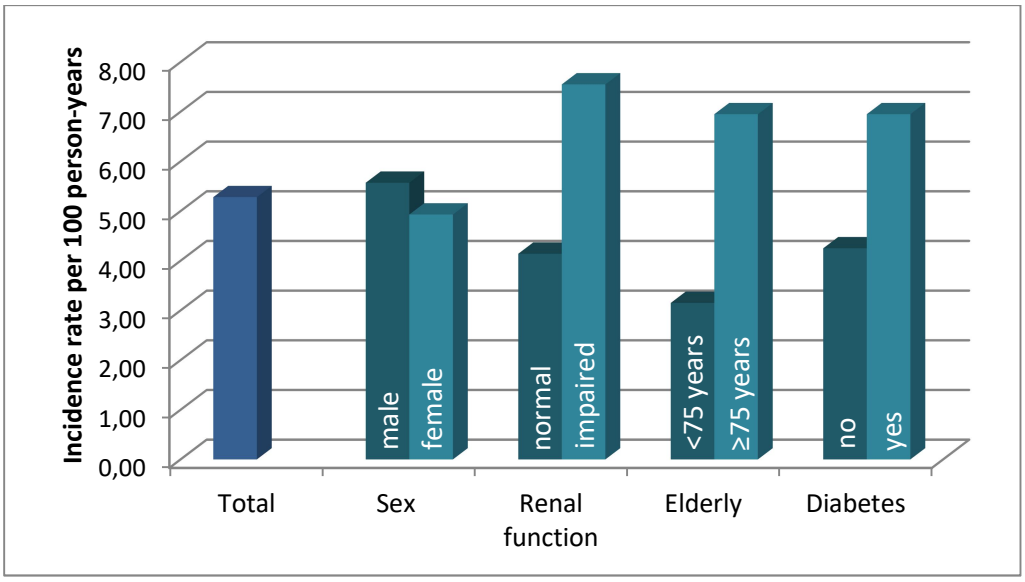

Figure 10–33: Incidence rate of myocardial infarction associated with first use of RVX

10.4.1.3.9 All-cause mortality

During the first treatment episode, 75 deaths were observed in 834.6 years of follow-up of first-time RVX users, resulting in an incidence rate of 8.99 (95% CI 7.07-11.26) per 100 person-years (see Annex 2.2 Table 78). One case was observed in the 24 first-time RVX users with the ACS indication and a start dispensing of 2.5 mg.

The incidence rate of death in male first-time RVX users was 7.79 (5.43-10.84) per 100 person-years and 10.38 (7.41-14.13) per 100 person-years in female first-time RVX users.

The incidence rate increased with age from 2.57 (0.07-14.33) per 100 person-years in first-time RVX users younger than 50 years to 36.60 (18.91-63.94) per 100 person-years in first-time RVX users aged 90 years or older. In the elderly, i.e. first-time RVX users aged 75 years or older, the incidence rate was 13.16 (10.09-16.87) per 100 person-years, compared with 3.58 (1.90-6.11) per 100 person-years in first-time RVX users younger than 75 years.

The incidence rate of death was higher in first-time RVX users with impaired renal function than in users with normal renal function (15.56 vs. 5.62 per 100 person-years) and in first-time RVX users with diabetes than in those without (12.73 vs. 6.54 per 100 person-years).

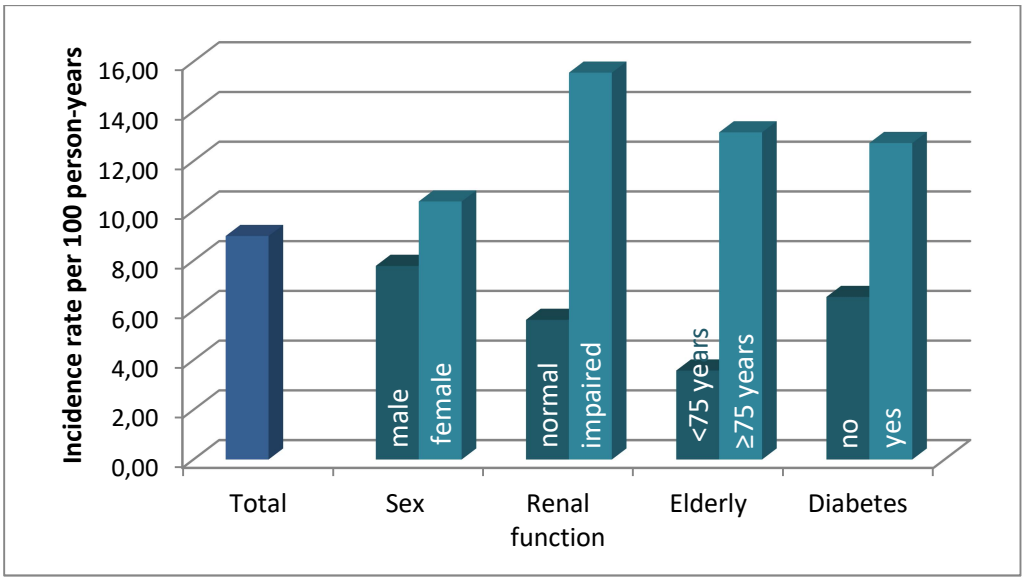

Figure 10–34: Incidence rate of all-cause mortality associated with first use of RVX

10.4.2 Nested case-control analysis

10.4.2.1 SPAF

10.4.2.1.1 IC hemorrhage

During follow-up, 3995 cases of IC hemorrhage were observed and matched to 39,881 controls (see Annex 2.2 Table 79 for demographics).

A previous history of IC hemorrhage increased the risk about 12 times (OR 11.85, 95% CI 10.79-13.00) whereas a history of GI or UG bleeding was not associated with an increased relative risk of IC hemorrhage (see Annex 2.2 Table 80). The risk of IC hemorrhage increased with increasing HAS-BLED score from 1.66 (1.15-2.38) in patients with a score of 2 to 4.18 (2.94-5.96) in patients with a score of 4 or more. This trend was also observed for the CHA_2DS_2VASc score, where the risk increased from 1.81 (1.07-3.06) in patients with a score of 2 to 5.57 (3.37-9.20) in patients with a score of 6 or more. Accordingly, the risk was increased in patients with the individual comorbidities included in the CHA_2DS_2VASc: 1.21 (1.13-1.29) in patients with heart failure, 1.46 (1.19-1.79) in patients with hypertension, 1.13 (1.06-1.21) in patients with diabetes, 1.74 (1.61-1.87) in patients with ischemic stroke, and 1.28 (1.17-1.39) in patients with TIA. The risk of IC hemorrhage was also increased in patients with a history of myocardial infarction (1.13, 1.05-1.23), renal failure (1.24, 1.16-1.33), depression (1.25, 1.17-1.33), and cancer (1.12, 1.04-1.20).

Polypharmacy increased the risk of IC hemorrhage: patients with dispensings of 5 to 9 medications with different ATC codes had a 30% increased risk of IC hemorrhage (1.31, 1.22-1.40), and patients with more than 10 medications with different ATC codes had a 59% increased risk (1.59, 1.21-2.10, see Annex 2.2 Table 79). Regarding individual medications of interest, an increased risk was observed for parenteral anticoagulants (1.59, 1.36-1.87), PPIs (1.19, 1.11-1.28), SSRIs (1.87 1.62-2.18), and antibiotics (1.68, 1.38-2.04, see Annex 2.2 Table 81).

The risk of IC hemorrhage was about 40% (1.43, 1.32-1.56) higher in patients who were hospitalized once in the year before, but not on the index date, and about twofold (1.94, 1.79-2.10) higher in patients who were hospitalized twice or more in the year before the index date (see Annex 2.2 Table 79). A diagnosis indicating alcohol abuse increased the relative risk of IC hemorrhage by 75%, whereas obesity and the degree of deprivation of place of residence were not associated with an increased risk of IC hemorrhage.

Current use of RVX increased the risk of IC hemorrhage by 28% when adjusted by matching variables (1.28, 1.12-1.45, see Annex 2.2 Table 82) and by 32% when adjusted by comorbidity and medications of interest (1.32, 1.15-1.51). The risk of IC hemorrhage increased with increasing assumed daily dose or tablet strength. In the 10,368 cases that had the event during their first treatment episode, stratification by time since first dispensing yielded a higher risk of IC hemorrhage in the first 30 days and after 180 day compared to 31 to 180 days.

Current use of PPC increased the risk of IC hemorrhage by 65% when adjusted by matching variables (1.65, 1.44-1.88) and by 85% adjusted by comorbidity and medications of interest (1.85, 1.61-2.14, see Annex 2.2 Table 82). When stratified by time since first dispensing, the risk of IC hemorrhage was lower after the first 180 days after cohort entry.

10.4.2.1.2 Gastrointestinal bleeding

During follow-up, 9769 cases of GI bleeding were observed and matched to 97,347 controls (see Annex 2.2 Table 87 for demographics).

A previous history of GI bleeding increased the relative risk about 4 times (4.08, 3.90-4.26), a history of IC hemorrhage by about 25% (1.27, 1.15-1.41), and a history of UG bleeding by 15% (1.15, 1.09-1.20, see Annex 2.2 Table 88). The relative risk of GI bleeding increased with increasing HAS-BLED score from 2.34 (1.80-3.04) in patients with a score of 2 to 9.69 (7.50-12.53) in patients with a score of 4 or more. A similar trend was observed for the CHA_2DS_2VASc score, where the relative risk increased from 1.23 (0.93-1.64) in patients with a score of 2 to 5.39 (4.13-7.03) in patients with a score of 6 or more. Accordingly, the relative risk was increased in patients with the individual comorbidities included in the CHA_2DS_2VASc: 1.92 (1.84-2.02) in patients with heart failure, 2.02 (1.75-2.35) in patients with hypertension, 1.35 (1.29-1.41) in patients with diabetes, and 1.24 (1.18-1.30) in patients with ischemic stroke. The relative risk of GI bleeding was also increased in patients with a history of coronary artery disease (1.45, 1.38-1.52), myocardial infarction (1.56, 1.48-1.64), DVT/PE (1.25, 1.16-1.34), renal failure (1. 90, 1.82-1.99), depression (1.27, 1.22-1.32), hyperlipidemia (1.16, 1.10-1.22), asthma (1.16, 1.10-1.23), COPD (1.48, 1.41-1.54) and cancer (1.26 1.21-1.32).

Polypharmacy increased the risk of GI bleeding: patients with dispensings of 5 to 9 medications with different ATC codes had a twofold increased risk of GI bleeding (1.94, 1.86-2.03), and patients with more than 10 medications with different ATC codes had a threefold increased risk (3.20, 2.78-3.68, see Annex 2.2 Table 87). For all assessed individual medications, an increased relative risk was observed: 2.47 (2.28-2.68) for parenteral anticoagulants, 1.11 (1.01-1.21) for other oral anticoagulants, 1.97 (1.89-2.05) for PPIs, 2.15 (1.99-2.32) for NSAIDs, 1.53 (1.38-1.69) for SSRIs, 2.05 (1.88-2.22) for oral steroids, 2.22 (1.99-2.48) for antibiotics, and 1.19 (1.13-1.24) for lipid-lowering medications (see Annex 2.2 Table 89).

The risk of GI bleeding was twofold (1.67, 1.58-1.77) higher in patients who were hospitalized once in the year before the index date and threefold (3.24, 3.08-3.42) higher in patients who were hospitalized twice or more in the year before the index date (see Annex 2.2 Table 87). A diagnosis indicating alcohol abuse increased the relative risk of GI bleeding twofold (2.26, 2.11-2.43) and obesity increased the relative risk by 30% (1.30, 1.25-1.36). The degree of deprivation of place of residence was not associated with an increased risk of GI bleeding.

Current use of RVX increased the risk of GI bleeding by 47% when adjusted by matching variables (1.47, 1.35-1.61, see Annex 2.2 Table 90) and by 72% when adjusted by comorbidity and medications of interest (1.72, 1.57-1.88). Neither the assumed daily dose nor the tablet strength had an impact on the risk of GI bleeding. The risk of GI bleeding increased with increasing assumed daily dose or tablet strength

Current use of PPC increased the risk of GI bleeding by 19% when adjusted by matching variables (1.19, 1.09-1.30) and by 43% when adjusted by comorbidity and medications of interest (1.43, 1.30-1.58), see Annex 2.2 Table 90). The risk of GI bleeding decreased with increasing time since first dispensing from 1.59 (1.32-1.91) in the first 30 days, to 1.46 (1.26-1.69) for 31 to 180 days and 1.26 (1.14-1.40) after 180 days or more.

10.4.2.1.3 Urogenital bleeding

During follow-up, 2774 cases of UG bleeding were observed and matched to 27,604 controls (see Annex 2.2 Table 95).

A previous history of UG bleeding increased the risk sevenfold (7.50, 6.87-8.19), a history of IC hemorrhage by about 36% (1.36, 1.13-1.64), and a history of GI bleeding by 27% (1.27, 1.16-1.39, see Annex 2.2 Table 96).The risk of UG bleeding increased with increasing HAS-BLED score from 3.18 (2.09-4.83) in patients with a score of 2 to 10.33 (6.84-15.61) in patients with a score of 4 or more. A similar trend was observed for the CHA_2DS_2VASc score, where the relative risk increased from 2.80 (1.71-4.61) in patients with a score of 2 to 5.99 (3.68-9.75) in patients with a score of 6 or more. Accordingly, the relative risk was increased in patients with the individual comorbidities included in the CHA_2DS_2VASc: 1.58 (1.45-1.72) in patients with heart failure, 1.82 (1.43-2.31) in patients with hypertension, 1.32 (1.22-1.43) in patients with diabetes, 1.47 (1.34-1.61) in patients with ischemic stroke, and 1.23 (1.11-1.37) in patients with TIA. The relative risk of UG bleeding was also increased in patients with a history of coronary artery disease (1.30, 1.19-1.41), myocardial infarction (1.23, 1.12-1.36), renal failure (1.48, 1.36-1.61), depression (1.29, 1.19-1.40), COPD (1.11, 1.02-1.21) and cancer (1.80, 1.67-1.96).

Polypharmacy increased the risk of UG bleeding: patients with dispensings of 5 to 9 medications with different ATC codes had a twofold increased relative risk of UG bleeding (2.15, 1.98-2.33), and patients with more than 10 medications with different ATC codes had a sixfold increased risk (6.04, 4.84-7.53, see Annex 2.2 Table 95). Regarding individual medications, an increased risk of UG bleedings was observed for parenteral anticoagulants (7.60, 6.78-8.53), PPIs (1.38, 1.27-1.49), SSRIs (1.78, 1.48-2.14), oral steroids (1.36, 1.14-1.63), antibiotics (5.64, 4.82-6.60), and lipid-lowering medications (1.10, 1.01-1.20, see Annex 2.2 Table 97).

The risk of UG bleeding was twofold (2.09, 1.88-2.33) higher in patients who were hospitalized once in the year before the index date and more than threefold (3.67, 3.31-4.07) higher in patients who were hospitalized twice or more in the year before the index date (see Annex 2.2 Table 95). Obesity increased the relative risk of UG bleeding by 29% (1.29, 1.19-1.40). A diagnosis indicating alcohol abuse or the degree of deprivation of place of residence was not associated with an increased risk of UG bleeding.

Current use of RVX increased the risk of UG bleeding by 64% when adjusted by matching variables (1.64, 1.41-1.92, see Annex 2.2 Table 98) and by 69% when adjusted by comorbidity and medications of interest (1.69, 1.43-2.00). The risk of UG bleeding decreased with increasing assumed daily dose or tablet strength. In the 7731 cases that had the event during their first treatment episode, the risk UG bleeding increased with increasing time since first dispensing from 1.33 (0.92-1.93) in the first 30 days to 1.60 (1.22-2.09) for 31 to 180 days and 1.64 (1.36-1.98) after 180 days or more.

Current use of PPC increased the risk of UG bleeding by 32% when adjusted by matching variables (1.32, 1.12-1.55) and by 45% when adjusted by comorbidity and medications of interest (1.45, 1.21-1.73, see Annex 2.2 Table 98).

When stratified by time since first dispensing, the odds ratio of UG bleeding was highest in the first 180 days after cohort entry: 1.73 (1.19-2.52) in the first 30 days, 1.85 (1.40-2.43) in 31 to 180 days vs. 1.25 (1.03-1.53) after 180 days.

10.4.2.1.4 Other bleeding

During follow-up, 4,924 cases of other bleeding were observed and matched to 49,129 controls (see Annex 2.2 Table 103 for demographics).

A previous history of GI and UG bleeding increased the risk by 47% (1.47, 1.37-1.57) and 20% (1.20, 1.12-1.28), whereas a history of IC bleeding did not significantly increase the risk of other bleedings (see Annex 2.2 Table 104).

The risk of other bleeding increased with increasing HAS-BLED score from 2.07 (1.52-2.82) in patients with a score of 2 to 7.13 (5.29-9.62) in patients with a score of 4 or more. A similar trend was observed for the CHA_2DS_2VASc score, where the risk increased from 1.81 (1.28-2.57) in patients with a score of 2 to 5.00 (3.58-7.00) in patients with a score of 6 or more. Accordingly, the odds ratio was increased in patients with several individual comorbidities included in the CHA_2DS_2VASc: 1.68 (1.58-1.80) in patients with heart failure, 2.16 (1.76-2.65) in patients with hypertension, 1.24 (1.17-1.32) in patients with diabetes. The risk of other bleedings was also increased in patients with a history of CAD (1.39, 1.30-1.48), MI (1.45, 1.36-1.56), DVT/PE (1.18, 1.06-1.30), renal failure (1.67, 1.57-1.775), depression (1.20, 1.13-1.27), hyperlipidemia (1.18, 1.10-1.26), asthma (1.23, 1.14-1.32), COPD (1.32, 1.24-1.41) and cancer (1.24, 1.17-1.32).

Polypharmacy increased the risk of other bleeding: patients with dispensings of 5 to 9 medications with different ATC codes had twofold increased risk of other bleedings (1.97, 1.85-2.09), and patients with more than 10 medications with different ATC codes had an almost threefold increased risk (2.61, 2.13-3.20, see Annex 2.2 Table 103). Regarding individual medications, an increased risk of other bleedings was observed for antiplatelets (2.18, 2.00-2.38), parenteral anticoagulants (3.08, 2.77-3.41), PPIs (1.59, 1.50-1.69), NSAIDs (1.52, 1.35-1.70), oral steroids (1.55, 1.36-1.76), antibiotics (2.97, 2.57-3.43) and lipid-lowering medication (1.24, 1.17-1.33, see Annex 2.2 Table 105).

The risk of other bleedings was 61% (1.61, 1.48-1.74) higher in patients who were hospitalized once in the year before the index date and almost threefold (2.78, 2.58-3.00) higher in patients who were hospitalized twice or more in the year before the index date (see Annex 2.2 Table 103). A diagnosis indicating alcohol abuse increased the odds ratio of other bleedings by 65% (1.65, 1.48-1.84) and obesity increased the odds ratio by 21% (1.21, 1.14-1.29, see table 101).

Current use of RVX increased the risk of other bleedings by 79% when adjusted by matching variables (1.79, 1.55-2.06) and by 92% when adjusted by comorbidity and medications of interest (1.92, 1.66-2.22, see Annex 2.2 Table 106). The risk of other bleeding increased with increasing assumed daily dose. Regarding tablet strength, the lowest risk was seen for 10 mg (1.73, 1.24-2.42), followed by 20mg (1.86, 1.60-2.17) and the highest risk was seen for 15 mg (2.02, 1.73-2.36). When stratified by time since first dispensing, the risk of other bleedings was lowest between 31 to 180 days.

Current use of PPC was associated with an about threefold increased risk of other bleeding, both when adjusted by matching variables (2.66, 2.31-3.07) and when adjusted by comorbidity and medications of interest (2.84, 2.46-3.28, see Annex 2.2 Table 106). The risk of other bleeding decreased with increasing time since first dispensing form 3.29 (2.54-4.26) in the first 30 days to 3.01 (2.46-3.69) in 31 to 180 days and 2.53 (2.17-2.95) after 180 days.

10.4.2.2 VTE

10.4.2.2.1 Intercranial bleeding

During follow-up, 360 cases of IC hemorrhage were observed and matched to 3,481 controls (see Annex 2.2 Table 83 for demographics).

A previous history of IC hemorrhage increased the risk of IC hemorrhage about 15 times (14.98, 10.85-20.69) whereas a history of GI or UG bleeding was not associated with a significantly increased risk of IC hemorrhage (see Annex 2.2 Table 84). The risk of IC hemorrhage was increased in patients with a history of coronary artery disease 1.41 (1.13-1.78), heart failure 1.28 (1.01-1.62), ischemic stroke 2.31 (1.74-3.05), TIA 1.84 (1.33-2.53), depression 1.36 (1.08-1.70), hypertension 1.49 (1.04-2.14), and COPD 1.29 (1.01-1.64, see Annex 2.2 Table 84).

Polypharmacy did not increase the risk of IC hemorrhage (see Annex 2.2 Table 83). Regarding individual medications, an increased risk was observed for parenteral anticoagulants (2.15, 1.39-3.33) and SSRIs (1.64, 1.06-2.52, see Annex 2.2 Table 85).

The risk of IC hemorrhage was about twofold (2.03, 1.53-2.71) higher in patients who were hospitalized once in the year before the index date and about threefold (3.24, 2.43-4.32) higher in patients who were hospitalized twice or more in the year before the index date (see Annex 2.2 Table 83). A diagnosis indicating alcohol abuse increased the risk of IC hemorrhage almost threefold (2.62, 1.81-3.77), whereas obesity and the degree of deprivation of place of residence were not associated with an increased risk of IC hemorrhage (see Annex 2.2 Table 83).

Current use of RVX increased the risk of IC hemorrhage by 92% when adjusted by matching variables (1.92, 1.34-2.74, see Annex 2.2 Table 86) and by 73% when adjusted by comorbidity and medications of interest (1.73, 1.16-2.58). The risk of IC hemorrhage increased with increasing assumed daily dose. Regarding tablet strength, the highest risk was seen for 10mg. The risk of IC hemorrhage decreased with increasing time since first dispensing from 2.34 (0.63-8.78) in the first 30 days to 1.88 (0.92-3.85) in 31 to 180 days and 1.31 (0.77-2.23) after 180 days.

Current use of PPC increased the risk of IC hemorrhage, more than twofold, both when adjusted by matching variables (2.50, 1.74-3.59) and when adjusted by comorbidity and medications of interest (2.42, 1.62-3.61, see Annex 2.2 Table 86). When stratified by time since first dispensing, the risk of IC hemorrhage was highest between 31 to 180 days.

10.4.2.2.2 Gastrointestinal bleeding

During follow-up, 1080 cases of GI bleeding were observed and matched to 10,484 controls (see Annex 2.2 Table 91 for demographics).

A previous history of GI bleeding increased the risk about 4 times (4.34, 3.80-4.96), whereas a history of IC or UG bleeding was not associated with an increased risk of GI bleeding (see Annex 2.2 Table 92). The risk of GI bleeding was increased in patients with a history of CAD (1.50, 1.31-1.71), MI (1.71, 1.43-2.04), heart failure (1.82, 1.59-2.09), ischemic stroke 2.01 (1.70-2.39), TIA 1.62 (1.34-1.96), AF (1.45, 1.15-1.82), renal failure (1.76, 1.53-2.02), depression (1.41, 1.24-1.61), hypertension (2.01, 1.60-2.52), hyperlipidemia (1.16, 1.01-1.34), diabetes (1.35, 1.18-1.54), asthma (1.26, 1.08-1.46), and COPD (1.58, 1.38-1.80).

Polypharmacy increased the risk of GI bleeding: patients with dispensings of 5 to 9 medications with different ATC codes had a 84% increased the risk of GI bleeding (1.84, 1.61-2.11), and patients with more than 10 medications with different ATC codes had a threefold increased risk (3.00, 1.77-5.08, see Annex 2.2 Table 91). For all assessed individual medications, an increased risk was observed: 1.82 (1.47-2.24) for antiplatelets, 2.18 (1.73-2.76) for parenteral anticoagulants, 1.48 (1.00-2.21) for other oral anticoagulants, 2.04 (1.80-2.33) for PPIs, 1.90 (1.53-2.35) for NSAIDs, 2.02 (1.58-2.59) for SSRIs, 1.98 (1.59-2.45) for oral steroids, 2.40 (1.74-3.30) for antibiotics, and 1.25 (1.06-1.46) for lipid-lowering medications (see Annex 2.2 Table 93).

The risk of GI bleeding was twofold (1.95, 1.63-2.33) higher in patients who were hospitalized once in the year before the index date and fourfold (4.23, 3.57-5.03) higher in patients who were hospitalized twice or more in the year before the index date (see Annex 2.2 Table 91). A diagnosis indicating alcohol abuse increased the risk of GI bleeding twofold (2.33, 1.86-2.91) and a diagnosis of obesity increased the risk by 20% (1.22, 1.07-1.39, see Annex 2.2 Table 91). The degree of deprivation of place of residence was not associated with an increased risk of GI bleeding.

Current use of RVX increased the risk of GI bleeding more than twofold both when adjusted by matching variables (2.42, 1.96-2.98, see Annex 2.2 Table 94) and when adjusted by comorbidity and medications of interest (2.24, 1.79-2.82). The risk of GI bleeding was highest with an assumed daily dose of 15 mg or tablet strength of 15 mg. Regarding time since first dispensing, the highest risk was observed for up to 30 days.

Current use of PPC increased the risk of GI bleeding about twofold, both when adjusted by matching variables (2.18, 1.75-2.71) and when adjusted by comorbidity and medications of interest (2.24, 1.76-2.84, see Annex 2.2 Table 94). When stratified by time since first dispensing, the risk of GI bleeding was lowest between 31 to 180 days.

10.4.2.2.3 Urogenital bleeding

During follow-up, 465 cases of UG bleeding were observed and matched to 4,571 controls (see Annex 2.2 Table 99 for demographics).

A previous history of UG bleeding increased the risk about eightfold (8.33, 6.36-10.90) and a history of IC hemorrhage about twofold (1.95, 1.09-3.49), whereas a history of GI bleeding was not associated with an increased risk of UG bleeding.

The risk of GI bleeding was increased in patients with a history of CAD (1.33, 1.04-1.70, see Annex 2.2 Table 100), heart failure (1.31, 1.03-1.69), TIA 1.53 (1.04-2.26), renal failure (1.57, 1.20-2.06), depression (1.27, 1.04-1.54), hypertension (1.71, 1.35-2.17), asthma (1.29, 1.03-1.62), and a history of cancer (1.98, 1.54-2.54).

Polypharmacy increased the risk of UG bleeding: patients with dispensings of 5 to 9 medications with different ATC codes had a 81% increased risk of UG bleeding (1.81, 1.46-2.23), and patients with more than 10 medications with different ATC codes had a threefold increased risk (2.72, 1.18-6.24, see Annex 2.2 Table 99). Regarding individual medications, an increased risk of UG bleedings was observed for parenteral anticoagulants (4.39, 3.32-5.82), PPIs (1.54, 1.25-1.90), and antibiotics (3.46, 2.22-5.38, see Annex 2.2 Table 101).

The risk of UG bleeding was twofold (2.10, 1.62-2.73) higher in patients who were hospitalized once in the year before the index date and more than 3 times (3.47, 2.66-4.51) higher in patients who were hospitalized twice or more in the year before the index date (see Annex 2.2 Table 99). Obesity increased the risk of UG bleeding by 44% (1.44, 1.19-1.74), but a diagnosis indicating alcohol abuse was not associated with an increased risk of UG bleeding. The risk of UG bleeding was also higher in patients whose place of residence was in the 4^{th} and 5^{th} quintile of deprivation (1.36, 1.01-1.83 and 1.47, 1.08-2.00).

Current use of RVX increased risk of UG bleeding about threefold, both when adjusted by matching variables (3.55, 2.51-5.03, see Annex 2.2 Table 102) and adjusted by comorbidity and medications of interest (3.02, 2.07-4.41). The risk of UG bleeding increased with increasing dose. Regarding tablet strength, the highest risk was seen for 15 mg. Stratification by time since first dispensing showed the highest risk in the first 30 days.

Current use of PPC increased the risk of UG bleeding about twofold, both when adjusted by matching variables (2.22, 1.54-3.20) and when adjusted by comorbidity and medications of interest (1.79, 1.20-2.68, see Annex 2.2 Table 102). The risk of UG bleeding increased with increasing time since first dispensing: from 0.99 (0.43-2.27) in the first 30 days to 1.19 (0.63-2.24) in 31 to 180 days and 2.20 (1.39-3.48) after 180 days.

10.4.2.2.4 Other bleeding

During follow-up, 520 cases of other bleeding were observed and matched to 5,065 controls (see Annex 2.2 Table 107 for demographics).

A previous history of GI bleeding increased the risk of other bleedings by 80% (1.80, 1.46-2.23), whereas a history of IC and UG bleeding was not associated with an increased risk of other bleedings.

The risk of other bleedings was increased in patients with a history of CAD (1.71, 1.40-2.07, see Annex 2.2 Table 108), MI (1.79, 1.38-2.34), heart failure (1.94, 1.59-2.37), ischemic stroke (1.34, 1.01-1.79), AF (2.11, 1.52-2.94), renal failure (2.21, 1.79-2.72), hypertension (1.56, 1.18-2.06), hyperlipidemia (1.26, 1.02-1.54), diabetes (1.39, 1.14-1.69), COPD (1.56, 1.28-1.90) and in cancer (1.31, 1.03-1.66).

Polypharmacy increased the risk of other bleeding: patients with dispensings of 5 to 9 medications with different ATC codes had an increased risk of 83% of other bleedings (1.83, 1.51-2.22), and patients with more than 10 medications with different ATC codes had a more than threefold increased risk (3.47, 1.68-7.18, see Annex 2.2 Table 107). Regarding individual medications, an increased risk of other bleedings was observed for antiplatelets (2.01, 1.48-2.72), parenteral anticoagulants (3.14, 2.35-4.19), PPIs (1.94, 1.61-2.34), NSAIDs (1.52, 1.10-2.10), oral steroids (2.04, 1.50-2.76) and antibiotics (2.88, 1.90-4.35, see Annex 2.2 Table 109).

The risk of other bleedings was 88% higher (1.88, 1.46-2.42, see Annex 2.2 Table 107) in patients who were hospitalized once in the year before the index date and more than threefold higher (3.40, 2.66-4.35) in patients who were hospitalized twice or more in the year before the index date. A diagnosis indicating alcohol abuse increased the risk of other bleedings twofold (2.23, 1.62-3.08) and obesity increased the risk by 39% (1.39, 1.15-1.67, see Annex 2.2 Table 107).

Current use of RVX was associated with a threefold increased risk of other bleeding, both when adjusted by matching variables (3.26, 2.23-4.78 see Annex 2.2 Table 110) and adjusted by comorbidity and medications of interest (3.02, 2.03-4.48). The highest risk was seen for an assumed daily dose of 15 mg and for tablet strength 15 mg. The risk of UG bleeding increased with increasing time since first dispensing: from 1.54 (0.76-3.14) in the first 30 days to 1.86 (1.02-3.39) in 31 to 180 days and 4.41 (2.77-7.03) after 180 days.

Current use of PPC was associated with a sixfold increased risk of other bleeding, both when adjusted by matching variables (6.00, 4.12-8.75, see Annex 2.2 Table 110) and when adjusted by comorbidity and medications of interest (5.85, 3.95-8.65). Regarding time since first dispensing, the highest risk was observed for up to 30 days.

10.4.2.2.5 Other Analyses

None

10.5 Safety data (Adverse events/adverse reactions)

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for noninterventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. No expedited reporting of adverse events or reactions is required.

11. Discussion

11.1 Key results and interpretation

In this post-authorization "Pharmacoepidemiological Study of Rivaroxaban Use and Potential Adverse Outcomes in Routine Clinical Practice in Germany" we assessed patterns of drug utilization and quantified outcomes related to safety and effectiveness in a large cohort of more than 260,000 first-time users of RVX.

11.1.1 SPAF

First-time users of RVX with the SPAF indication in this study were more often female (48.5% vs. 39.7%) and older (median age 75.0 years vs. 73 years) than the patients randomized to RVX in the randomized controlled trial (RCT) ROCKET-AF. The duration of the first treatment episode in first-time RVX users observed in this study was comparable to the treatment duration in patients randomized to RVX in ROCKET-AF (median 503 days vs. 589 days), but the total follow-up time in this study was with a median of 1077 days (about 35 months) longer than in ROCKET-AF with a median follow-up of 22 months.

Regarding comorbidity, first-time users of RVX in this study had less often a previous diagnosis of ischemic stroke (18.6% vs. 34.3%), TIA (12.4% vs. 22.1%) congestive heart failure (48.8% vs. 62.7%) or diabetes mellitus (32.8% vs. 40.4%), but more often a previous diagnosis of cancer (16.2% vs. 4.4) than the patients randomized to RVX in ROCKET-AF. The frequency of patients with a previous diagnosis of myocardial infarction (15.7% vs. 16.6%) or hypertension (92.0% vs. 90.3%) was comparable between both groups. Median CHA_2DS_2VASc score was higher in the first-time users of RVX of this study than in the patients randomized to RVX in ROCKET-AF. Particularly, 33.5% of first-time users of RVX in this study had a CHA_2DS_2VASc score of 6 or more, whereas only 30% of the patients randomized to RVX in ROCKET-AF had a CHA_2DS_2VASc score of 6. In ROCKET-AF history of serious bleeding was an exclusion criterion whereas 1.3% of first-time users of RVX in this study had a history of IC bleeding, 3.8% of GI bleeding and 1.2% a history of UG bleeding. In this study, 22.6% of first-time users of RVX had severe or moderate renal impairment defined as chronic kidney disease stage 3 to 5 (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²) or dialysis, whereas 21.2% of patients randomized to RVX in ROCKET-AF had a baseline creatinine clearance < 50 ml/min. The proportion of patients with a HAS-BLED score of 4 or more was 35.1% first-time users of RVX in this study compared to 20.7% in the patients randomized to RVX in ROCKET-AF, although INR values were not available in GePaRD.

Unadjusted incidence rates of IC, GI and UG bleedings observed in first-time RVX users were higher than those observed in PPC users (see Table 11–1). This might be explained by underlying differences in the characteristics between both cohorts and the much longer median follow-up and median duration of the first treatment episode in PPC users. Due to the latter a larger proportion of time accumulated in the early high-risk period (most bleedings occur early after start of treatment) in the RVX than in the SOC cohort. The cumulative incidence, i.e. the number of cases divided by the number of patients in the cohort is for all four bleeding events smaller for first-time RVX users than first-time PPC users. This calculation, however, favors shorter first treatment episodes and thus RVX, as the number of events that can be observed increases over time.

Table 11–1: Incidence rate and cumulative incidence of bleeding events – SPAF cohort

	Events	Person-years	N	Incidence rate per 100 person-years	Cumulative incidence per 100 persons
IC bleeding					
RVX	938	175,578.2	127,743	0.53	0.73
PPC	946	194,598.6	88,655	0.49	1.06
GI bleeding					
RVX	2,988	173,832.2	127,743	1.72	2.34
PPC	2,219	192,655.8	88,655	1.15	2.50
UG bleeding					
RVX	849	175,133.2	127,743	0.48	0.66
PPC	665	194,178.4	88,655	0.34	0.75
Other bleeding					
RVX	103	23,402.7	127,743	0.44	0.08
PPC	204	28,038.7	88,655	0.73	0.23

GI, gastrointestinal; IC, intracranial; PPC, phenprocoumon; RVX, rivaroxaban; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

The unadjusted incidence rate of IC bleeding in first-time RVX users in this study is similar to the rates reported for published RVX clinical studies like ROCKET-AF(29, 30), XANTUS(31), ARISTOPHANES(32), and the study of Yao et al.(33) (see Table 11–2). Regarding GI bleeding, the unadjusted incidence rate in this study is slightly lower than those observed in the published RVX studies, probably due to the fact that we only used hospital diagnoses for the case definition. We found no study reporting the incidence of UG bleeding; most studies only provide relative estimates such as hazard ratios. The comparison of the incidence rate of other bleeding is hampered by the different definitions used for this outcome. The definition of major bleeding also differs between studies but unadjusted incidence rate for bleedings requiring hospitalization in this study is well within the range of other studies.

Table 11–2: Comparison of incidence rate of bleeding events (all per 100 person-years) and 95% confidence intervals – SPAF cohort

	IC bleeding	GI bleeding	UG bleeding	Major bleeding [a]
This study	0.53 (0.50–0.57)	1.72 (1.66–1.78)	0.48 (0.45–0.52)	3.4
ROCKET-AF [b]	0.57	2.00	-	3.6
XANTUS	0.4 (0.3–0.6)	-	-	2.1 (1.8–2.5)
ARISTOPHANES	0.57	3.28	-	5.83
Yao et al.	0.44	3.26		4.04

a: defined as bleeding requiring hospitalization
b: safety population, up to follow-up visit
GI, gastrointestinal; IC, intracranial; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

The unadjusted incidence rates of PE, ischemic stroke and myocardial infarction in this study are in the range of those reported for ROCKET-AF, XANTUS, ARISTOPHANES, and the

study of Yao et al. (see Table 11–3). All-cause mortality in this study is higher than in the RCT ROCKET-AF and the observational study XANTUS, but comparable to the rate observed in ARISTOPHANES. We did not find data on the incidence DVT or noninfective liver disease for comparison.

Table 11–3: Comparison of incidence rates of secondary outcomes (all per 100 person-years) and 95% confidence intervals – SPAF cohort

	All-cause mortality	PE	Ischemic stroke	Myocardial infarction
This study	6.08 (5.97–6.20)	0.11 (0.09–0.12)	1.13 (1.08–1.18)	0.79 (0.74–0.83)
ROCKET-AF [a]	1.87	0.04	1.34	0.91
XANTUS	1.9 (1.6–2.3)	0.1 (0.1–0.3)	0.7 (0.5–0.9)	0.4 (0.3–0.6)
ARISTOPHANES	7.11	0.10[1]	1.11	-
Yao et al.	-	-	0.95	-

a: safety population, up to follow-up visit
PE, pulmonary embolism; SPAF, stroke prevention in nonvalvular atrial fibrillation

Unadjusted incidence rates of bleedings were 20% to 70% higher in the populations of special interest, i.e. elderly patients, patients with renal impairment, and patients with diabetes (see Table 11–4) compared to the overall population. We assumed that patients with renal impairment were using the recommended lower dose of 15 mg. If the normal dose of 20 mg is used and the supply is finished earlier, the duration of the first treatment episode will be overestimated and – under the assumption that most bleeding events occur at the beginning of the treatment – underestimate the incidence rate.

Table 11–4: Incidence rates of bleedings per 100 person-years and 95% confidence intervals in populations of interest – SPAF cohort

	Overall	Elderly	Renal impairment	Diabetes
IC bleeding	0.53 (0.50–0.57)	0.32 (0.28–0.36)	0.68 (0.60–0.76)	0.62 (0.56–0.68)
		0.6	1.3	1.2
GI bleeding	1.72 (1.66–1.78)	2.45 (2.35–2.56)	2.86 (2.70–3.02)	2.14 (2.03–2.26)
		1.4	1.7	1.2
UG bleeding	0.48 (0.45–0.52)	0.62 (0.57–0.67)	0.69 (0.61–0.77)	0.57 (0.52–0.63)
		1.3	1.4	1.2
Other bleeding	0.69 (0.65–0.73)	0.95 (0.86–1.04)	0.89 (0.83–0.96)	0.85 (0.78–0.92)
		1.4	1.3	1.2

GI, gastrointestinal; IC, intracranial; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

According to the nested case-control analyses, current use of RVX increased the risk of IC hemorrhage (OR: 1.32, 95% CI: 1.15-1.51), GI bleeding (1.85, 1.61-2.14) UG bleeding (1.69, 1.43-2.00), and other bleeding (1.45, 1.21-1.73) compared to nonuse of RVX or PPC.

11.1.2 VTE without recent history of cancer

First-time users of RVX with the VTE without cancer indication in this study were more often female (54.2% vs. 42.3% and 46.4%) and older (median age 62.0 years vs. 56.0 and 59.0 years) than the patients randomized to RVX in RCTs EINSTEIN-DVT (34–36) and EINSTEIN-PE (37, 38). The duration of the first treatment episode in first-time RVX users observed in this study was longer than the treatment duration in patients randomized to RVX in EINSTEIN-DVT and EINSTEIN-PE with no cancer (median 207 days vs. 182 and 183 days).

Regarding comorbidity, first-time users of RVX without a diagnosis of cancer in the last three years in this study had more often a previous diagnosis (i.e. older than three years) of cancer (11.4% vs. 0.1% and < 0.1%), heart failure (21.1% vs. 0% and < 0.1%), obesity (35.5% vs. 0.9% and 4%) previous history of DVT/PE (28.1% vs. 20.3% and 19.3%) than the patients in EINSTEIN-DVT and EINSTEIN-PE.

Similarly to the patients with the SPAF indication, unadjusted incidence rates of GI and UG bleedings observed in first-time RVX users were higher than those observed in first-time PPC users. The observed cumulative incidence of GI bleeding was lower in first-time RVX users and the cumulative incidences of UG bleeding higher that those observed in first-time users of PPC.

Table 11–5: Incidence rate and cumulative incidence of bleeding events – VTE without recent history of cancer cohort

	Events	Person-years	N	Incidence rate per 100 person-years	Cumulative incidence per 100 persons
IC bleeding					
RVX	67	23,448.5	25,914	0.29	0.26
PPC	88	28,192,9	20,502	0.31	0.43
GI bleeding					
RVX	264	23,294.5	25,914	1.13	1.02
PPC	263	28,004.4	20,502	0.94	1.28
UG bleeding					
RVX	155	23,354.1	25,914	0.66	0.60
PPC	102	28,103.0	20,502	0.36	0.50
Other bleeding					
RVX	103	23,402.7	25,914	0.44	0.40
PPC	204	28,038.7	20,502	0.73	1.00

GI, gastrointestinal; IC, intracranial; PPC, phenprocoumon; RVX, rivaroxaban; UG, urogenital; VTE, venous thromboembolism

Unadjusted incidence rates of IC, GI and other bleedings were up to twofold higher in the populations of special interest, i.e. elderly patients, patients with renal impairment, and patients with diabetes (see

Table 11–6).

Table 11–6: Incidence rates of bleedings per 100 person-years and 95% confidence intervals in populations of interest – VTE without recent history of cancer cohort

VTE	Overall	Elderly	Renal impairment	Diabetes
IC bleeding	0.29 (0.22–0.36)	**0.54 (0.38–0.75)** **1.9**	**0.38 (0.21–0.64)** **1.3**	**0.33 (0.20–0.51)** **1.1**
GI bleeding	1.13 (1.00–1.28)	**2.41 (2.05–2.81)** **2.1**	**2.41 (1.93–2.98)** **2.1**	**1.68 (1.36–2.05)** **1.5**
UG bleeding	0.66 (0.56–0.78)	0.47 (0.32–0.66) 0.7	0.55 (0.33–0.84) 0.8	0.57 (0.39–0.81) 0.9
Other bleeding	0.44 (0.36–0.53)	**0.79 (0.53–1.14)** **1.8**	**0.69 (0.51–0.93)** **1.6**	**0.56 (0.38–0.79)** **1.3**

GI, gastrointestinal; IC, intracranial; UG, urogenital; VTE, venous thromboembolism

According to the nested case-control analyses, current use of RVX increased the risk of IC hemorrhage (OR 1.73, 1.16-2.58), GI bleeding (2.24, 1.79-2.82), UG bleeding (3.02, 2.07-4.41) and other bleeding (3.02, 2.03-4.48) compared to nonuse of RVX or PPC.

11.1.3 ACS

Only 546 patients with a relevant diagnosis (acute myocardial infarction, unstable angina or other acute ischemic diseases) in the 30 days before cohort entry were identified and only 24 of these patients received RVX tablets with a strength of 2.5 mg. Overall, only 122 of 235,194 (0.05%) patients with an assigned indication received RVX tablets with a strength of 2.5 mg, including 74 patients in the SPAF cohort, 8 patients in the VTE-T without recent history of cancer cohort, 1 patient in the VTE-T with recent history of cancer cohort, and 15 patients in the THR/TKR cohort.

The likely misclassification of indication in patients who received RVX tablets with a strength of 10 mg or more leads to an underestimation of the actual daily dose (we assumed 2x 2.5 mg) and thus an overestimation of the supply and duration of the first treatment episode. For this reason and given the low number of patients in the ACS cohort, all results in the ACS cohort have to be interpreted with caution.

First-time users of RVX with the ACS indication in this study were more often female (42.3% vs. 25.4%) and older (median age 76 years vs. 61 years) than the patients randomized to RVX in RCT ATLAS ACS 2–TIMI 51. Total follow-up time in this study was with a mean 2.7 years longer than ATLAS ACS 2–TIMI 51 with a mean follow-up of 1.3 years.

Regarding comorbidity, first-time users of RVX in this study had more often a previous history congestive heart failure (67% vs. 11%), diabetes (41.9% vs. 32%), ischemic stroke (18.1% vs. 1.9%), and TIA (12.6% vs. 0.9%) than the patients randomized to RVX in ATLAS ACS 2–TIMI 51.

The unadjusted incidence rate of IC bleeding in first-time RVX users in this study is similar to the rates in the ATLAS ACS 2–TIMI 51 (39, 40), but the unadjusted incidence of GI bleeding is much higher in this study. The TIMI major bleeding definition, however, is a very narrow definition, which hampers – especially for GI bleedings – the comparison of incidence rates.

Table 11–7: Comparison of incidence rate of bleeding events (all per 100 person-years) and 95% confidence intervals – ACS cohort

	IC bleeding	GI bleeding	UG bleeding
This study	0.24 (0.03–0.87)	3.55 (2.38–5.10)	0.73 (0.27–1.58)
ATLAS ACS 2–TIMI 51 [a]	0.24	0.71	-

a: safety population, up to follow-up visit
ACS, acute coronary syndrome; GI, gastrointestinal; IC, intracranial; UG, urogenital

11.2 Limitations

The limitations of this study are mainly attributable to the nature of the administrative data.

In Germany, the indication of the medication is not noted on the prescription and thus not available in GePaRD. Characteristics of patients as well as patterns of drug use suggest that identification of indication was successful for patients with the SPAF, VTE-T and TKR/THR indications, but not for the ACS indication.

No information on the prescribed dose or the actually used dose is available in GePaRD and the exposure periods had to be estimated. RVX is usually used in a fixed dose, whereas PPC is up- or down-titrated according to the INR. Therefore, two different methods to estimate the exposure periods had to be applied. This hampers comparison of results between both exposure groups. For RVX, the results of the drug utilization analysis showed that – at least for the SPAF, VTE-T and TKR/THR indication – the estimation of the exposure periods was plausible.

The duration of the first treatment episode is longer for first-time users of PPC than for first-time users of RVX (670 days vs. 303 days for SPAF, 260 days vs. 207 days for VTE). This might be due to the differences in the estimation of the first treatment episode and the longer total follow-up of first-time users of PPC. Anyway, as usually the highest risk for side-effects such as bleedings is seen in the beginning of the therapy, incidence rates based on overall person-time have to be interpreted with caution and cannot be compared between RVX and PPC.

It is likely that RVX was selectively prescribed to patients at the beginning of the study when the SPAF indication was new. Given the long duration of the study and the increasing volume of RVX use, it is also very likely that the reasons for the decision to prescribe RVX instead of PPC changed over time. Thus, the reasons for decision to prescribe either RVX or PPC depended not only on the characteristics of the patient and the physician (such as specialty, region, but also personal preference) but also changed during the study period. Other novel oral anticoagulants became available during the study period, which probably had an additional impact on the treatment decision. It is not possible to assess all these factors, especially with claims data. This might result in residual confounding and biased comparisons between RVX and PPC. Therefore, no direct comparison between first-time RVX and first-time PPC users were made and the rates of events in the PPC cohort should only be used for contextual purposes.

GePaRD has no information on OTC medications, resulting in a probable underestimation of, for example, NSAIDs or St. John's Wort. Low-dose aspirin is reimbursable in Germany in some indications, such as following a myocardial infarction. For patients who are not exempted from co-payment, however, the price is the same independent of whether they have a prescription or not. As the purchase of low-dose aspirin OTC is not captured by claims data, an underestimation of low-dose aspirin use is likely. This might lead to an overestimation of the risk of bleeding associated with RVX or PPC use in the nested case-control study. However, this overestimation does probably not differ between RVX and PPC.

As reason of death is not available in GePaRD, bleedings resulting in death without prior hospitalization cannot be included in this study. This might lead to bias in the risk study if the short-term mortality of bleedings differs between RVX and SOC.

Many patients with DVT are treated as outpatients. Physicians in the outpatient setting are expected to code the disease(s) for which they treat their patients once per quarter and to code the diagnostic certainty. This coding differentiates between "confirmed", "suspected", "status post", and "excluded" diagnoses. For recurring events, it is not always possible to differentiate between the initial and new events as usually the same codes are used in both instances. In the VTE-T cohort, the diagnostic codes for repeat visits due to the initial DVT and for new DVTs are the same. Using outpatient diagnoses will lead to a substantial overestimation of the rate of new DVTs, but using only hospital diagnoses might lead to an underestimation of the rate of DVT. Thus, the true incidence of DVT can be assumed to lie in-between the extremes.

In Germany, hospital main discharge diagnoses are assumed to have a high validity as they are based on all information (including laboratory tests and imaging results) during the hospital stay and are the basis for reimbursement and therefore subject to inspections. A validation study conducted in Sweden, which has a similar healthcare system and where also ICD-10 codes are used, demonstrated high sensitivity (85.5%) and specificity (95.9%) for the detection of major bleeding events associated with hospitalization (41). It would have been interesting to assess the correspondence between major bleedings according to the classifications used in the clinical trial program versus "major" bleedings classified based on hospitalization data or to examine how many of the VTE cases are no new events, but repeat visits. Unfortunately, it was not possible to examine this in GePaRD as linkage of patients with their hospital or outpatient charts is not possible. As cause of death is not available in GePaRD it was also not possible to assess how many patients die due to the bleeding event before they reach the hospital and whether the short-term mortality of bleedings differs between RVX and PPC.

11.3 Generalizability

Strengths of the study are its size and the representativeness of the data providing a complete coverage of all age groups, lack of nonresponse due to the administrative nature of the data and the possibility to study rare events as well as rare exposures (42). In previous studies, GePaRD has been shown to be adequately representative with respect to age, sex, and region of residence (43, 44). GePaRD data have been used successfully in both risk assessment (15–17) and drug utilization (19) of oral anticoagulants.

The oral anticoagulants examined in this study are available on prescription only thus assessment of exposure based on pharmacy dispensing data is assumed to be complete. By using these data recall bias can be ruled out and information is precise in time, product and dispensed strength (45). Overall, this study reflects routine clinical practice in Germany and generalizability can be assumed.

12. Other information

None. All relevant aspects have already been addressed.

13. Conclusion

In conclusion, the results presented in this final report confirm and expand evidence from previous studies on use and safety of RVX.

Uptake of RVX in Germany increased during the study period. For all indications, characteristics of first RVX dispensation corresponded well with label recommendations. Characteristics of patients differed from those included in the RCTs, patients in this study were more often female and had more comorbidities.

For the more recently approved ACS indication, limited conclusions can be made regarding the safety and effectiveness of rivaroxaban owing to very low patient numbers. For the other indications, incidence rates of bleedings were in the range of those observed in the respective observational studies and RCTs. All-cause mortality was a bit higher than in the RCTs but comparable to the rates observed in ARISTOPHANES.

Overall, this study does not raise any new safety concerns and does not indicate that the incidence of bleeding is higher than expected in the real life setting in Germany.

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Appendices

Annex 1 List of stand-alone documents

None.

Annex 2 Additional information

Annex 2.1 Code lists

Indication	ICD-10	OPS codes
VTE-T	DVT: I80.1, I80.2- PE: I26.-	
SPAF	I48.- without I34.2, I05.0 ,I05.2,I05.8, I05.9, I08.0, I08.1, I08.3, I08.8, Q23.2,Q23.9 Z95.2, Z95.4, T82.0, T82.6	without 5-351.14, 5-351.24, 5-352.10, 5-352.12
THR/ TKR		5-820, 5-822, 5-821, 5-823
ACS	I20.0, I21.-, I22.-, I24.0, I24.1	
Other indication	I20- I25, I70- I73, I800, I803, I808, I809	5-784.0d, 5-784.1d, 5-784.2d, 5-784.3d, 5-784.4d, 5-784.5d, 5-784.6d, 5-784.7d, 5-784.8d, 5-784.9d, 5-784.ad, 5-784.bd, 5-784.xd, 5-785.0d, 5-785.1d, 5-785.2d, 5-785.3d, 5-785.4d, 5-785.5d, 5-785.6d, 5-785.7d, 5-785.xd, 5-791, 5-791.0, 5-791.02, 5-791.05, 5-791.08, 5-791.1, 5-791.12, 5-791.15, 5-791.18, 5-791.2, 5-791.22, 5-791.25, 5-791.28, 5-791.3, 5-791.32, 5-791.35, 5-791.38, 5-791.4, 5-791.42, 5-791.45, 5-791.48, 5-791.5, 5-791.52, 5-791.55, 5-791.55, 5-791.58, 5-791.58, 5-791.6, 5-791.62, 5-791.65, 5-791.68, 5-791.7, 5-791.72, 5-791.75, 5-791.78, 5-791.8, 5-791.82, 5-791.85, 5-791.88, 5-791.9, 5-791.92, 5-791.95, 5-791.98, 5-791.c, 5-791.c2, 5-791.c2, 5-791.c5, 5-791.c5, 5-791.c8, 5-791.c8, 5-791.d, 5-791.d2, 5-791.d5, 5-791.d8, 5-791.e, 5-791.e2, 5-791.e5, 5-791.e8, 5-791.f, 5-791.f2, 5-791.f5, 5-791.f8, 5-791.g, 5-791.g2, 5-791.g5, 5-791.g8, 5-791.h, 5-791.h2, 5-791.h5, 5-791.h8, 5-791.k, 5-791.k2, 5-791.k5, 5-791.k8, 5-791.m, 5-791.m2, 5-791.m5, 5-791.m8, 5-791.x, 5-791.x2, 5-791.x5, 5-791.x8, 5-792, 5-792.0, 5-792.02, 5-792.05, 5-792.08, 5-792.1, 5-792.12, 5-792.15, 5-792.18, 5-792.2, 5-792.22, 5-792.25, 5-792.28, 5-792.3, 5-792.32, 5-792.35, 5-792.38, 5-792.4, 5-792.42, 5-792.45, 5-792.48, 5-792.5, 5-792.52, 5-792.55, 5-792.55, 5-792.58, 5-792.58, 5-792.6, 5-792.62, 5-792.65, 5-792.68, 5-792.7, 5-792.72, 5-792.75, 5-792.78, 5-792.8, 5-792.82, 5-792.85, 5-792.88, 5-792.9, 5-792.92, 5-792.95, 5-792.98, 5-792.g, 5-792.g2, 5-792.g5, 5-792.g8, 5-792.h, 5-792.h2, 5-792.h5, 5-792.h8, 5-792.k, 5-792.k2, 5-792.k5, 5-792.k8, 5-792.m, 5-792.m2, 5-792.m5, 5-792.m8, 5-792.x, 5-792.x2, 5-792.x5, 5-792.x8, 5-793, 5-793.0, 5-793.01, 5-793.03, 5-793.04, 5-793.06, 5-793.07, 5-793.09, 5-793.1, 5-793.11, 5-793.13, 5-793.14, 5-793.16, 5-793.17, 5-793.19, 5-793.2, 5-793.21, 5-793.23, 5-793.24, 5-793.26, 5-793.27, 5-793.29, 5-793.3, 5-793.31, 5-793.33, 5-793.34, 5-793.36, 5-793.37, 5-793.39, 5-793.4, 5-793.41, 5-793.43, 5-793.44, 5-793.46, 5-793.47, 5-793.49, 5-793.5, 5-793.51, 5-793.53, 5-793.54, 5-793.56, 5-793.57, 5-793.59, 5-793.6, 5-793.61, 5-793.63, 5-793.64, 5-793.66, 5-793.67, 5-793.69, 5-793.7, 5-793.71, 5-793.73, 5-793.74, 5-793.76, 5-793.77, 5-793.79, 5-793.8, 5-793.81, 5-793.83, 5-793.84, 5-793.86, 5-793.87, 5-793.89, 5-793.9, 5-793.91, 5-793.93, 5-793.94, 5-793.96, 5-793.97, 5-793.99, 5-793.a, 5-793.a1, 5-793.a3, 5-793.a3, 5-793.a4, 5-793.a4, 5-793.a6, 5-793.a7, 5-

793.a7, 5-793.a9, 5-793.a9, 5-793.b, 5-793.b1, 5-793.b3, 5-793.b4, 5-793.b6, 5-793.b7, 5-793.b9, 5-793.c, 5-793.c1, 5-793.c1, 5-793.c3, 5-793.c3, 5-793.c4, 5-793.c4, 5-793.c6, 5-793.c6, 5-793.c7, 5-793.c7, 5-793.c9, 5-793.c9, 5-793.e, 5-793.e1, 5-793.e3, 5-793.e4, 5-793.e6, 5-793.e7, 5-793.e9, 5-793.f, 5-793.f1, 5-793.f3, 5-793.f4, 5-793.f6, 5-793.f7, 5-793.f9, 5-793.g, 5-793.g1, 5-793.g3, 5-793.g4, 5-793.g6, 5-793.g7, 5-793.g9, 5-793.h, 5-793.h1, 5-793.h3, 5-793.h4, 5-793.h6, 5-793.h7, 5-793.h9, 5-793.k, 5-793.k1, 5-793.k3, 5-793.k4, 5-793.k6, 5-793.k7, 5-793.k9, 5-793.m, 5-793.m1, 5-793.m3, 5-793.m4, 5-793.m6, 5-793.m7, 5-793.m9, 5-793.x, 5-793.x1, 5-793.x3, 5-793.x4, 5-793.x6, 5-793.x7, 5-793.x9, 5-794, 5-794.0, 5-794.01, 5-794.03, 5-794.04, 5-794.06, 5-794.07, 5-794.09, 5-794.1, 5-794.11, 5-794.13, 5-794.14, 5-794.16, 5-794.17, 5-794.19, 5-794.2, 5-794.21, 5-794.23, 5-794.24, 5-794.26, 5-794.27, 5-794.29, 5-794.3, 5-794.31, 5-794.33, 5-794.34, 5-794.36, 5-794.37, 5-794.39, 5-794.4, 5-794.41, 5-794.43, 5-794.44, 5-794.46, 5-794.47, 5-794.49, 5-794.5, 5-794.51, 5-794.53, 5-794.54, 5-794.56, 5-794.57, 5-794.59, 5-794.6, 5-794.61, 5-794.63, 5-794.64, 5-794.66, 5-794.67, 5-794.69, 5-794.7, 5-794.71, 5-794.73, 5-794.74, 5-794.76, 5-794.77, 5-794.79, 5-794.8, 5-794.81, 5-794.83, 5-794.84, 5-794.86, 5-794.87, 5-794.89, 5-794.a, 5-794.a1, 5-794.a3, 5-794.a4, 5-794.a4, 5-794.a6, 5-794.a6, 5-794.a7, 5-794.a7, 5-794.a9, 5-794.a9, 5-794.b, 5-794.b1, 5-794.b3, 5-794.b4, 5-794.b6, 5-794.b7, 5-794.b9, 5-794.c, 5-794.c1, 5-794.c1, 5-794.c3, 5-794.c3, 5-794.c4, 5-794.c4, 5-794.c6, 5-794.c6, 5-794.c7, 5-794.c7, 5-794.c9, 5-794.c9, 5-794.e, 5-794.e1, 5-794.e3, 5-794.e4, 5-794.e6, 5-794.e7, 5-794.e9, 5-794.f, 5-794.f1, 5-794.f3, 5-794.f4, 5-794.f6, 5-794.f7, 5-794.f9, 5-794.g, 5-794.g1, 5-794.g3, 5-794.g4, 5-794.g6, 5-794.g7, 5-794.g9, 5-794.h, 5-794.h1, 5-794.h3, 5-794.h4, 5-794.h6, 5-794.h7, 5-794.h9, 5-794.k, 5-794.k1, 5-794.k3, 5-794.k4, 5-794.k6, 5-794.k7, 5-794.k9, 5-794.m, 5-794.m1, 5-794.m3, 5-794.m4, 5-794.m6, 5-794.m7, 5-794.m9, 5-794.n, 5-794.x, 5-794.x1, 5-794.x3, 5-794.x4, 5-794.x6, 5-794.x7, 5-794.x9, 5-799, 5-799.1, 5-799.2, 5-799.3, 5-799.4, 5-799.5, 5-799.6, 5-799.7, 5-799.8, 5-799.m, 5-799.x, 5-799.y, 5-79a.07, 5-79a.17, 5-79a.67, 5-79a.77, 5-79a.87, 5-79a.c7, 5-79a.e7, 5-79a.f7, 5-79a.g7, 5-79a.x7, 5-79b.07, 5-79b.0g, 5-79b.0h, 5-79b.17, 5-79b.1g, 5-79b.1h, 5-79b.27, 5-79b.2g, 5-79b.2h, 5-79b.67, 5-79b.6g, 5-79b.6h, 5-79b.77, 5-79b.7g, 5-79b.7h, 5-79b.87, 5-79b.8g, 5-79b.8h, 5-79b.c7, 5-79b.cg, 5-79b.ch, 5-79b.e7, 5-79b.eg, 5-79b.eh, 5-79b.f7, 5-79b.fg, 5-79b.fh, 5-79b.g7, 5-79b.gg, 5-79b.gh, 5-79b.h7, 5-79b.hg, 5-79b.hh, 5-79b.x7, 5-79b.xg, 5-79b.xh, 5-800.07, 5-800.17, 5-800.27, 5-800.37, 5-800.47, 5-800.57, 5-800.67, 5-800.77, 5-800.87, 5-800.97, 5-800.a7, 5-800.b7, 5-800.c7, 5-800.x7, 5-800.xg, 5-800.xh, 5-801.07, 5-801.17, 5-801.27, 5-801.37, 5-801.47, 5-801.a7, 5-801.b7, 5-801.c7, 5-801.g7, 5-801.h7, 5-801.k7, 5-801.m7, 5-801.n7, 5-801.p7, 5-801.x7, 5-802, 5-802.0, 5-802.1, 5-802.2, 5-802.3, 5-802.4, 5-802.5, 5-802.6, 5-802.7, 5-802.8, 5-802.9, 5-802.x, 5-802.y, 5-803, 5-803.0, 5-803.1, 5-803.2, 5-803.3, 5-803.4, 5-803.5, 5-803.6, 5-803.7, 5-803.8, 5-803.9, 5-803.a, 5-803.x, 5-803.y, 5-805, 5-805.0, 5-805.1, 5-805.2, 5-805.3, 5-805.4, 5-805.5, 5-805.6, 5-805.7, 5-805.8, 5-805.9, 5-805.a, 5-805.b, 5-805.x, 5-805.y, 5-808.4, 5-808.6, 5-809.07, 5-809.0g, 5-809.0h, 5-809.17, 5-809.1h, 5-809.27, 5-809.2g, 5-809.2h, 5-809.3h, 5-809.x7, 5-809.xg, 5-809.xh, 5-814, 5-814.0, 5-814.1, 5-

	814.2, 5-814.3, 5-814.4, 5-814.5, 5-814.6, 5-814.7, 5-814.8, 5-814.9, 5-814.a, 5-814.b, 5-814.c, 5-814.d, 5-814.e, 5-814.x, 5-814.y, 5-824.2, 5-824.20, 5-824.21, 5-824.8, 5-825.00, 5-825.02, 5-825.11, 5-825.12, 5-825.2, 5-825.20, 5-825.21, 5-825.2x, 5-825.5, 5-825.8, 5-825.b, 5-825.k, 5-825.k0, 5-825.k1, 5-825.kx, 5-829.0, 5-829.00, 5-829.01, 5-829.0x, 5-829.1, 5-829.2, 5-829.3, 5-829.5, 5-829.h, 5-864.2, 5-860, 5-860.0, 5-860.1, 5-860.2, 5-860.3, 5-860.4, 5-860.5, 5-860.6, 5-860.x, 5-860.y, 5-862, 5-862.0, 5-862.1, 5-862.2, 5-862.3, 5-862.4, 5-862.x, 5-862.y, 5-866.2, 5-866.0, 5-866.1

ICD-10-GM codes for intracranial bleeding

ICD-10-GM Code	Description
I60-	Subarachnoid hemorrhage
I61-	Intracerebral hemorrhage
I62-	Subdural hemorrhage (nontraumatic)
S0633	Circumscribed cerebral hematoma
S0634	Circumscribed cerebellar hematoma
S064	Epidural hemorrhage
S065	Traumatic subdural hemorrhage
S066	Traumatic subarachnoid hemorrhage

ICD-10-GM codes for gastrointestinal bleeding

ICD-10-GM Code	Description
I850	Esophageal varices with bleeding
I983	Esophageal and gastric varices in diseases with bleeding
K226	Mallory-Weiss syndrome
K228-	Hemorrhage of esophagus NOS
K250	Gastric ulcer, acute with hemorrhage
K252	Gastric ulcer, acute with both hemorrhage and perforation
K254	Gastric ulcer, chronic or unspecified with hemorrhage
K256	Gastric ulcer, chronic or unspecified with both hemorrhage and perforation
K260	Duodenal ulcer, acute with hemorrhage
K262	Duodenal ulcer, acute with both hemorrhage and perforation
K264	Duodenal ulcer, chronic or unspecified with hemorrhage
K266	Duodenal ulcer, chronic or unspecified with both hemorrhage and perforation
K270	Peptic ulcer, site unspecified, acute with hemorrhage
K272	Peptic ulcer, site unspecified, acute with both hemorrhage and perforation
K274	Peptic ulcer, site unspecified, chronic or unspecified with hemorrhage
K276	Peptic ulcer, site unspecified, chronic or unspecified with both hemorrhage and perforation
K280	Gastrojejunal ulcer, site unspecified, acute with hemorrhage
K282	Gastrojejunal ulcer, site unspecified, acute with both hemorrhage and perforation
K284	Gastrojejunal ulcer, site unspecified, chronic or unspecified with hemorrhage
K286	Gastrojejunal ulcer, site unspecified, chronic or unspecified with both hemorrhage and perforation
K290	Acute hemorrhagic gastritis
K3182	Angiodysplasia of the stomach and duodenum with hemorrhage
K5522	Angiodysplasia of colon [with bleeding]

ICD-10-GM Code	Description
K5532	Angiodysplasia of the small intestine with hemorrhage
K5582	Angiodysplasia of the small intestine with hemorrhage
K5701	Diverticulosis of the small intestine with perforation, abscess and bleeding
K5703	Diverticulitis of the small intestine with perforation, abscess and bleeding
K5711	Diverticulosis of the small intestine without perforation and abscess, with hemorrhage
K5713	Diverticulitis of the small intestine without perforation and abscess, with hemorrhage
K5721	Diverticulosis of the colon with perforation, abscess and bleeding
K5723	Diverticulitis of the colon with perforation, abscess and bleeding
K5731	Diverticulosis of the colon without perforation or abscess, with hemorrhage
K5733	Diverticulitis of the colon without perforation or abscess, with hemorrhage
K5741	Diverticular disease of both the small intestine and the large intestine with perforation, abscess and bleeding
K5743	Diverticulitis both the small intestine and the large intestine with perforation, abscess and bleeding
K5751	Diverticular disease of both the small intestine and the large intestine without perforation or abscess, with hemorrhage
K5753	Diverticulitis both the small intestine and the large intestine without perforation or abscess, with hemorrhage
K5781	Diverticulosis of intestine, part unspecified, with perforation, abscess and bleeding
K5783	Diverticulitis of the intestine, part unspecified, with perforation, abscess and bleeding
K5791	Diverticulitis of the intestine, part unspecified, without perforation, abscess or indication of bleeding
K5793	Diverticulitis of the intestine, part unspecified, without perforation or abscess, with hemorrhage
K625	Hemorrhage of anus and rectum
K661	Hemoperitoneum
K920	Hematemesis
K921	Melaena
K922	Gastrointestinal hemorrhage, unspecified

ICD-10-GM codes for urogenital bleeding

ICD-10-GM Code	Description
N02-	Recurrent and persistent hematuria
N421	Congestion and hemorrhage of prostate
N836	Hematosalpinx
N857	Hematometra
N897	Hematocolpos
N92-	Excessive and frequent menstruation with regular cycle
N93-	Postcoital and contact bleeding
N950	Postmenopausal bleeding
R31	Unspecified hematuria
S314	Open wound of vagina and vulva

ICD-10-GM codes for other bleeding

ICD-10-GM Code	Description
D683	Hemorrhagic disorder due to circulating anticoagulants
D698.-	Other specified hemorrhagic conditions
D699	Hemorrhagic condition, unspecified
H113	Conjunctival hemorrhage
H210	Hyphema
H313	Choroidal hemorrhage and rupture
H356	Retinal hemorrhage
H431	Vitreous hemorrhage
H922	Otorrhagia
I312	Hemopericardium, not elsewhere classified
J942	Hemothorax
M250.-	Hemarthrosis
R04.-	Hemorrhage from respiratory passages
R233	Spontaneous ecchymoses
R58	Hemorrhage, not elsewhere classified

ICD-10-GM codes for noninfective liver disease

ICD-10-GM Code	Description
K70	Alcoholic liver disease
K71	Toxic liver disease
K72	Hepatic failure, not elsewhere classified
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K75	Other inflammatory liver diseases
K76	Other diseases of liver
K77	Liver disorders in diseases classified elsewhere

ICD-10-GM codes for DVT/PE

ICD-10-GM Code	Description
I80.1	Phlebitis and thrombophlebitis of femoral vein
I80.2-	Phlebitis and thrombophlebitis of other and unspecified deep vessels of lower extremities
I26	Pulmonary embolism

ICD-10-GM codes for ischemic stroke

ICD-10-GM Code	Description
I63.-	Cerebral infarction
I64.-	Stroke, not specified as infarction or hemorrhage (only for the sensitivity analyses)

ICD-10-GM codes for myocardial infarction

ICD-10-GM Code	Description
I21.-	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction

ICD-10-GM codes for past medical history

Condition	Codes
Intracranial bleeding	See above + I690 and I691,
Intracerebral bleeding	I61-, I691
Other subarachnoid bleeding	I60-, I690, S066
Other intracranial bleeding	I62-, S0633, S0634, S064, S065
Gastrointestinal bleeding	See above
Urogenital bleeding	See above
Ischemic stroke	I63, I693, I64, I694
TIA	G45
VTE (DVT/PE)	I801, I802-, I26-
Myocardial infarction (acute and old myocardial infarction)	I21-I23, I240, I241, I252-
Hypertension	I10-15
Heart failure	I50-, I110-, I130-, I132-
CAD	I20-I25
Peripheral arterial disease (PAD)	I70-73
Hyperlipidemia	E78
Diabetes mellitus	E10-14 or use of antidiabetic drug (ATC A10)
Liver disease	K70-77 and Z944
Chronic obstructive pulmonary disease	J43- J44.-
Asthma	J45-46
Cancer	C0-C97 (excluding C44)
Dementia	F00-03, F051, G30-,G3182,
Depression	F32-F33, F341, F412, F432

ICD-10-GM codes for comorbidities

Condition	Codes
Anemia	D50-64
Coagulation or platelet defect	D65-69
Vascular disease (as in CHA_2DS_2-VASc)	I21.-,I22.-, I25.2-, I70.- -73.-
Mitral stenosis (indication)	I342, I050, I052, I058, I059, I080, I081, I083, I088, Q232, Q239
Prosthetic heart valve (mechanic)	Z952,Z953, Z954, T820, T826 + OPS code
Atrial fibrillation	I48
Abnormal renal function (Risk scores)	N18- N19, Z49, Z992
Obesity	E65, E66
Abnormal liver function (Risk scores)	K70- K77, Z944
Bleeding history	See intracranial bleeding, gastrointestinal bleeding, urogenital bleeding and other bleeding
Alcohol-related disorders	E244, E52, F10-, G312, G621, G721, I426, K292, K70-, K852-, K860, O354, P043, Q860, T510, T519, Z502
Peripheral systemic embolism	I74-
Previous stroke	I61-, I63.-, I64.-, I694, I693

ATC codes for co-medication

Medication	ATC Codes
Antiplatelet agents	
Acetylsalicylic acid	B01AC06, B01AC86
Acetylsalicylic acid + dipyridamole combination	B01AC36
Acetylsalicylic acid + clopidogrel combination	B01AC34
Acetylsalicylic acid combination	B01AC56, C10BX08, C10BX12, C10BX06, C07FX04, C07FX03, C10BX02, C10BX05, C10BX01, C10BX04, C07FX02
Clopidogrel	B01AC04, B01AC34
Dipyridamole	B01AC07, C01DX22, C01DX72
Prasugrel	B01AC22
Ticlopidine	B01AC05
Ticagrelor	B01AC24
Nonsteroidal anti-inflammatory drugs	M01A, C01EB16, G02CC01, G02CC02, M02AA13, N02AJ05, N02AJ08, N02AJ19, R01BA57, R02AX02
Other anticoagulants	
Edoxaban	B01AF03
Dabigatran etexilate	B01AE07
Apixaban	B01AF02
Heparin	B01AB (excluded B01AB02)
Antiarrhythmic agents	C01B
Antihypertensive agents	**C01D, C02, C09X**
Beta blockers	C07
ACE inhibitors	C09A, C09B
Angiotensin receptor blockers	C09C, C09D
Calcium channel blockers	C08
Diuretics	C03
Statins	C10AA, C10BA, C10BX
Antidiabetic agents	A10
Metformin	A10BA02
Insulin	A10A
DPP-4 Inhibitors	A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BH
SGLT2 Inhibitors	A10BD15, A10BD16, A10BD20, A10BK
Sulfonylureas	A10BB, A10BD01, A10BD02, A10BD31
Others	
Oral steroids	H02
PPIs	A02BC, A02BD
SSRI	N06AB
Antibiotics	J01

ATC codes for drugs not recommended for concomitant use

Medication	ATC Codes
Inhibitors of either cytochrome P450 3A4 or P-glycoprotein	
Ketoconazole	J02AB02
Itraconazole	J02AC02
Voriconazole	J02AC03
Posaconazole	J02AC04
Verapamil	C08DA01, C08DA51, C08DA81, C08GA23, C08GA53, C09BB10
Diltiazem	C08DB01
Clarithromycin	J01FA09, A02BD04, A02BD05, A02BD06, A02BD07, A02BD09, A02BD11, A02BD12, A02BD14
Quinidine	C01BA01, C01BA13, C01BA51, C01BA71
Amiodaron	C01BD01
Protease inhibitors	J05AE, J05AR10
Nefazodone	N06AX06
CYP3A4 inducers	
Rifampicin	J04AB02, J04AM02, J04AM05, J04AM06, J04AM07
Phenytoin	N03AB02, N03AB52
Carbamazepine	N03AF01
Phenobarbital	N03AA02, N05CA24
St John's Wort	, N06AP01, N06AP51, N06AX25

Annex 2.2 Statistical Table Set

Annex 2.2 Table 1: Cohort definition: first-time users of rivaroxaban and SOC

	Rivaroxaban N = 265,584		SOC N = 172,727	
Indication	**n**	**%**	**n**	**%**
SPAF	127,743	48.1	88,655	51.3
VTE-T without recent history of cancer [a]	25,914	9.8	20,502	11.9
VTE-T with recent history of cancer [a]	5198	2.0	-	-
TKR/THR	30,079	11.3	-	-
ACS	546	0.2	-	-
Other [b]	45,714	17.2	-	-
Total with assigned indication	235,194	88.6	109,157	63.2
Unknown indication	30,390	11.4	15,192	8.8

a: Recent history of cancer is defined as a diagnosis of cancer from 3 years before the start date to up to 1 month after

b: Off label-use (valvular SPAF, VTE additionally using codes for other thrombosis of lower limbs or DVT of upper limbs, ACS, PAD, CAD, surgery of upper limbs or other orthopedic surgery of lower limbs)

ACS, acute coronary syndrome; CAD, coronary artery disease; DVT, deep vein thrombosis; PAD, peripheral artery disease; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism; VTE-T, treatment and secondary prevention of VTE

Annex 2.2 Table 2: Follow-up time among first-time users of rivaroxaban and SOC

	SPAF	VTE-T without a recent history of cancer		VTE-T with a recent history of cancer		TKR/THR	ACS
	Rivaroxaban	SOC	Rivaroxaban	SOC	Rivaroxaban	Rivaroxaban	Rivaroxaban
	N = 127,743	N = 88,655	N = 25,914	N = 20,502	N = 5198	N = 30,079	N = 546
Time at risk, first episode of treatment [a] (used in the cohort analysis)							
Mean ± SD	502.8 ± 514.1	803.6 ± 646.9	330.9 ± 376.7	503.0 ± 555.6	323.5 ± 363.4	71.3 ± 149.6	558.3 ± 502.8
Median (IQR)	303.0 (98–788)	670.0 (192–1320)	207.0 (102–412)	260.0 (100–623)	201.0 (88–413)	42.0 (37–60)	394.0 (126–784)
Range	1–2215	1–2215	1–2208	1–2215	1–2177	5–2146	1–2048
Total follow-up time [b] (used in the nested case-control analysis)							
Mean ± SD	1087.2 ± 536.5	1282.9 ± 586.9	1055.5 ± 486.5	1405.7 ± 570.1	880.4 ± 534.1	1153.5 ± 523.6	997.8 ± 561.2
Median (IQR)	1077.0 (661–1520)	1321.0 (815–1791)	1033.0 (664–1434)	1494.0 (969–1896)	824.0 (450–1286)	1115.0 (704–1563)	940.5 (520–1462)
Range	0–2214	0–2214	0–2211	0–2214	1–2183	0–2214	1–2175

a: Until treatment switching/discontinuation, end of the study period, death or cohort exit

b: Until the end of the study period, death or cohort exit

ACS, acute coronary syndrome; IQR, interquartile range; SD, standard deviation; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation; THR, total hip replacement; TKR, total knee replacement; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 3: Characteristics of prescription/dispensation at start date among first-time users of study drugs – SPAF cohort

	Rivaroxaban N = 127,743	
	n	**%**
Rivaroxaban tablet strength at start date		
2.5 mg	74	0.1
10 mg	6596	5.2
15 mg	36,069	28.2
20 mg	84,062	65.8
Combination 15 + 20 mg	0	0.0
Multiple	942	0.7
Duration of first episode of rivaroxaban use (days)		
1-30	16,293	12.8
31-60	6963	5.5
61-90	6311	4.9
91-180	19,825	15.5
181-365	19,094	14.9
> 365	59,257	46.4

SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 4: Characteristics of prescription/dispensation at start date among first-time users of study drugs – VTE-T without recent history of cancer

	Rivaroxaban N = 25,914	
	n	**%**
Rivaroxaban tablet strength at start date		
2.5 mg	8	0.0
10 mg	603	2.3
15 mg	14,526	56.1
20 mg	6372	24.6
Combination 15 + 20 mg	0	0.0
Multiple	4405	17.0
Duration of first episode of rivaroxaban use (days)		
1-30	2777	10.7
31-60	1028	4.0
61-90	2266	8.7
91-180	5703	22.0
181-365	6713	25.9
> 365	7427	28.7

VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 5: Characteristics of prescription/dispensation at start date among first-time users of study drugs – VTE-T with recent history of cancer

	Rivaroxaban N = 5198	
	n	**%**
Rivaroxaban tablet strength at start date		
2.5 mg	1	0.0
10 mg	157	3.0
15 mg	2796	53.8
20 mg	1569	30.2
Combination 15 + 20 mg	0	0.0
Multiple	675	13.0
Duration of first episode of rivaroxaban use (days)		
1-30	622	12.0
31-60	272	5.2
61-90	498	9.6
91-180	1008	19.4
181-365	1240	23.9
> 365	1558	30.0

VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 6: Characteristics of prescription/dispensation at start date among first-time users of study drugs – THR/TKR cohort

	Rivaroxaban N = 30,079	
	n	**%**
Rivaroxaban tablet strength at start date		
2.5 mg	15	0.0
10 mg	27,813	92.5
15 mg	932	3.1
20 mg	1254	4.2
Combination 15 + 20 mg	0	0.0
Multiple	65	0.2
Duration of first episode of rivaroxaban use (days)		
1-30	5594	18.6
31-60	17,170	57.1
61-90	4639	15.4
91-180	1202	4.0
181-365	734	2.4
> 365	740	2.5

THR, total hip replacement; TKR, total knee replacement

Annex 2.2 Table 7: Characteristics of prescription/dispensation at start date among first-time users of study drugs – ACS cohort

	Rivaroxaban N = 546	
	n	**%**
Rivaroxaban tablet strength at start date		
2.5 mg	24	4.4
10 mg	46	8.4
15 mg	229	41.9
20 mg	237	43.4
Combination 15 + 20 mg	0	0.0
Multiple	10	1.8
Duration of first episode of rivaroxaban use (days)		
1-30	37	6.8
31-60	38	7.0
61-90	25	4.6
91-180	64	11.7
181-365	67	12.3
> 365	315	57.7

ACS, acute coronary syndrome

Annex 2.2 Table 8: Pattern of rivaroxaban use during first year of treatment – SPAF cohort

Limited to patients with at least 1 year of follow-up and 2 Rx in the year

	Rivaroxaban N = 98,682	
	n	**%**
Users with continuous use of rivaroxaban	**59,257**	**60.0**
Users who discontinued rivaroxaban [a]	**39,425**	**40.0**
Users who switched from rivaroxaban	5939	15.1
Switched to a different NOAC	*3230*	*54.4*
Switched to any VKA	*2705*	*45.5*
Switched to multiple	*4*	*0.1*
Users who reinitiated OAC therapy after rivaroxaban discontinuation [b]	22,195	56.3
Reinitiated with rivaroxaban	*19,566*	*88.2*
Reinitiated with a different NOAC	*1252*	*5.6*
Reinitiated with any VKA	*1371*	*6.2*
Reinitiated with multiple	*6*	*0.0*
Users who discontinued and did not reinitiate OAC therapy	11,291	28.6

a: Discontinuation was defined as a gap of more than 30 days after the end of supply of rivaroxaban

b: Restarted OAC therapy after a gap of more than 30 days between the end of the last prescription for rivaroxaban and the next prescription for an OAC

NOAC, non-VKA oral anticoagulant; OAC, oral anticoagulant; Rx, prescriptions; SPAF, stroke prevention in nonvalvular atrial fibrillation; VKA, vitamin K antagonist

Annex 2.2 Table 9: General characteristics of first-time users of rivaroxaban and SOC at the start date – SPAF cohort

	Rivaroxaban N = 127,743		SOC N = 88,655	
	n	%	n	%
Sex				
Male	65,779	51.5	46,643	52.6
Female	61,964	48.5	42,012	47.4
Age at first prescription/dispensing				
≤ 49	3413	2.7	1389	1.6
≥ 50–≤ 59	9369	7.3	5373	6.1
≥ 60–≤ 69	23,375	18.3	17,034	19.2
≥ 70–≤ 79	52,908	41.4	40,460	45.6
≥ 80–≤ 89	33,159	26.0	21,922	24.7
≥ 90	5519	4.3	2477	2.8
Mean ± SD	73.8 ± 10.7		73.9 ± 9.4	
Median (IQR)	75.0 (68–81)		75.0 (69–80)	
Range	17–100		3–100	
Naive status at first prescription/dispensing				
Naive	86,366	67.6	84,327	95.1
Non-naive	41,377	32.4	4328	4.9
Calendar year of first prescription/dispensing				
2011 (Dec only)	92	0.1	1674	1.9
2012 (Jan–Dec)	17,553	13.7	25,576	28.8
2013 (Jan–Dec)	31,756	24.9	20,131	22.7
2014 (Jan–Dec)	29,492	23.1	17,374	19.6
2015 (Jan–Dec)	27,359	21.4	14,023	15.8
2016 (Jan–Dec)	21,491	16.8	9877	11.1

IQR, interquartile range; SD, standard deviation; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 10: General characteristics among first-time users of rivaroxaban by calendar year – SPAF cohort

	Rivaroxaban													
	2011 [a] N = 92		2012 N = 17,553		2013 N = 31,756		2014 N = 29,492		2015 N = 27,359		2016 N = 21,491		Total N = 127,743	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	50	54.3	8916	50.8	16,129	50.8	15,090	51.2	14,268	52.2	11,326	52.7	65,779	51.5
Female	42	45.7	8637	49.2	15,627	49.2	14,402	48.8	13,091	47.8	10,165	47.3	61,964	48.5
Age														
≤ 49	3	3.3	334	1.9	796	2.5	790	2.7	799	2.9	691	3.2	3413	2.7
≥ 50–≤ 59	4	4.3	1049	6.0	2119	6.7	2165	7.3	2214	8.1	1818	8.5	9369	7.3
≥ 60–≤ 69	24	26.1	3184	18.1	5605	17.7	5280	17.9	5095	18.6	4187	19.5	23,375	18.3
≥ 70–≤ 79	37	40.2	7531	42.9	13,485	42.5	12,398	42.0	11,058	40.4	8399	39.1	52,908	41.4
≥ 80–≤ 89	18	19.6	4708	26.8	8371	26.4	7528	25.5	6967	25.5	5567	25.9	33,159	26.0
≥ 90	6	6.5	747	4.3	1380	4.3	1331	4.5	1226	4.5	829	3.9	5519	4.3
Naive status														
Naive	32	34.8	9025	51.4	19,948	62.8	20,610	69.9	20,417	74.6	16,334	76.0	86,366	67.6
Non-naive	60	65.2	8528	48.6	11,808	37.2	8882	30.1	6942	25.4	5157	24.0	41,377	32.4

a: December only

SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 11: General characteristics of first-time users of rivaroxaban and SOC at the start date – VTE-T without recent history of cancer

	Rivaroxaban N = 25,914		SOC N = 20,502	
	n	**%**	**n**	**%**
Sex				
Male	11,860	45.8	9290	45.3
Female	14,054	54.2	11,212	54.7
Age at first prescription/dispensing				
≤ 49	6730	26.0	4750	23.2
≥ 50–≤ 59	4846	18.7	3511	17.1
≥ 60–≤ 69	4571	17.6	3788	18.5
≥ 70–≤ 79	6133	23.7	5456	26.6
≥ 80–≤ 89	3064	11.8	2603	12.7
≥ 90	570	2.2	394	1.9
Mean ± SD	60.9 ± 17.4		62.4 ± 16.7	
Median (IQR)	62.0 (49–75)		65.0 (51–75)	
Range	14–100		10–99	
Naive status at first prescription/dispensing				
Naive	22,809	88.0	20,323	99.1
Non-naive	3105	12.0	179	0.9
Calendar year of first prescription/dispensing				
2011 (Dec only)	14	0.1	510	2.5
2012 (Jan–Dec)	2027	7.8	6995	34.1
2013 (Jan–Dec)	5370	20.7	4890	23.9
2014 (Jan–Dec)	6194	23.9	3648	17.8
2015 (Jan–Dec)	6287	24.3	2705	13.2
2016 (Jan–Dec)	6022	23.2	1754	8.6

IQR, interquartile range; SD, standard deviation; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 12: General characteristics among first-time users of rivaroxaban by calendar year – VTE-T without recent history of cancer

	Rivaroxaban													
	2011 [a] N = 14		2012 N = 2027		2013 N = 5370		2014 N = 6194		2015 N = 6287		2016 N = 6022		Total N = 25,914	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	8	57.1	904	44.6	2431	45.3	2774	44.8	2910	46.3	2833	47.0	11,860	45.8
Female	6	42.9	1123	55.4	2939	54.7	3420	55.2	3377	53.7	3189	53.0	14,054	54.2
Age														
≤ 49	3	21.4	528	26.0	1432	26.7	1665	26.9	1580	25.1	1522	25.3	6730	26.0
≥ 50–≤ 59	5	35.7	335	16.5	987	18.4	1113	18.0	1214	19.3	1192	19.8	4846	18.7
≥ 60–≤ 69	1	7.1	324	16.0	900	16.8	1058	17.1	1160	18.5	1128	18.7	4571	17.6
≥ 70–≤ 79	4	28.6	478	23.6	1282	23.9	1506	24.3	1490	23.7	1373	22.8	6133	23.7
≥ 80–≤ 89	1	7.1	305	15.0	644	12.0	690	11.1	727	11.6	697	11.6	3064	11.8
≥ 90	0	0.0	57	2.8	125	2.3	162	2.6	116	1.8	110	1.8	570	2.2
Naive status														
Naive	9	64.3	1596	78.7	4577	85.2	5528	89.2	5673	90.2	5426	90.1	22,809	88.0
Non-naive	5	35.7	431	21.3	793	14.8	666	10.8	614	9.8	596	9.9	3105	12.0

a: December only

VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 13: General characteristics among first-time users of rivaroxaban at the start date – VTE-T with recent history of cancer

	Rivaroxaban N = 5198	
	n	**%**
Sex		
Male	2388	45.9
Female	2810	54.1
Age at first prescription/dispensing		
≤ 49	293	5.6
≥ 50–≤ 59	609	11.7
≥ 60–≤ 69	1214	23.4
≥ 70–≤ 79	2112	40.6
≥ 80–≤ 89	841	16.2
≥ 90	129	2.5
Mean ± SD	70.1 ± 11.7	
Median (IQR)	72.0 (63–78)	
Range	18–98	
Naive status at first prescription/dispensing		
Naive	4533	87.2
Non-naive	665	12.8
Calendar year of first prescription/dispensing		
2011 (Dec only)	1	0.0
2012 (Jan–Dec)	478	9.2
2013 (Jan–Dec)	1086	20.9
2014 (Jan–Dec)	1198	23.0
2015 (Jan–Dec)	1264	24.3
2016 (Jan–Dec)	1171	22.5

IQR, interquartile range; SD, standard deviation; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 14: General characteristics among first-time users of rivaroxaban by calendar year – VTE-T with recent history of cancer

	Rivaroxaban													
	2011 [a] N = 1		2012 N = 478		2013 N = 1086		2014 N = 1198		2015 N = 1264		2016 N = 1171		Total N = 5198	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	1	100.0	222	46.4	490	45.1	544	45.4	605	47.9	526	44.9	2388	45.9
Female	0	0.0	256	53.6	596	54.9	654	54.6	659	52.1	645	55.1	2810	54.1
Age														
≤ 49	0	0.0	26	5.4	70	6.4	65	5.4	69	5.5	63	5.4	293	5.6
≥ 50–≤ 59	0	0.0	63	13.2	109	10.0	143	11.9	154	12.2	140	12.0	609	11.7
≥ 60–≤ 69	0	0.0	100	20.9	242	22.3	288	24.0	331	26.2	253	21.6	1214	23.4
≥ 70–≤ 79	1	100.0	193	40.4	461	42.4	476	39.7	491	38.8	490	41.8	2112	40.6
≥ 80–≤ 89	0	0.0	79	16.5	169	15.6	199	16.6	185	14.6	209	17.8	841	16.2
≥ 90	0	0.0	17	3.6	35	3.2	27	2.3	34	2.7	16	1.4	129	2.5
Naive status														
Naive	1	100.0	370	77.4	923	85.0	1039	86.7	1142	90.3	1058	90.4	4533	87.2
Non-naive	0	0.0	108	22.6	163	15.0	159	13.3	122	9.7	113	9.6	665	12.8

a: December only

VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 15: General characteristics among first-time users of rivaroxaban at the start date – THR/TKR cohort

	Rivaroxaban N = 30,079	
	n	**%**
Sex		
Male	10,411	34.6
Female	19,668	65.4
Age at first prescription/dispensing		
≤ 49	1640	5.5
≥ 50–≤ 59	5363	17.8
≥ 60–≤ 69	9004	29.9
≥ 70–≤ 79	10,972	36.5
≥ 80–≤ 89	2922	9.7
≥ 90	178	0.6
Mean ± SD	67.3 ± 10.6	
Median (IQR)	68.0 (60–75)	
Range	17–100	
Calendar year of first prescription/dispensing		
2011 (Dec only)	201	0.7
2012 (Jan–Dec)	4369	14.5
2013 (Jan–Dec)	5540	18.4
2014 (Jan–Dec)	6328	21.0
2015 (Jan–Dec)	6789	22.6
2016 (Jan–Dec)	6852	22.8

IQR, interquartile range; SD, standard deviation; THR, total hip replacement; TKR, total knee replacement

Annex 2.2 Table 16: General characteristics among first-time users of rivaroxaban by calendar year – THR/TKR cohort

	Rivaroxaban													
	2011 [a] N = 201		2012 N = 4369		2013 N = 5540		2014 N = 6328		2015 N = 6789		2016 N = 6852		Total N = 30,079	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	78	38.8	1537	35.2	1872	33.8	2208	34.9	2329	34.3	2387	34.8	10,411	34.6
Female	123	61.2	2832	64.8	3668	66.2	4120	65.1	4460	65.7	4465	65.2	19,668	65.4
Age														
≤ 49	18	9.0	291	6.7	332	6.0	353	5.6	355	5.2	291	4.2	1640	5.5
≥ 50–≤ 59	41	20.4	808	18.5	1001	18.1	1121	17.7	1194	17.6	1198	17.5	5363	17.8
≥ 60–≤ 69	63	31.3	1327	30.4	1637	29.5	1866	29.5	2028	29.9	2083	30.4	9004	29.9
≥ 70–≤ 79	69	34.3	1564	35.8	1992	36.0	2367	37.4	2478	36.5	2502	36.5	10,972	36.5
≥ 80–≤ 89	10	5.0	355	8.1	554	10.0	584	9.2	690	10.2	729	10.6	2922	9.7
≥ 90	0	0.0	24	0.5	24	0.4	37	0.6	44	0.6	49	0.7	178	0.6

a: December only

THR, total hip replacement; TKR, total knee replacement

Annex 2.2 Table 17: General characteristics among first-time users of rivaroxaban at the start date, stratified by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Sex						
Male	15	62.5	301	57.7	316	57.9
Female	9	37.5	221	42.3	230	42.1
Age at first prescription/dispensing						
≤ 49	3	12.5	27	5.2	30	5.5
≥ 50–≤ 59	8	33.3	56	10.7	64	11.7
≥ 60–≤ 69	7	29.2	66	12.6	73	13.4
≥ 70–≤ 79	5	20.8	191	36.6	196	35.9
≥ 80–≤ 89	1	4.2	154	29.5	155	28.4
≥ 90	0	0.0	28	5.4	28	5.1
Mean ± SD	62.0 ± 12.2		73.7 ± 12.3		73.2 ± 12.5	
Median (IQR)	62.5 (55–70)		76.0 (66–82)		76.0 (66–82)	
Range	32–85		32–94		32–94	
Calendar year of first prescription/dispensing						
2011 (Dec only)-2013 (Jan–April)	0	0.0	126	24.1	126	23.1
2013 (May–Dec) [a]	0	0.0	77	14.8	77	14.1
2014 (Jan–Dec)	3	12.5	97	18.6	100	18.3
2015 (Jan–Dec)	7	29.2	113	21.6	120	22.0
2016 (Jan–Dec)	14	58.3	109	20.9	123	22.5

a: May 2013–December 2013 as ACS indication approved in May

ACS, acute coronary syndrome; IQR, interquartile range; SD, standard deviation

Annex 2.2 Table 18: General characteristics among first-time users of rivaroxaban by calendar year – ACS cohort

	Rivaroxaban											
	2011-2013 [a] N = 126		2013 [b] N = 77		2014 N = 100		2015 N = 120		2016 N = 123		Total N = 546	
	n	%	n	%	n	%	n	%	n	%	n	%
Sex												
Male	73	57.9	43	55.8	55	55.0	67	55.8	78	63.4	316	57.9
Female	53	42.1	34	44.2	45	45.0	53	44.2	45	36.6	230	42.1
Age												
≤ 49	3	2.4	6	7.8	6	6.0	5	4.2	10	8.1	30	5.5
≥ 50–≤ 59	13	10.3	2	2.6	12	12.0	20	16.7	17	13.8	64	11.7
≥ 60–≤ 69	16	12.7	9	11.7	11	11.0	18	15.0	19	15.4	73	13.4
≥ 70–≤ 79	47	37.3	32	41.6	30	30.0	45	37.5	42	34.1	196	35.9
≥ 80–≤ 89	38	30.2	23	29.9	35	35.0	27	22.5	32	26.0	155	28.4
≥ 90	9	7.1	5	6.5	6	6.0	5	4.2	3	2.4	28	5.1

a: December 2011–April 2013
b: May 2013–December 2013 as ACS indication approved in May
ACS, acute coronary syndrome

Annex 2.2 Table 19: Healthcare resource utilization in first-time users of study drugs – SPAF cohort

	Rivaroxaban N = 127,743		SOC N = 88,655	
	n	%	n	%
Number of hospitalizations during 12 months prior to start date				
None	33,469	26.2	23,538	26.6
1	54,840	42.9	39,222	44.2
≥ 2	39,434	30.9	25,895	29.2
Number of hospitalizations during 12 months after start date				
None	56,033	43.9	40,267	45.4
1	34,757	27.2	23,671	26.7
≥ 2	36,953	28.9	24,717	27.9

SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 20: Healthcare resource utilization in first-time users of study drugs – VTE-T without recent history of cancer

	Rivaroxaban N = 25,914		SOC N = 20,502	
	n	%	n	%
Number of hospitalizations during 12 months prior to start date				
None	6897	26.6	4346	21.2
1	11,984	46.2	9875	48.2
≥ 2	7033	27.1	6281	30.6
Number of hospitalizations during 12 months after start date				
None	15,800	61.0	12,375	60.4
1	5772	22.3	4572	22.3
≥ 2	4342	16.8	3555	17.3

SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 21: Healthcare resource utilization in first-time users of rivaroxaban – VTE-T with recent history of cancer

	Rivaroxaban N = 5198	
	n	**%**
Number of hospitalizations during 12 months prior to start date		
None	653	12.6
1	1524	29.3
≥ 2	3021	58.1
Number of hospitalizations during 12 months after start date		
None	2055	39.5
1	1229	23.6
≥ 2	1914	36.8

VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 22: Healthcare resource utilization in first-time users of rivaroxaban, stratified by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Number of hospitalizations during 12 months prior to start date						
None	0	0.0	0	0.0	0	0.0
1	12	50.0	278	53.3	290	53.1
≥ 2	12	50.0	244	46.7	256	46.9
Number of hospitalizations during 12 months after start date						
None	10	41.7	168	32.2	178	32.6
1	9	37.5	148	28.4	157	28.8
≥ 2	5	20.8	206	39.5	211	38.6

ACS, acute coronary syndrome

Annex 2.2 Table 23: Lifestyle characteristics any time prior to start date or one month after in first-time users of study drugs – SPAF cohort

	Rivaroxaban N = 127,743		SOC N = 88,655	
	n	%	n	%
Obesity diagnosis				
Yes	49,142	38.5	34,828	39.3
No	78,601	61.5	53,827	60.7
Diagnosis indicating alcohol abuse				
Yes	8244	6.5	5361	6.0
No	119,499	93.5	83,294	94.0
Deprivation index of place of residence				
Quintile 1 [a]	34,737	27.2	18,454	20.8
Quintile 2	26,223	20.5	17,764	20.0
Quintile 3	28,104	22.0	24,127	27.2
Quintile 4	19,704	15.4	15,835	17.9
Quintile 5 [b]	18,168	14.2	12,159	13.7
Unknown	807	0.6	316	0.4

a: Lowest degree of deprivation/highest socioeconomic status
b: Highest degree of deprivation/lowest socioeconomic status
SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 24: Lifestyle characteristics any time prior to start date or one month after in first-time users of study drugs – VTE-T without recent history of cancer

	Rivaroxaban N = 25,914		SOC N = 20,502	
	n	%	n	%
Obesity diagnosis				
Yes	9194	35.5	7473	36.5
No	16,720	64.5	13,029	63.5
Diagnosis indicating alcohol abuse				
Yes	1451	5.6	1089	5.3
No	24,463	94.4	19,413	94.7
Deprivation index of place of residence				
Quintile 1 [a]	7163	27.6	4552	22.2
Quintile 2	5365	20.7	4123	20.1
Quintile 3	5788	22.3	5346	26.1
Quintile 4	3941	15.2	3738	18.2
Quintile 5 [b]	3491	13.5	2667	13.0
Unknown	166	0.6	76	0.4

a: Lowest degree of deprivation/highest socioeconomic status

b: Highest degree of deprivation/lowest socioeconomic status

SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 25: Lifestyle characteristics any time prior to start date or one month after in first-time users of rivaroxaban – VTE-T with recent history of cancer

	Rivaroxaban N = 5198	
	n	**%**
Obesity diagnosis		
Yes	1861	35.8
No	3337	64.2
Diagnosis indicating alcohol abuse		
Yes	275	5.3
No	4923	94.7
Deprivation index of place of residence		
Quintile 1 [a]	1452	27.9
Quintile 2	1061	20.4
Quintile 3	1204	23.2
Quintile 4	795	15.3
Quintile 5 [b]	659	12.7
Unknown	27	0.5

a: Lowest degree of deprivation/highest socioeconomic status
b: Highest degree of deprivation/lowest socioeconomic status
VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 26: Lifestyle characteristics any time prior to start date or one month after in first-time users of rivaroxaban, stratified by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Obesity diagnosis						
Yes	8	33.3	177	33.9	185	33.9
No	16	66.7	345	66.1	361	66.1
Diagnosis indicating alcohol abuse						
Yes	0	0.0	23	4.4	23	4.2
No	24	100.0	499	95.6	523	95.8
Deprivation index of place of residence						
Quintile 1 [a]	6	25.0	156	29.9	162	29.7
Quintile 2	8	33.3	101	19.3	109	20.0
Quintile 3	4	16.7	136	26.1	140	25.6
Quintile 4	4	16.7	77	14.8	81	14.8
Quintile 5 [b]	2	8.3	52	10.0	54	9.9
Unknown	0	0.0	0	0.0	0	0.0

a: Lowest degree of deprivation/highest socioeconomic status
b: Highest degree of deprivation/lowest socioeconomic status
ACS, acute coronary syndrome

Annex 2.2 Table 27: Medications of interest prescribed/dispensed in the 90 days before or on the start date in first-time users of rivaroxaban by calendar year and first-time users of SOC – SPAF cohort

	Rivaroxaban														SOC	
	2011 [a] N = 92		2012 N = 17,553		2013 N = 31,756		2014 N = 29,492		2015 N = 27,359		2016 N = 21,491		Total N = 127,743		Total N = 88,655	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Polypharmacy [b]																
< 5	24	26.1	5726	32.6	12,388	39.0	12,974	44.0	12,883	47.1	10,618	49.4	54,613	42.8	39,399	44.4
5-9	54	58.7	8979	51.2	15,328	48.3	13,440	45.6	12,013	43.9	9074	42.2	58,888	46.1	40,700	45.9
≥ 10	14	15.2	2848	16.2	4040	12.7	3078	10.4	2463	9.0	1799	8.4	14,242	11.1	8556	9.7
Medications of interest prescribed/dispensed up to 90 days before or on the start date																
Antiplatelets	16	17.4	2239	12.8	3828	12.1	3479	11.8	3218	11.8	2632	12.2	15,412	12.1	17,343	19.6
NSAIDs	25	27.2	3023	17.2	5319	16.7	4741	16.1	4229	15.5	3317	15.4	20,654	16.2	13,484	15.2
Antiarrhythmic agents	17	18.5	2405	13.7	3558	11.2	2837	9.6	2419	8.8	1698	7.9	12,934	10.1	8100	9.1
Antihypertensive medication	73	79.3	15,230	86.8	27,649	87.1	25,721	87.2	23,764	86.9	18,656	86.8	111,093	87.0	78,978	89.1
ACEis	*33*	*45.2*	*6059*	*39.8*	*11,367*	*41.1*	*10,347*	*40.2*	*9358*	*39.4*	*7090*	*38.0*	*44,254*	*39.8*	*36,002*	*45.6*
ARBs	*19*	*26.0*	*4126*	*27.1*	*7022*	*25.4*	*6687*	*26.0*	*6194*	*26.1*	*5099*	*27.3*	*29,147*	*26.2*	*19,845*	*25.1*
Calcium channel blockers	*11*	*15.1*	*3868*	*25.4*	*7092*	*25.7*	*6507*	*25.3*	*5929*	*24.9*	*4604*	*24.7*	*28,011*	*25.2*	*22,985*	*29.1*
Beta blockers	*57*	*78.1*	*11,814*	*77.6*	*21,964*	*79.4*	*20,707*	*80.5*	*19,292*	*81.2*	*15,121*	*81.1*	*88,955*	*80.1*	*63,413*	*80.3*
Diuretics	39	42.4	6423	36.6	11,555	36.4	10,388	35.2	9141	33.4	7195	33.5	44,741	35.0	32,898	37.1
Statins	24	26.1	4710	26.8	8335	26.2	7743	26.3	7057	25.8	5831	27.1	33,700	26.4	27,056	30.5
Antidiabetic agents	9	9.8	2815	16.0	5017	15.8	4375	14.8	3954	14.5	3134	14.6	19,304	15.1	14,539	16.4
Metformin	*4*	*44.4*	*1330*	*47.2*	*2421*	*48.3*	*2106*	*48.1*	*1914*	*48.4*	*1598*	*51.0*	*9373*	*48.6*	*7384*	*50.8*
Insulin	*3*	*33.3*	*1167*	*41.5*	*2040*	*40.7*	*1781*	*40.7*	*1550*	*39.2*	*1247*	*39.8*	*7788*	*40.3*	*5903*	*40.6*
DPP-4 inhibitors	*3*	*33.3*	*539*	*19.1*	*1126*	*22.4*	*1062*	*24.3*	*1053*	*26.6*	*832*	*26.5*	*4615*	*23.9*	*2954*	*20.3*
SGLT2 inhibitors	*0*	*0.0*	*0*	*0.0*	*16*	*0.3*	*38*	*0.9*	*77*	*1.9*	*103*	*3.3*	*234*	*1.2*	*87*	*0.6*
Sulfonylureas	*0*	*0.0*	*438*	*15.6*	*727*	*14.5*	*615*	*14.1*	*458*	*11.6*	*310*	*9.9*	*2548*	*13.2*	*2242*	*15.4*
Oral steroids	7	7.6	1337	7.6	2513	7.9	2153	7.3	2129	7.8	1554	7.2	9693	7.6	6371	7.2
PPIs	33	35.9	5773	32.9	10,500	33.1	9784	33.2	9008	32.9	7085	33.0	42,183	33.0	28,219	31.8
SSRIs	3	3.3	680	3.9	1207	3.8	1048	3.6	905	3.3	690	3.2	4533	3.5	2564	2.9
Antibiotics	22	23.9	3069	17.5	5961	18.8	5130	17.4	4993	18.2	3637	16.9	22,812	17.9	14,766	16.7

Special warning/precaution																
CYP3A4 or P-GP inhibitors [c]	13	14.1	1832	10.4	2911	9.2	2442	8.3	2059	7.5	1532	7.1	10,789	8.4	8134	9.2
CYP3A4 inducers	3	3.3	124	0.7	236	0.7	224	0.8	183	0.7	121	0.6	891	0.7	515	0.6

a: December only
b: Number of individual ATC codes; in the year before start date
c: List of medications as specified in the report

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; ATC, Anatomical Therapeutic Chemical (Classification System); CYP3A4, cytochrome P450 3A4; DPP-4, dipeptidyl peptidase-4; NSAID, nonsteroidal anti-inflammatory drug; P-GP, P-glycoprotein; PPI, proton pump inhibitor; SGLT2, sodium–glucose co-transporter-2; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation; SSRI, selective serotonin reuptake inhibitor

Annex 2.2 Table 28: Medications of interest prescribed/dispensed in the 90 days before or on the start date in first-time users of rivaroxaban by calendar year and first-time users of SOC – VTE-T without recent history of cancer

	Rivaroxaban														SOC	
	2011 [a] N = 14		2012 N = 2027		2013 N = 5370		2014 N = 6194		2015 N = 6287		2016 N = 6022		Total N = 25,914		Total N = 20,502	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Polypharmacy [b]																
< 5	8	57.1	1256	62.0	3511	65.4	4207	67.9	4315	68.6	4222	70.1	17,519	67.6	13,185	64.3
5-9	4	28.6	651	32.1	1622	30.2	1775	28.7	1756	27.9	1619	26.9	7427	28.7	6407	31.3
≥ 10	2	14.3	120	5.9	237	4.4	212	3.4	216	3.4	181	3.0	968	3.7	910	4.4
Medications of interest prescribed/dispensed up to 90 days before or on the start date																
Antiplatelets	0	0.0	122	6.0	265	4.9	290	4.7	328	5.2	290	4.8	1295	5.0	1135	5.5
NSAIDs	2	14.3	510	25.2	1408	26.2	1601	25.8	1671	26.6	1564	26.0	6756	26.1	5147	25.1
Antiarrhythmic agents	1	7.1	13	0.6	12	0.2	9	0.1	17	0.3	8	0.1	60	0.2	54	0.3
Antihypertensive medication	8	57.1	902	44.5	2447	45.6	2733	44.1	2795	44.5	2623	43.6	11,508	44.4	9859	48.1
ACEis	*3*	*37.5*	*437*	*48.4*	*1172*	*47.9*	*1245*	*45.6*	*1290*	*46.2*	*1137*	*43.3*	*5284*	*45.9*	*4736*	*48.0*
ARBs	*4*	*50.0*	*251*	*27.8*	*688*	*28.1*	*830*	*30.4*	*852*	*30.5*	*902*	*34.4*	*3527*	*30.6*	*2769*	*28.1*
Calcium channel blockers	*1*	*12.5*	*225*	*24.9*	*569*	*23.3*	*696*	*25.5*	*673*	*24.1*	*676*	*25.8*	*2840*	*24.7*	*2657*	*26.9*
Beta blockers	*3*	*37.5*	*469*	*52.0*	*1211*	*49.5*	*1393*	*51.0*	*1389*	*49.7*	*1296*	*49.4*	*5761*	*50.1*	*5174*	*52.5*
Diuretics	3	21.4	350	17.3	932	17.4	1005	16.2	924	14.7	901	15.0	4115	15.9	3688	18.0
Statins	3	21.4	216	10.7	544	10.1	608	9.8	679	10.8	666	11.1	2716	10.5	2322	11.3
Antidiabetic agents	2	14.3	158	7.8	388	7.2	432	7.0	440	7.0	432	7.2	1852	7.1	1622	7.9
Metformin	*2*	*100.0*	*71*	*44.9*	*201*	*51.8*	*230*	*53.2*	*223*	*50.7*	*224*	*51.9*	*951*	*51.3*	*764*	*47.1*
Insulin	*0*	*0.0*	*81*	*51.3*	*144*	*37.1*	*156*	*36.1*	*168*	*38.2*	*170*	*39.4*	*719*	*38.8*	*686*	*42.3*
DPP-4 inhibitors	*0*	*0.0*	*31*	*19.6*	*85*	*21.9*	*93*	*21.5*	*103*	*23.4*	*101*	*23.4*	*413*	*22.3*	*355*	*21.9*
SGLT2 inhibitors	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*7*	*1.6*	*10*	*2.3*	*17*	*3.9*	*34*	*1.8*	*12*	*0.7*
Sulfonylureas	1	50.0	22	13.9	67	17.3	55	12.7	48	10.9	41	9.5	234	12.6	225	13.9
Oral steroids	1	7.1	204	10.1	495	9.2	550	8.9	599	9.5	543	9.0	2392	9.2	2324	11.3
PPIs	4	28.6	632	31.2	1813	33.8	2099	33.9	2121	33.7	2001	33.2	8670	33.5	6985	34.1
SSRIs	1	7.1	85	4.2	226	4.2	292	4.7	214	3.4	262	4.4	1080	4.2	727	3.5
Antibiotics	5	35.7	435	21.5	1355	25.2	1480	23.9	1492	23.7	1391	23.1	6158	23.8	4809	23.5

Special warning/precaution																
CYP3A4 or P-GP inhibitors [c]	0	0.0	75	3.7	198	3.7	204	3.3	195	3.1	186	3.1	858	3.3	817	4.0
CYP3A4 inducers	0	0.0	23	1.1	38	0.7	50	0.8	47	0.7	55	0.9	213	0.8	163	0.8

a: December only
b: Number of individual ATC codes; in the year before start date
c: List of medications as specified in the report

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; ATC, Anatomical Therapeutic Chemical (Classification System); CYP3A4, cytochrome P450 3A4; DPP-4, dipeptidyl peptidase-4; NSAID, nonsteroidal anti-inflammatory drug; P-GP, P-glycoprotein; PPI, proton pump inhibitor; SGLT2, sodium–glucose co-transporter-2; SOC, standard of care; SSRI, selective serotonin reuptake inhibitor; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 29: Medications of interest prescribed/dispensed in the 90 days before or on the start date in first-time users of rivaroxaban by calendar year – VTE-T with recent history of cancer

	Rivaroxaban													
	2011 [a] N = 1		2012 N = 478		2013 N = 1086		2014 N = 1198		2015 N = 1264		2016 N = 1171		Total N = 5198	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Polypharmacy [b]														
< 5	1	100.0	207	43.3	496	45.7	585	48.8	628	49.7	600	51.2	2517	48.4
5-9	0	0.0	222	46.4	514	47.3	525	43.8	540	42.7	491	41.9	2292	44.1
≥ 10	0	0.0	49	10.3	76	7.0	88	7.3	96	7.6	80	6.8	389	7.5
Medications of interest prescribed/dispensed up to 90 days before or on the start date														
Antiplatelets	0	0.0	40	8.4	63	5.8	83	6.9	65	5.1	86	7.3	337	6.5
NSAIDs	0	0.0	106	22.2	220	20.3	232	19.4	257	20.3	255	21.8	1070	20.6
Antiarrhythmic agents	0	0.0	0	0.0	7	0.6	1	0.1	2	0.2	1	0.1	11	0.2
Antihypertensive agents	0	0.0	238	49.8	618	56.9	601	50.2	668	52.8	635	54.2	2760	53.1
ACEis	*0*	*0.0*	*129*	*54.2*	*258*	*41.7*	*278*	*46.3*	*267*	*40.0*	*267*	*42.0*	*1199*	*43.4*
ARBs	*0*	*0.0*	*54*	*22.7*	*183*	*29.6*	*163*	*27.1*	*199*	*29.8*	*196*	*30.9*	*795*	*28.8*
Calcium channel blockers	*0*	*0.0*	*55*	*23.1*	*158*	*25.6*	*170*	*28.3*	*155*	*23.2*	*173*	*27.2*	*711*	*25.8*
Beta blockers	*0*	*0.0*	*131*	*55.0*	*340*	*55.0*	*334*	*55.6*	*369*	*55.2*	*341*	*53.7*	*1515*	*54.9*
Diuretics	1	100.0	103	21.5	265	24.4	280	23.4	247	19.5	250	21.3	1146	22.0
Statins	0	0.0	73	15.3	137	12.6	166	13.9	167	13.2	169	14.4	712	13.7
Antidiabetic agents	0	0.0	47	9.8	118	10.9	125	10.4	108	8.5	125	10.7	523	10.1
Metformin	*0*	*0.0*	*19*	*40.4*	*46*	*39.0*	*58*	*46.4*	*53*	*49.1*	*58*	*46.4*	*234*	*44.7*
Insulin	*0*	*0.0*	*24*	*51.1*	*49*	*41.5*	*57*	*45.6*	*43*	*39.8*	*55*	*44.0*	*228*	*43.6*
DPP-4 inhibitors	*0*	*0.0*	*13*	*27.7*	*23*	*19.5*	*19*	*15.2*	*28*	*25.9*	*31*	*24.8*	*114*	*21.8*
SGLT2 inhibitors	*0*	*0.0*	*0*	*0.0*	*1*	*0.8*	*0*	*0.0*	*4*	*3.7*	*7*	*5.6*	*12*	*2.3*
Sulfonylureas	*0*	*0.0*	*7*	*14.9*	*24*	*20.3*	*25*	*20.0*	*12*	*11.1*	*8*	*6.4*	*76*	*14.5*
Oral steroids	0	0.0	107	22.4	248	22.8	243	20.3	304	24.1	249	21.3	1151	22.1
PPIs	0	0.0	209	43.7	466	42.9	528	44.1	556	44.0	496	42.4	2255	43.4
SSRIs	0	0.0	21	4.4	54	5.0	53	4.4	46	3.6	37	3.2	211	4.1
Antibiotics	0	0.0	143	29.9	322	29.7	356	29.7	399	31.6	341	29.1	1561	30.0
Special warning/precaution														
CYP3A4 or P-GP inhibitors [c]	0	0.0	13	2.7	35	3.2	30	2.5	40	3.2	32	2.7	150	2.9
CYP3A4 inducers	0	0.0	5	1.0	9	0.8	9	0.8	8	0.6	5	0.4	36	0.7

a: December only
b: Number of individual ATC codes; in the year before start date
c: List of medications as specified in the report

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; ATC, Anatomical Therapeutic Chemical (Classification System); CYP3A4, cytochrome P450 3A4; DPP-4, dipeptidyl peptidase-4; NSAID, nonsteroidal anti-inflammatory drug; P-GP, P-glycoprotein; PPI, proton pump inhibitor; SGLT2, sodium–glucose co-transporter-2; SSRI, selective serotonin reuptake inhibitor; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 30: Medications of interest prescribed/dispensed in the 90 days before or on the start date in first-time users of rivaroxaban by calendar year and by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban															
	Calendar year												Tablet strength			
	2011- 2013 [a] N = 126		2013 [b] N = 77		2014 N = 100		2015 N = 120		2016 N = 123		Total N = 546		2.5 mg N = 24		≥ 10 mg N = 522	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Polypharmacy [c]																
< 5	30	23.8	29	37.7	36	36.0	50	41.7	61	49.6	206	37.7	12	50.0	194	37.2
5-9	57	45.2	35	45.5	50	50.0	59	49.2	47	38.2	248	45.4	11	45.8	237	45.4
≥ 10	39	31.0	13	16.9	14	14.0	11	9.2	15	12.2	92	16.8	1	4.2	91	17.4
Medications of interest prescribed/dispensed up to 90 days before or on the start date																
Antiplatelets	79	62.7	41	53.2	57	57.0	69	57.5	77	62.6	323	59.2	23	95.8	300	57.5
NSAIDs	28	22.2	11	14.3	18	18.0	18	15.0	15	12.2	90	16.5	3	12.5	87	16.7
Antiarrhythmic agents	7	5.6	9	11.7	6	6.0	8	6.7	5	4.1	35	6.4	1	4.2	34	6.5
Antihypertensive agents	122	96.8	76	98.7	96	96.0	112	93.3	117	95.1	523	95.8	22	91.7	501	96.0
ACEis	*69*	*56.6*	*42*	*55.3*	*58*	*60.4*	*69*	*61.6*	*61*	*52.1*	*299*	*57.2*	*13*	*59.1*	*286*	*57.1*
ARBs	*26*	*21.3*	*19*	*25.0*	*23*	*24.0*	*30*	*26.8*	*38*	*32.5*	*136*	*26.0*	*10*	*45.5*	*126*	*25.1*
Calcium channel blockers	*43*	*35.2*	*21*	*27.6*	*25*	*26.0*	*33*	*29.5*	*38*	*32.5*	*160*	*30.6*	*5*	*22.7*	*155*	*30.9*
Beta blockers	*94*	*77.0*	*59*	*77.6*	*75*	*78.1*	*96*	*85.7*	*99*	*84.6*	*423*	*80.9*	*19*	*86.4*	*404*	*80.6*
Diuretics	70	55.6	38	49.4	55	55.0	58	48.3	54	43.9	275	50.4	9	37.5	266	51.0
Statins	69	54.8	47	61.0	61	61.0	76	63.3	82	66.7	335	61.4	21	87.5	314	60.2
Antidiabetic agents	24	19.0	17	22.1	19	19.0	16	13.3	16	13.0	92	16.8	1	4.2	91	17.4
Metformin	*10*	*41.7*	*9*	*52.9*	*11*	*57.9*	*6*	*37.5*	*7*	*43.8*	*43*	*46.7*	*1*	*100.0*	*42*	*46.2*
Insulin	*10*	*41.7*	*6*	*35.3*	*7*	*36.8*	*8*	*50.0*	*7*	*43.8*	*38*	*41.3*	*0*	*0.0*	*38*	*41.8*
DPP-4 inhibitors	*6*	*25.0*	*4*	*23.5*	*4*	*21.1*	*3*	*18.8*	*5*	*31.3*	*22*	*23.9*	*0*	*0.0*	*22*	*24.2*
SGLT2 inhibitors	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Sulfonylureas	4	16.7	2	11.8	1	5.3	2	12.5	3	18.8	12	13.0	0	0.0	12	13.2
Oral steroids	13	10.3	5	6.5	9	9.0	5	4.2	16	13.0	48	8.8	3	12.5	45	8.6
PPIs	71	56.3	38	49.4	52	52.0	63	52.5	60	48.8	284	52.0	13	54.2	271	51.9
SSRIs	8	6.3	4	5.2	4	4.0	2	1.7	6	4.9	24	4.4	1	4.2	23	4.4
Antibiotics	20	15.9	13	16.9	20	20.0	24	20.0	17	13.8	94	17.2	5	20.8	89	17.0
Special warning/precaution																
CYP3A4 or P-GP inhibitors [d]	12	9.5	9	11.7	13	13.0	8	6.7	6	4.9	48	8.8	4	16.7	44	8.4
CYP3A4 inducers	2	1.6	0	0.0	1	1.0	1	0.8	1	0.8	5	0.9	0	0.0	5	1.0

a: December 2011–April 2013

b: May 2013–December 2013 as ACS indication approved in May

c: Number of individual ATC codes; in the year before start date
d: List of medications as specified in the report

ACEi, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blockers; ATC, Anatomical Therapeutic Chemical (Classification System); CYP3A4, cytochrome P450 3A4; DPP-4, dipeptidyl peptidase-4; NSAID, nonsteroidal anti-inflammatory drug; P-GP, P-glycoprotein; PPI, proton pump inhibitor; SGLT2, sodium–glucose co-transporter-2; SSRI, selective serotonin reuptake inhibitor

Annex 2.2 Table 31: Use of antiplatelets in the year prior to start date among first-time users of rivaroxaban, stratified by daily dose of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Any antiplatelet						
No use for 1 year prior to start date	14	58.3	333	63.8	347	63.6
Use in 1–31 days prior to start date	5	20.8	85	16.3	90	16.5
Use in > 31 days prior to start date	7	29.2	141	27.0	148	27.1
Aspirin						
No use for 1 year prior to start date	20	83.3	391	74.9	411	75.3
Use in 1–31 days prior to start date	1	4.2	48	9.2	49	9.0
Use in > 31 days prior to start date	4	16.7	101	19.3	105	19.2
Clopidogrel						
No use for 1 year prior to start date	18	75.0	428	82.0	446	81.7
Use in 1–31 days prior to start date	4	16.7	40	7.7	44	8.1
Use in > 31 days prior to start date	2	8.3	65	12.5	67	12.3
Prasugrel						
No use for 1 year prior to start date	24	100.0	513	98.3	537	98.4
Use in 1–31 days prior to start date	0	0.0	6	1.1	6	1.1
Use in > 31 days prior to start date	0	0.0	4	0.8	4	0.7
Ticagrelor						
No use for 1 year prior to start date	21	87.5	506	96.9	527	96.5
Use in 1–31 days prior to start date	1	4.2	10	1.9	11	2.0
Use in > 31 days prior to start date	3	12.5	7	1.3	10	1.8
Ticlopidine						
No use for 1 year prior to start date	24	100.0	522	100.0	546	100.0
Use in 1–31 days prior to start date	0	0.0	0	0.0	0	0.0
Use in > 31 days prior to start date	0	0.0	0	0.0	0	0.0

ACS, acute coronary syndrome

Annex 2.2 Table 32: Use of antiplatelets on the start date and in the month after start date among first-time users of rivaroxaban, stratified by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Any antiplatelet						
No use in0–30 days after start date	3	12.5	294	56.3	297	54.4
Use in 0–30 days after start date	21	87.5	228	43.7	249	45.6
Aspirin						
No use in0–30 days after start date	19	79.2	412	78.9	431	78.9
Use in 0–30 days after start date	5	20.8	110	21.1	115	21.1
Clopidogrel						
No use in0–30 days after start date	9	37.5	395	75.7	404	74.0
Use in 0–30 days after start date	15	62.5	127	24.3	142	26.0
Prasugrel						
No use in0–30 days after start date	23	95.8	504	96.6	527	96.5
Use in 0–30 days after start date	1	4.2	18	3.4	19	3.5
Ticagrelor						
No use in 0–30 days after start date	19	79.2	486	93.1	505	92.5
Use in 0–30 days after start date	5	20.8	36	6.9	41	7.5
Ticlopidine						
No use in0–30 days after start date	24	100.0	522	100.0	546	100.0
Use in 0–30 days after start date	0	0.0	0	0.0	0	0.0

ACS, acute coronary syndrome

Annex 2.2 Table 33: Use of antiplatelets on the start date or up to one month after among first-time users of rivaroxaban, stratified by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Number of antiplatelet medications						
None	3	12.5	294	56.3	297	54.4
One	15	62.5	160	30.7	175	32.1
Two	6	25.0	60	11.5	66	12.1
Three	0	0.0	7	1.3	7	1.3
Combinations of antiplatelet medications						
No use	3	12.5	301	57.7	304	55.7
Only aspirin	1	4.2	61	11.7	62	11.4
Only clopidogrel	12	50.0	82	15.7	94	17.2
Only ticagrelor	4	16.7	27	5.2	31	5.7
Aspirin and clopidogrel	3	12.5	42	8.0	45	8.2
Aspirin and ticagrelor	1	4.2	6	1.1	7	1.3
Aspirin, clopidogrel and ticagrelor	0	0.0	1	0.2	1	0.2

ACS, acute coronary syndrome

Annex 2.2 Table 34: Time interval between ACS event and start date (i.e. date of first prescription) among first-time users of rivaroxaban, stratified by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Time interval from ACS event to start date (days)						
0	0	0.0	3	0.6	3	0.5
1-7	11	45.8	135	25.9	146	26.7
8-15	10	41.7	192	36.8	202	37.0
16-30	3	12.5	192	36.8	195	35.7

ACS, acute coronary syndrome

Annex 2.2 Table 35: Medical history any time prior to the start date in first-time users of rivaroxaban by calendar year and first-time users of SOC – SPAF cohort

	Rivaroxaban														SOC	
	2011 [a]		2012		2013		2014		2015		2016		Total		Total	
	N = 92		N = 17,553		N = 31,756		N = 29,492		N = 27,359		N = 21,491		N = 127,743		N = 88,655	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Medical history: past medical events and comorbidities occurring any time prior to start date																
Intracranial bleeding	2	2.2	303	1.7	447	1.4	365	1.2	338	1.2	267	1.2	1722	1.3	560	0.6
Intracerebral bleeding	*1*	*50.0*	*135*	*44.6*	*197*	*44.1*	*162*	*44.4*	*145*	*42.9*	*108*	*40.4*	*748*	*43.4*	*240*	*42.9*
Subarachnoid bleeding	*0*	*0.0*	*59*	*19.5*	*87*	*19.5*	*78*	*21.4*	*73*	*21.6*	*63*	*23.6*	*360*	*20.9*	*138*	*24.6*
Intracranial bleeding	*1*	*50.0*	*131*	*43.2*	*194*	*43.4*	*146*	*40.0*	*139*	*41.1*	*117*	*43.8*	*728*	*42.3*	*210*	*37.5*
GI bleeding	5	5.4	787	4.5	1281	4.0	1116	3.8	948	3.5	704	3.3	4841	3.8	2393	2.7
UG bleeding	0	0.0	243	1.4	403	1.3	301	1.0	355	1.3	262	1.2	1564	1.2	716	0.8
Ischemic stroke	21	22.8	3870	22.0	6308	19.9	5462	18.5	4628	16.9	3471	16.2	23,760	18.6	14,360	16.2
TIA	11	12.0	2483	14.1	4120	13.0	3631	12.3	3145	11.5	2482	11.5	15,872	12.4	9859	11.1
VTE (DVT/PE)	17	18.5	2716	15.5	4495	14.2	4090	13.9	3526	12.9	2749	12.8	17,593	13.8	8621	9.7
Myocardial infarction	14	15.2	3020	17.2	5059	15.9	4549	15.4	4105	15.0	3292	15.3	20,039	15.7	16,885	19.0
Hypertension	84	91.3	16,440	93.7	29,476	92.8	27,121	92.0	25,010	91.4	19,438	90.4	117,569	92.0	82,629	93.2
Heart failure	50	54.3	9256	52.7	15,942	50.2	14,370	48.7	12,880	47.1	9949	46.3	62,447	48.9	41,911	47.3
CAD [b]	54	58.7	10,141	57.8	17,027	53.6	15,117	51.3	13,468	49.2	10,497	48.8	66,304	51.9	45,125	50.9
PAD	29	31.5	6375	36.3	10,925	34.4	10,142	34.4	9365	34.2	7419	34.5	44,255	34.6	31,125	35.1
Hyperlipidemia	68	73.9	12,284	70.0	21,876	68.9	20,408	69.2	18,745	68.5	14,923	69.4	88,304	69.1	62,968	71.0
Diabetes mellitus	26	28.3	6892	39.3	12,310	38.8	11,129	37.7	10,096	36.9	7848	36.5	48,301	37.8	34,154	38.5
Liver disease	1	1.1	898	5.1	1647	5.2	1628	5.5	1504	5.5	1266	5.9	6944	5.4	4251	4.8
COPD	20	21.7	4463	25.4	7926	25.0	7299	24.7	6978	25.5	5363	25.0	32,049	25.1	21,755	24.5
Asthma	12	13.0	2723	15.5	4893	15.4	4737	16.1	4595	16.8	3687	17.2	20,647	16.2	13,382	15.1
Cancer	28	30.4	5387	30.7	9313	29.3	8753	29.7	8127	29.7	6443	30.0	38,051	29.8	24,793	28.0
Dementia	12	13.0	1978	11.3	3759	11.8	3566	12.1	3220	11.8	2406	11.2	14,941	11.7	6686	7.5
Depression	42	45.7	7349	41.9	13,353	42.0	12,749	43.2	11,960	43.7	9633	44.8	55,086	43.1	34,233	38.6

a: December only
b: Including myocardial infarction

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; PAD, peripheral artery disease; PE, pulmonary embolism; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation; TIA, transient ischemic attack; UG, urogenital; VTE, venous thromboembolism

Annex 2.2 Table 36: Medical history any time prior to the start date in first-time users of rivaroxaban by calendar year and first-time users of SOC – VTE-T without recent history of cancer

	Rivaroxaban														SOC	
	2011 [a] N = 14		2012 N = 2027		2013 N = 5370		2014 N = 6194		2015 N = 6287		2016 N = 6022		Total N = 25,914		Total N = 20,502	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Medical history: past medical events and comorbidities occurring any time prior to start date																
Intracranial bleeding	0	0.0	28	1.4	42	0.8	57	0.9	56	0.9	46	0.8	229	0.9	104	0.5
Intracerebral bleeding	*0*	*0.0*	*8*	*28.6*	*20*	*47.6*	*26*	*45.6*	*15*	*26.8*	*19*	*41.3*	*88*	*38.4*	*42*	*40.4*
Other subarachnoid bleeding	*0*	*0.0*	*6*	*21.4*	*9*	*21.4*	*20*	*35.1*	*19*	*33.9*	*15*	*32.6*	*69*	*30.1*	*37*	*35.6*
Other intracranial bleeding	*0*	*0.0*	*16*	*57.1*	*16*	*38.1*	*15*	*26.3*	*27*	*48.2*	*14*	*30.4*	*88*	*38.4*	*34*	*32.7*
GI bleeding	0	0.0	47	2.3	106	2.0	102	1.6	99	1.6	93	1.5	447	1.7	334	1.6
UG bleeding	0	0.0	22	1.1	58	1.1	49	0.8	40	0.6	49	0.8	218	0.8	138	0.7
Ischemic stroke	1	7.1	187	9.2	377	7.0	454	7.3	434	6.9	368	6.1	1821	7.0	1340	6.5
TIA	2	14.3	131	6.5	324	6.0	350	5.7	373	5.9	329	5.5	1509	5.8	1169	5.7
VTE (DVT/PE) [b]	8	57.1	754	37.2	1614	30.1	1691	27.3	1631	25.9	1584	26.3	7282	28.1	4381	21.4
Myocardial infarction	1	7.1	142	7.0	331	6.2	375	6.1	376	6.0	374	6.2	1599	6.2	1335	6.5
Hypertension	8	57.1	1298	64.0	3445	64.2	3859	62.3	3957	62.9	3758	62.4	16,325	63.0	13,525	66.0
Heart failure	3	21.4	469	23.1	1175	21.9	1304	21.1	1305	20.8	1229	20.4	5485	21.2	4556	22.2
CAD [c]	3	21.4	535	26.4	1289	24.0	1413	22.8	1429	22.7	1378	22.9	6047	23.3	5053	24.6
PAD	4	28.6	426	21.0	1072	20.0	1197	19.3	1236	19.7	1194	19.8	5129	19.8	4258	20.8
Hyperlipidemia	9	64.3	1028	50.7	2676	49.8	3042	49.1	3172	50.5	3072	51.0	12,999	50.2	10,791	52.6
Diabetes mellitus	4	28.6	467	23.0	1154	21.5	1327	21.4	1321	21.0	1293	21.5	5566	21.5	4738	23.1
Liver disease	0	0.0	93	4.6	258	4.8	336	5.4	340	5.4	366	6.1	1393	5.4	1082	5.3
COPD	0	0.0	356	17.6	957	17.8	1088	17.6	1111	17.7	1051	17.5	4563	17.6	3958	19.3
Asthma	1	7.1	327	16.1	926	17.2	1067	17.2	1111	17.7	1135	18.8	4567	17.6	3490	17.0
Cancer [d]	3	21.4	242	11.9	586	10.9	704	11.4	709	11.3	719	11.9	2963	11.4	2369	11.6
Dementia	1	7.1	224	11.1	486	9.1	549	8.9	488	7.8	399	6.6	2147	8.3	1313	6.4
Depression	5	35.7	831	41.0	2240	41.7	2704	43.7	2645	42.1	2695	44.8	11,120	42.9	8468	41.3

a: December only

b: Prior event that is unrelated to the event necessitating treatment at start date (i.e. DVT/PE events occurring any time prior to start date, excluding the indication time window of 90 days)
c: Including myocardial infarction
d: Cancer recorded any time before or at start date; however, by definition, patients within this cohort do not have any record of cancer within the 3 years before or 1 month after the start date

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; PAD, peripheral artery disease; PE, pulmonary embolism; SOC, standard of care; TIA, transient ischemic attack; UG, urogenital; VTE, venous thromboembolism; VTE-T, treatment and secondary prevention of VTE

Annex 2.2 Table 37: Medical history any time prior to the start date in first-time users of rivaroxaban by calendar year – VTE-T with recent history of cancer

	Rivaroxaban													
	2011 [a] N = 1		2012 N = 478		2013 N = 1086		2014 N = 1198		2015 N = 1264		2016 N = 1171		Total N = 5198	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Medical history: past medical events and comorbidities occurring any time prior to start date														
Intracranial bleeding	0	0.0	4	0.8	9	0.8	11	0.9	10	0.8	6	0.5	40	0.8
Intracerebral bleeding	*0*	*0.0*	*1*	*25.0*	*5*	*55.6*	*5*	*45.5*	*6*	*60.0*	*3*	*50.0*	*20*	*50.0*
Subarachnoid bleeding	*0*	*0.0*	*1*	*25.0*	*2*	*22.2*	*1*	*9.1*	*3*	*30.0*	*0*	*0.0*	*7*	*17.5*
Intracranial bleeding	*0*	*0.0*	*2*	*50.0*	*2*	*22.2*	*6*	*54.5*	*2*	*20.0*	*3*	*50.0*	*15*	*37.5*
GI bleeding	0	0.0	15	3.1	29	2.7	37	3.1	25	2.0	28	2.4	134	2.6
UG bleeding	0	0.0	7	1.5	20	1.8	27	2.3	23	1.8	22	1.9	99	1.9
Ischemic stroke	0	0.0	52	10.9	88	8.1	114	9.5	114	9.0	105	9.0	473	9.1
TIA	0	0.0	41	8.6	61	5.6	108	9.0	105	8.3	78	6.7	393	7.6
VTE (DVT/PE) [b]	1	100.0	202	42.3	396	36.5	402	33.6	382	30.2	363	31.0	1746	33.6
Myocardial infarction	0	0.0	48	10.0	76	7.0	93	7.8	83	6.6	92	7.9	392	7.5
Hypertension	1	100.0	375	78.5	874	80.5	912	76.1	958	75.8	933	79.7	4053	78.0
Heart failure	1	100.0	140	29.3	316	29.1	321	26.8	340	26.9	344	29.4	1462	28.1
CAD [c]	0	0.0	172	36.0	350	32.2	349	29.1	380	30.1	390	33.3	1641	31.6
PAD	0	0.0	144	30.1	316	29.1	328	27.4	314	24.8	335	28.6	1437	27.6
Hyperlipidemia	1	100.0	299	62.6	672	61.9	732	61.1	752	59.5	714	61.0	3170	61.0
Diabetes mellitus	1	100.0	133	27.8	347	32.0	391	32.6	358	28.3	349	29.8	1579	30.4
Liver disease	0	0.0	38	7.9	72	6.6	91	7.6	93	7.4	95	8.1	389	7.5
COPD	0	0.0	113	23.6	269	24.8	309	25.8	297	23.5	292	24.9	1280	24.6
Asthma	0	0.0	90	18.8	160	14.7	189	15.8	228	18.0	185	15.8	852	16.4
Cancer [d]	1	100.0	474	99.2	1081	99.5	1189	99.2	1253	99.1	1161	99.1	5159	99.2
Dementia	0	0.0	61	12.8	99	9.1	84	7.0	94	7.4	87	7.4	425	8.2
Depression	1	100.0	252	52.7	535	49.3	643	53.7	651	51.5	590	50.4	2672	51.4

a: December only
b: Prior event that is unrelated to the event necessitating treatment at start date(i.e. DVT/PE events occurring any time prior to start date, excluding the indication time window of 90 days)
c: Including myocardial infarction
d: Cancer recorded any time before or at start date; however, by definition, patients within this cohort do not have any record of cancer within the 3 years before or 1 month after the start date

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; PAD, peripheral artery disease; PE, pulmonary embolism; TIA, transient ischemic attack; UG, urogenital; VTE, venous thromboembolism; VTE-T, treatment and secondary prevention of VTE

Annex 2.2 Table 38: Medical history at the start date in first-time users of rivaroxaban by calendar year and by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban															
	Calendar year												Tablet strength			
	2011-2013 [a] N = 126		2013 [b] N = 77		2014 N = 100		2015 N = 120		2016 N = 123		Total N = 546		2.5 mg N = 24		≥ 10 mg N = 522	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Medical history: past medical events and comorbidities occurring any time prior to start date																
Intracranial bleeding	3	2.4	2	2.6	1	1.0	2	1.7	3	2.4	11	2.0	0	0.0	11	2.1
Intracerebral bleeding	*1*	*33.3*	*2*	*100.0*	*1*	*100.0*	*2*	*100.0*	*1*	*33.3*	*7*	*63.6*	*0*	*0.0*	*7*	*63.6*
Subarachnoid bleeding	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Intracranial bleeding	*2*	*66.7*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*2*	*66.7*	*4*	*36.4*	*0*	*0.0*	*4*	*36.4*
GI bleeding	11	8.7	2	2.6	7	7.0	4	3.3	3	2.4	27	4.9	0	0.0	27	5.2
UG bleeding	3	2.4	0	0.0	1	1.0	3	2.5	4	3.3	11	2.0	0	0.0	11	2.1
Ischemic stroke	28	22.2	20	26.0	14	14.0	17	14.2	20	16.3	99	18.1	2	8.3	97	18.6
TIA	23	18.3	11	14.3	11	11.0	11	9.2	13	10.6	69	12.6	2	8.3	67	12.8
VTE (DVT/PE)	28	22.2	15	19.5	21	21.0	17	14.2	16	13.0	97	17.8	3	12.5	94	18.0
Myocardial infarction [c]	107	84.9	68	88.3	82	82.0	101	84.2	103	83.7	461	84.4	22	91.7	439	84.1
Hypertension	120	95.2	75	97.4	91	91.0	110	91.7	113	91.9	509	93.2	21	87.5	488	93.5
Heart failure	90	71.4	53	68.8	64	64.0	85	70.8	74	60.2	366	67.0	7	29.2	359	68.8
PAD	68	54.0	40	51.9	43	43.0	45	37.5	51	41.5	247	45.2	5	20.8	242	46.4
Hyperlipidemia	110	87.3	66	85.7	84	84.0	104	86.7	105	85.4	469	85.9	19	79.2	450	86.2
Diabetes mellitus	51	40.5	43	55.8	48	48.0	41	34.2	46	37.4	229	41.9	4	16.7	225	43.1
Liver disease	5	4.0	5	6.5	9	9.0	5	4.2	2	1.6	26	4.8	0	0.0	26	5.0
COPD	48	38.1	29	37.7	22	22.0	28	23.3	29	23.6	156	28.6	4	16.7	152	29.1
Asthma	20	15.9	10	13.0	10	10.0	16	13.3	20	16.3	76	13.9	8	33.3	68	13.0
Cancer	34	27.0	18	23.4	35	35.0	33	27.5	41	33.3	161	29.5	6	25.0	155	29.7
Dementia	10	7.9	8	10.4	10	10.0	17	14.2	16	13.0	61	11.2	1	4.2	60	11.5
Depression	66	52.4	32	41.6	54	54.0	56	46.7	58	47.2	266	48.7	11	45.8	255	48.9

a: December 2011–April 2013
b: May 2013–December 2013 as ACS indication approved in May
c: Including events necessitating treatment at start date
ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; PAD, peripheral artery disease; PE, pulmonary embolism; TIA, transient ischemic attack; UG, urogenital; VTE, venous thromboembolism

Annex 2.2 Table 39: CHA_2DS_2VASc score at start date [a] in first-time users of study drugs – SPAF cohort

CHA_2DS_2VASc score	Rivaroxaban N = 127,743		SOC N = 88,655	
	n	%	n	%
0	2885	2.3	981	1.1
1	5555	4.3	2741	3.1
2	12,082	9.5	7912	8.9
3	18,198	14.2	14,089	15.9
4	22,670	17.7	17,809	20.1
5	23,596	18.5	17,965	20.3
≥ 6	42,757	33.5	27,158	30.6
Mean (SD)	4.6 ± 2.0		4.6 ± 1.9	
Median (IQR)	5.0 (3–6)		5.0 (3–6)	
Range	0–9		0–9	

a: Calculated using information any time prior recorded before or on the start date

IQR, interquartile range; SD, standard deviation; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 40: Modified HAS-BLED score [a] at start date [b] in first-time users of study drugs – SPAF cohort

Modified HAS-BLED score	Rivaroxaban N = 127,743		SOC N = 88,655	
	n	%	n	%
0	2726	2.1	1033	1.2
1	12,275	9.6	7078	8.0
2	31,200	24.4	23,877	26.9
3	35,671	27.9	26,088	29.4
≥ 4	45,871	35.9	30,579	34.5
Mean (SD)	3.0 ± 1.3		3.0 ± 1.3	
Median (IQR)	3.0 (2–4)		3.0 (2–4)	
Range	0–8		0–8	

a: Labile INR not included

b: Calculated using information any time prior recorded before or on the start date

INR, international normalized ratio; IQR, interquartile range; SD, standard deviation; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 41: Renal function in first-time users of study drugs according to the information available at start date – SPAF cohort

	Rivaroxaban N = 127,743		SOC N = 88,655	
	n	%	n	%
Renal function in year prior to start date by chronic kidney disease stage (recorded in in- and outpatient data) [a]				
Stage 1 (eGFR ≥ 90)	1256	1.0	777	0.9
Stage 2 (eGFR 60–89)	6441	5.0	4029	4.5
Stage 3 (eGFR 30–59)	15,992	12.5	10,588	11.9
Stage 4 (eGFR 15–29)	3053	2.4	2919	3.3
Stage 5 (eGFR < 15)	725	0.6	1825	2.1
Unclassified	8876	6.9	6221	7.0
No diagnosis	91,400	71.5	62,296	70.3
Dialysis				
Yes	841	0.7	1730	2.0
No	126,902	99.3	86,925	98.0
Renal impairment				
Severe or moderate renal impairment [b]	28,850	22.6	21,759	24.5
Mild renal impairment [c]	7642	6.0	4754	5.4
Unclassified renal impairment	0	0.0	0	0.0
No indication for renal impairment	91,251	71.4	62,142	70.1

a: Based on diagnosis any time prior to or at start date
b: CKD 3-5 or a code indicating dialysis
c: CKD 1-2, no dialysis
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 42: Renal function in first-time users of study drugs according to the information available at start date – VTE-T without recent history of cancer

	Rivaroxaban N = 25,914		SOC N = 20,502	
	n	%	n	%
Renal function in year prior to start date by chronic kidney disease stage (recorded in in- and outpatient data) [a]				
Stage 1 (eGFR ≥ 90)	132	0.5	125	0.6
Stage 2 (eGFR 60–89)	761	2.9	554	2.7
Stage 3 (eGFR 30–59)	1555	6.0	1559	7.6
Stage 4 (eGFR 15–29)	232	0.9	418	2.0
Stage 5 (eGFR < 15)	72	0.3	200	1.0
Unclassified	1118	4.3	976	4.8
No diagnosis	22,044	85.1	16,670	81.3
Dialysis				
Yes	64	0.2	153	0.7
No	25,850	99.8	20,349	99.3
Renal impairment				
Severe or moderate renal impairment [b]	3004	11.6	3183	15.5
Mild renal impairment [c]	888	3.4	675	3.3
Unclassified renal impairment	0	0.0	0	0.0
No indication for renal impairment	22,022	85.0	16,644	81.2

a: Based on diagnosis any time prior to or at start date
b: CKD 3-5 or a code indicating dialysis
c: CKD 1-2, no dialysis
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 43: Renal function in first-time users of rivaroxaban at start date – VTE-T with recent history of cancer

	Rivaroxaban N = 5198	
	n	**%**
Renal function in year prior to start date by chronic kidney disease stage (recorded in in- and outpatient data) [a]		
Stage 1 (eGFR ≥ 90)	35	0.7
Stage 2 (eGFR 60–89)	222	4.3
Stage 3 (eGFR 30–59)	562	10.8
Stage 4 (eGFR 15–29)	93	1.8
Stage 5 (eGFR < 15)	23	0.4
Unclassified	371	7.1
No diagnosis	3892	74.9
Dialysis		
Yes	28	0.5
No	5170	99.5
Renal impairment		
Severe or moderate renal impairment [b]	1058	20.4
Mild renal impairment [c]	256	4.9
Unclassified renal impairment	0	0.0
No indication for renal impairment	3884	74.7

a: Based on diagnosis any time prior to or at start date
b: CKD 3-5 or a code indicating dialysis
c: CKD 1-2, no dialysis
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 44: Renal function in first-time users of rivaroxaban at start date, stratified by tablet strength of first prescription/dispensing – ACS cohort

	Rivaroxaban					
	2.5 mg N = 24		≥ 10 mg N = 522		Total N = 546	
	n	%	n	%	n	%
Renal function in year prior to start date by chronic kidney disease stage (recorded in in- and outpatient data) [a]						
Stage 1 (eGFR ≥ 90)	0	0.0	3	0.6	3	0.5
Stage 2 (eGFR 60–89)	0	0.0	32	6.1	32	5.9
Stage 3 (eGFR 30–59)	3	12.5	120	23.0	123	22.5
Stage 4 (eGFR 15–29)	0	0.0	21	4.0	21	3.8
Stage 5 (eGFR < 15 or dialysis)	0	0.0	2	0.4	2	0.4
Unclassified	1	4.2	41	7.9	42	7.7
No diagnosis	20	83.3	303	58.0	323	59.2
Dialysis						
Yes	0	0.0	1	0.2	1	0.2
No	24	100.0	521	99.8	545	99.8
Renal impairment						
Severe or moderate renal impairment [b]	4	16.7	184	35.2	188	34.4
Mild renal impairment [c]	0	0.0	35	6.7	35	6.4
Unclassified renal impairment	0	0.0	0	0.0	0	0.0
No indication for renal impairment	20	83.3	303	58.0	323	59.2

a: Based on diagnosis any time prior to or at start date
b: CKD 3-5 or a code indicating dialysis
c: CKD 1-2, no dialysis
ACS, acute coronary syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Annex 2.2 Table 45: Pregnancy and pregnancy outcomes [a] at start date and any time after the start date in first-time users of rivaroxaban – overall cohort

	Rivaroxaban N = 14,953 [b]	
	n	**%**
Pregnant women at the start date	**15**	**0.1**
Pregnant women identified after the start date	**699**	**4.7**
Pregnancies: [c]	**778**	**5.2**
Live childbirths	692	88.9
Stillbirths	1	0.1
Miscarriages	10	1.3
Terminations	52	6.7
Ectopic pregnancies	23	3.0
Unknown outcomes	0	0

a: As pregnancy and pregnancy outcomes were ascertained during the entire follow-up period, not all fetuses were exposed to rivaroxaban
b: All woman of childbearing age (11-50 years of age) at cohort entry
c: Multiple pregnancies per woman possible

Annex 2.2 Table 46: Incidence rate of intracranial bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)			SOC (N = 88,655)		
	Events n	Person-years	Incidence rate [b] (95% CI)	Events n	Person-years	Incidence rate [b] (95% CI)
Any intracranial bleed	**938**	**175,578.2**	**0.53 (0.50–0.57)**	**946**	**194,598.6**	**0.49 (0.46–0.52)**
Intracerebral	556	175,746.2	0.32 (0.29–0.34)	419	194,952.3	0.21 (0.19–0.24)
Subarachnoid	136	175,791.6	0.08 (0.06–0.09)	152	194,950.5	0.08 (0.07–0.09)
Subdural/extradural	246	175,770.9	0.14 (0.12–0.16)	375	194,813.7	0.19 (0.17–0.21)
Sex						
Male	489	89,634.7	0.55 (0.50–0.60)	511	104,262.5	0.49 (0.45–0.53)
Female	449	85,943.5	0.52 (0.48–0.57)	435	90,336.1	0.48 (0.44–0.53)
Age group						
≤ 49	2	2597.9	0.08 (0.01–0.28)	5	2201.7	0.23 (0.07–0.53)
≥ 50–≤ 59	8	11,392.8	0.07 (0.03–0.14)	22	11,369.1	0.19 (0.12–0.29)
≥ 60–≤ 69	100	36,213.5	0.28 (0.22–0.34)	112	41,336.5	0.27 (0.22–0.33)
≥ 70–≤ 79	431	80,296.3	0.54 (0.49–0.59)	457	95,642.5	0.48 (0.44–0.52)
≥ 80–≤ 89	342	39,957.4	0.86 (0.77–0.95)	321	40,970.6	0.78 (0.70–0.87)
≥ 90	55	5120.4	1.07 (0.81–1.40)	29	3078.1	0.94 (0.63–1.35)
Renal function						
Normal	645	132,264.8	0.49 (0.45–0.53)	NA	NA	NA
Impaired	293	43,313.4	0.68 (0.60–0.76)	NA	NA	NA
Elderly						
No (< 75 years)	284	88,955.6	0.32 (0.28–0.36)	NA	NA	NA
Yes (≥ 75 years)	654	86,622.6	0.75 (0.70–0.82)	NA	NA	NA
Diabetes						
No	519	108,209.4	0.48 (0.44–0.52)	NA	NA	NA
Yes	419	67,368.8	0.62 (0.56–0.68)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 47: Incidence rate of intracranial bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)			SOC (N = 20,502)		
	Events n	Person-years	Incidence rate [b] (95% CI)	Events n	Person-years	Incidence rate [b] (95% CI)
Any intracranial bleed	**67**	**23,448.5**	**0.29 (0.22–0.36)**	**88**	**28,192.9**	**0.31 (0.25–0.38)**
Intracerebral	28	23,468.2	0.12 (0.08–0.17)	42	28,221.9	0.15 (0.11–0.20)
Subarachnoid	14	23,461.6	0.06 (0.03–0.10)	15	28,226.4	0.05 (0.03–0.09)
Subdural/extradural	25	23,465.8	0.11 (0.07–0.16)	31	28,216.5	0.11 (0.07–0.16)
Sex						
Male	27	11,159.3	0.24 (0.16–0.35)	39	13,647.8	0.29 (0.20–0.39)
Female	40	12,289.2	0.33 (0.23–0.44)	49	14,545.1	0.34 (0.25–0.45)
Age group						
≤ 49	3	4786.5	0.06 (0.01–0.18)	5	5462.1	0.09 (0.03–0.21)
≥ 50–≤ 59	14	4387.9	0.32 (0.17–0.54)	5	4982.1	0.10 (0.03–0.23)
≥ 60–≤ 69	3	4496.9	0.07 (0.01–0.19)	14	5603.3	0.25 (0.14–0.42)
≥ 70–≤ 79	23	6352.7	0.36 (0.23–0.54)	35	8428.2	0.42 (0.29–0.58)
≥ 80–≤ 89	20	2949.5	0.68 (0.41–1.05)	25	3371.9	0.74 (0.48–1.09)
≥ 90	4	475.0	0.84 (0.23–2.16)	4	345.3	1.16 (0.32–2.97)
Renal function						
Normal	53	19,777.3	0.27 (0.20–0.35)	NA	NA	NA
Impaired	14	3671.2	0.38 (0.21–0.64)	NA	NA	NA
Elderly						
No (< 75 years)	31	16,797.5	0.18 (0.13–0.26)	NA	NA	NA
Yes (≥ 75 years)	36	6651.0	0.54 (0.38–0.75)	NA	NA	NA
Diabetes						
No	48	17,672.1	0.27 (0.20–0.36)	NA	NA	NA
Yes	19	5776.4	0.33 (0.20–0.51)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 48: Incidence rate of intracranial bleeding associated with first use of rivaroxaban (first episode of treatment [a]) – ACS (all doses)

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Any intracranial bleed	**2**	**833.6**	**0.24 (0.03–0.87)**
Intracerebral	2	833.6	0.24 (0.03–0.87)
Subarachnoid	0	834.6	0.00 (0.00–0.44)
Subdural/extradural	0	834.6	0.00 (0.00–0.44)
Sex			
Male	0	449.1	0.00 (0.00–0.82)
Female	2	384.5	0.52 (0.06–1.88)
Age group			
≤ 49	0	38.9	0.00 (0.00–9.49)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	0	112.0	0.00 (0.00–3.29)
≥ 70–≤ 79	1	331.7	0.30 (0.01–1.68)
≥ 80–≤ 89	1	232.6	0.43 (0.01–2.39)
≥ 90	0	32.8	0.00 (0.00–11.25)
Renal function			
Normal	1	551.9	0.18 (0.00–1.01)
Impaired	1	281.7	0.35 (0.01–1.98)
Elderly			
No (< 75 years)	0	363.6	0.00 (0.00–1.01)
Yes (≥ 75 years)	2	470.0	0.43 (0.05–1.54)
Diabetes			
No	1	504.7	0.20 (0.01–1.10)
Yes	1	328.9	0.30 (0.01–1.69)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 49: Incidence rate of gastrointestinal bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)			SOC (N = 88,655)		
	Events n	Person-years	Incidence rate [b] (95% CI)	Events n	Person-years	Incidence rate [b] (95% CI)
Any gastrointestinal bleed	**2988**	**173,832.2**	**1.72 (1.66–1.78)**	**2219**	**192,655.8**	**1.15 (1.10–1.20)**
Sex						
Male	1472	88,806.7	1.66 (1.57–1.74)	1173	103,210.7	1.14 (1.07–1.20)
Female	1516	85,025.5	1.78 (1.69–1.88)	1046	89,445.1	1.17 (1.10–1.24)
Age group						
≤ 49	11	2589.4	0.42 (0.21–0.76)	13	2193.6	0.59 (0.32–1.01)
≥ 50–≤ 59	66	11,348.0	0.58 (0.45–0.74)	69	11,287.0	0.61 (0.48–0.77)
≥ 60–≤ 69	305	35,988.9	0.85 (0.76–0.95)	305	41,006.1	0.74 (0.66–0.83)
≥ 70–≤ 79	1248	79,546.1	1.57 (1.48–1.66)	1015	94,692.4	1.07 (1.01–1.14)
≥ 80–≤ 89	1165	39,317.6	2.96 (2.80–3.14)	747	40,438.6	1.85 (1.72–1.98)
≥ 90	193	5042.2	3.83 (3.31–4.41)	70	3038.2	2.30 (1.80–2.91)
Renal function						
Normal	1772	131,250.8	1.35 (1.29–1.41)	NA	NA	NA
Impaired	1216	42,581.4	2.86 (2.70–3.02)	NA	NA	NA
Elderly						
No (< 75 years)	893	88,317.6	1.01 (0.95–1.08)	NA	NA	NA
Yes (≥ 75 years)	2095	85,514.6	2.45 (2.35–2.56)	NA	NA	NA
Diabetes						
No	1561	107,194.9	1.46 (1.38–1.53)	NA	NA	NA
Yes	1427	66,637.2	2.14 (2.03–2.26)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 50: Incidence rate of gastrointestinal bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)			SOC (N = 20,502)		
	Events n	Person-years	Incidence rate [b](95% CI)	Events n	Person-years	Incidence rate [b](95% CI)
Any gastrointestinal bleed	**264**	**23,294.5**	**1.13 (1.00–1.28)**	**263**	**28,004.4**	**0.94 (0.83–1.06)**
Sex						
Male	96	11,100.9	0.86 (0.70–1.06)	98	13,580.5	0.72 (0.59–0.88)
Female	168	12,193.6	1.38 (1.18–1.60)	165	14,423.9	1.14 (0.98–1.33)
Age group						
≤ 49	19	4766.4	0.40 (0.24–0.62)	15	5451.6	0.28 (0.15–0.45)
≥ 50–≤ 59	21	4378.5	0.48 (0.30–0.73)	27	4941.0	0.55 (0.36–0.80)
≥ 60–≤ 69	31	4481.3	0.69 (0.47–0.98)	27	5584.3	0.48 (0.32–0.70)
≥ 70–≤ 79	82	6301.8	1.30 (1.03–1.62)	111	8338.0	1.33 (1.10–1.60)
≥ 80–≤ 89	83	2907.3	2.85 (2.27–3.54)	74	3345.0	2.21 (1.74–2.78)
≥ 90	28	459.2	6.10 (4.05–8.81)	9	344.5	2.61 (1.19–4.96)
Renal function						
Normal	177	19,690.7	0.90 (0.77–1.04)	NA	NA	NA
Impaired	87	3603.8	2.41 (1.93–2.98)	NA	NA	NA
Elderly						
No (< 75 years)	106	16,730.7	0.63 (0.52–0.77)	NA	NA	NA
Yes (≥ 75 years)	158	6563.8	2.41 (2.05–2.81)	NA	NA	NA
Diabetes						
No	168	17,569.0	0.96 (0.82–1.11)	NA	NA	NA
Yes	96	5725.6	1.68 (1.36–2.05)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 51: Incidence rate of gastrointestinal bleeding associated with first use of rivaroxaban (first episode of treatment [a]) – ACS (all doses)

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Any gastrointestinal bleed	**29**	**816.6**	**3.55 (2.38–5.10)**
Sex			
Male	19	435.7	4.36 (2.63–6.81)
Female	10	380.9	2.63 (1.26–4.83)
Age group			
≤ 49	0	38.9	0.00 (0.00–9.49)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	2	110.8	1.80 (0.22–6.52)
≥ 70–≤ 79	14	322.8	4.34 (2.37–7.28)
≥ 80–≤ 89	11	225.8	4.87 (2.43–8.72)
≥ 90	2	32.7	6.12 (0.74–22.10)
Renal function			
Normal	16	538.1	2.97 (1.70–4.83)
Impaired	13	278.5	4.67 (2.49–7.98)
Elderly			
No (< 75 years)	7	360.4	1.94 (0.78–4.00)
Yes (≥ 75 years)	22	456.2	4.82 (3.02–7.30)
Diabetes			
No	19	488.8	3.89 (2.34–6.07)
Yes	10	327.9	3.05 (1.46–5.61)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 52: Incidence rate of urogenital bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)			SOC (N = 88,655)		
	Events n	Person-years	Incidence rate [b] (95% CI)	Events n	Person-years	Incidence rate [b] (95% CI)
Any urogenital bleed	**849**	**175,113.2**	**0.48 (0.45–0.52)**	**665**	**194,178.4**	**0.34 (0.32–0.37)**
Sex						
Male	514	89,422.6	0.57 (0.53–0.63)	408	104,029.7	0.39 (0.36–0.43)
Female	335	85,690.5	0.39 (0.35–0.44)	257	90,148.6	0.29 (0.25–0.32)
Age group						
≤ 49	20	2574.2	0.78 (0.47–1.20)	10	2186.6	0.46 (0.22–0.84)
≥ 50–≤ 59	47	11,345.4	0.41 (0.30–0.55)	31	11,321.3	0.27 (0.19–0.39)
≥ 60–≤ 69	100	36,143.3	0.28 (0.23–0.34)	120	41,208.9	0.29 (0.24–0.35)
≥ 70–≤ 79	368	80,100.6	0.46 (0.41–0.51)	305	95,481.9	0.32 (0.28–0.36)
≥ 80–≤ 89	279	39,841.3	0.70 (0.62–0.79)	179	40,919.0	0.44 (0.38–0.51)
≥ 90	35	5108.5	0.69 (0.48–0.95)	20	3060.6	0.65 (0.40–1.01)
Renal function						
Normal	551	131,940.8	0.42 (0.38–0.45)	NA	NA	NA
Impaired	298	43,172.3	0.69 (0.61–0.77)	NA	NA	NA
Elderly						
No (< 75 years)	316	88,708.7	0.36 (0.32–0.40)	NA	NA	NA
Yes (≥ 75 years)	533	86,404.5	0.62 (0.57–0.67)	NA	NA	NA
Diabetes						
No	464	107,950.0	0.43 (0.39–0.47)	NA	NA	NA
Yes	385	67,163.2	0.57 (0.52–0.63)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 53: Incidence rate of urogenital bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)			SOC (N = 20,502)		
	Events n	Person-years	Incidence rate [b] (95% CI)	Events n	Person-years	Incidence rate [b] (95% CI)
Any urogenital bleed	**155**	**23,354.1**	**0.66 (0.56–0.78)**	**102**	**28,103.0**	**0.36 (0.30–0.44)**
Sex						
Male	21	11,153.3	0.19 (0.12–0.29)	26	13,645.9	0.19 (0.12–0.28)
Female	134	12,200.8	1.10 (0.92–1.30)	76	14,457.1	0.53 (0.41–0.66)
Age group						
≤ 49	79	4734.1	1.67 (1.32–2.08)	36	5409.1	0.67 (0.47–0.92)
≥ 50–≤ 59	26	4377.1	0.59 (0.39–0.87)	17	4964.9	0.34 (0.20–0.55)
≥ 60–≤ 69	11	4486.1	0.25 (0.12–0.44)	14	5589.5	0.25 (0.14–0.42)
≥ 70–≤ 79	18	6346.2	0.28 (0.17–0.45)	19	8420.8	0.23 (0.14–0.35)
≥ 80–≤ 89	19	2938.7	0.65 (0.39–1.01)	13	3372.5	0.39 (0.21–0.66)
≥ 90	2	471.9	0.42 (0.05–1.53)	3	346.1	0.87 (0.18–2.53)
Renal function						
Normal	135	19,691.5	0.69 (0.57–0.81)	NA	NA	NA
Impaired	20	3662.6	0.55 (0.33–0.84)	NA	NA	NA
Elderly						
No (< 75 years)	124	16,721.9	0.74 (0.62–0.88)	NA	NA	NA
Yes (≥ 75 years)	31	6632.2	0.47 (0.32–0.66)	NA	NA	NA
Diabetes						
No	122	17,601.2	0.69 (0.58–0.83)	NA	NA	NA
Yes	33	5752.9	0.57 (0.39–0.81)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 54: Incidence rate of urogenital bleeding associated with first use of rivaroxaban (first episode of treatment [a]) – ACS (all doses)

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Any urogenital bleed	**6**	**826.9**	**0.73 (0.27–1.58)**
Sex			
Male	2	445.7	0.45 (0.05–1.62)
Female	4	381.2	1.05 (0.29–2.69)
Age group			
≤ 49	0	38.9	0.00 (0.00–9.49)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	1	109.5	0.91 (0.02–5.09)
≥ 70–≤ 79	1	331.7	0.30 (0.01–1.68)
≥ 80–≤ 89	3	228.6	1.31 (0.27–3.83)
≥ 90	1	32.6	3.07 (0.08–17.11)
Renal function			
Normal	5	545.1	0.92 (0.30–2.14)
Impaired	1	281.8	0.35 (0.01–1.98)
Elderly			
No (< 75 years)	2	361.1	0.55 (0.07–2.00)
Yes (≥ 75 years)	4	465.8	0.86 (0.23–2.20)
Diabetes			
No	4	498.7	0.80 (0.22–2.05)
Yes	2	328.2	0.61 (0.07–2.20)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 55: Incidence rate of other bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)			SOC (N = 88,655)		
	Events n	Person-years	Incidence rate [b] (95% CI)	Events n	Person-years	Incidence rate [b] (95% CI)
Any other bleed	**1205**	**174,797.0**	**0.69 (0.65–0.73)**	**1719**	**192,833.7**	**0.89 (0.85–0.93)**
Sex						
Male	645	89,240.7	0.72 (0.67–0.78)	912	103,294.7	0.88 (0.83–0.94)
Female	560	85,556.3	0.65 (0.60–0.71)	807	89,539.0	0.90 (0.84–0.97)
Age group						
≤ 49	5	2596.3	0.19 (0.06–0.45)	15	2199.5	0.68 (0.38–1.12)
≥ 50–≤ 59	36	11,352.6	0.32 (0.22–0.44)	61	11,284.1	0.54 (0.41–0.69)
≥ 60–≤ 69	170	36,071.0	0.47 (0.40–0.55)	270	40,996.7	0.66 (0.58–0.74)
≥ 70–≤ 79	529	79,952.8	0.66 (0.61–0.72)	836	94,752.6	0.88 (0.82–0.94)
≥ 80–≤ 89	411	39,723.0	1.03 (0.94–1.14)	491	40,549.4	1.21 (1.11–1.32)
≥ 90	54	5101.4	1.06 (0.80–1.38)	46	3051.5	1.51 (1.10–2.01)
Renal function						
Normal	798	131,742.4	0.61 (0.56–0.65)	NA	NA	NA
Impaired	407	43,054.6	0.95 (0.86–1.04)	NA	NA	NA
Elderly						
No (< 75 years)	436	88,588.3	0.49 (0.45–0.54)	NA	NA	NA
Yes (≥ 75 years)	769	86,208.8	0.89 (0.83–0.96)	NA	NA	NA
Diabetes						
No	637	107,740.6	0.59 (0.55–0.64)	NA	NA	NA
Yes	568	67,056.4	0.85 (0.78–0.92)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 56: Incidence rate of other bleeding associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)			SOC (N = 20,502)		
	Events n	Person-years	Incidence rate [b] (95% CI)	Events n	Person-years	Incidence rate [b] (95% CI)
Any other bleed	**103**	**23,402.7**	**0.44 (0.36–0.53)**	**204**	**28,038.7**	**0.73 (0.63–0.83)**
Sex						
Male	43	11,139.0	0.39 (0.28–0.52)	75	13,585.8	0.55 (0.43–0.69)
Female	60	12,263.8	0.49 (0.37–0.63)	129	14,453.0	0.89 (0.75–1.06)
Age group						
≤ 49	17	4772.9	0.36 (0.21–0.57)	10	5459.1	0.18 (0.09–0.34)
≥ 50–≤ 59	8	4391.8	0.18 (0.08–0.36)	29	4951.2	0.59 (0.39–0.84)
≥ 60–≤ 69	16	4484.1	0.36 (0.20–0.58)	36	5568.6	0.65 (0.45–0.90)
≥ 70–≤ 79	32	6343.7	0.50 (0.35–0.71)	74	8378.6	0.88 (0.69–1.11)
≥ 80–≤ 89	28	2936.0	0.95 (0.63–1.38)	49	3335.6	1.47 (1.09–1.94)
≥ 90	2	474.3	0.42 (0.05–1.52)	6	345.6	1.74 (0.64–3.78)
Renal function						
Normal	74	19,745.4	0.37 (0.29–0.47)	NA	NA	NA
Impaired	29	3657.3	0.79 (0.53–1.14)	NA	NA	NA
Elderly						
No (< 75 years)	57	16,769.7	0.34 (0.26–0.44)	NA	NA	NA
Yes (≥ 75 years)	46	6633.1	0.69 (0.51–0.93)	NA	NA	NA
Diabetes						
No	71	17,648.3	0.40 (0.31–0.51)	NA	NA	NA
Yes	32	5754.4	0.56 (0.38–0.79)	NA	NA	NA

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; NA, not applicable; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 57: Incidence rate of other bleeding associated with first use of rivaroxaban (first episode of treatment [a]) – ACS (all doses)

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Any other bleed	**9**	**828.6**	**1.09 (0.50–2.06)**
Sex			
Male	3	447.8	0.67 (0.14–1.96)
Female	6	380.8	1.58 (0.58–3.43)
Age group			
≤ 49	1	38.3	2.61 (0.07–14.56)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	0	112.0	0.00 (0.00–3.29)
≥ 70–≤ 79	3	329.8	0.91 (0.19–2.66)
≥ 80–≤ 89	3	230.7	1.30 (0.27–3.80)
≥ 90	2	32.2	6.21 (0.75–22.44)
Renal function			
Normal	6	548.1	1.09 (0.40–2.38)
Impaired	3	280.5	1.07 (0.22–3.13)
Elderly			
No (< 75 years)	2	361.1	0.55 (0.07–2.00)
Yes (≥ 75 years)	7	467.5	1.50 (0.60–3.09)
Diabetes			
No	4	502.3	0.80 (0.22–2.04)
Yes	5	326.3	1.53 (0.50–3.58)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 58: Incidence rate of noninfective liver disease associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Noninfective liver disease [c]	**335**	**175,630.2**	**0.19 (0.17–0.21)**
Sex			
Male	166	89,678.2	0.19 (0.16–0.22)
Female	169	85,952.0	0.20 (0.17–0.23)
Age group			
≤ 49	6	2594.0	0.23 (0.08–0.50)
≥ 50–≤ 59	23	11,373.3	0.20 (0.13–0.30)
≥ 60–≤ 69	72	36,191.0	0.20 (0.16–0.25)
≥ 70–≤ 79	149	80,330.2	0.19 (0.16–0.22)
≥ 80–≤ 89	76	40,015.1	0.19 (0.15–0.24)
≥ 90	9	5126.5	0.18 (0.08–0.33)
Renal function			
Normal	223	132,272.5	0.17 (0.15–0.19)
Impaired	112	43,357.7	0.26 (0.21–0.31)
Elderly			
No (< 75 years)	183	88,902.2	0.21 (0.18–0.24)
Yes (≥ 75 years)	152	86,728.0	0.18 (0.15–0.21)
Diabetes			
No	162	108,228.9	0.15 (0.13–0.17)
Yes	173	67,401.2	0.26 (0.22–0.30)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: 81 (0.1%) patients with noninfective liver disease had recent history of cancer

CI, confidence interval; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 59: Incidence rate of noninfective liver disease associated with first use of rivaroxaban (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Noninfective liver disease	**46**	**23,453.4**	**0.20 (0.14–0.26)**
Sex			
Male	23	11,157.3	0.21 (0.13–0.31)
Female	23	12,296.1	0.19 (0.12–0.28)
Age group			
≤ 49	9	4782.1	0.19 (0.09–0.36)
≥ 50–≤ 59	10	4392.2	0.23 (0.11–0.42)
≥ 60–≤ 69	12	4491.5	0.27 (0.14–0.47)
≥ 70–≤ 79	9	6359.8	0.14 (0.06–0.27)
≥ 80–≤ 89	6	2952.0	0.20 (0.07–0.44)
≥ 90	0	475.8	0.00 (0.00–0.78)
Renal function			
Normal	35	19,779.2	0.18 (0.12–0.25)
Impaired	11	3674.3	0.30 (0.15–0.54)
Elderly			
No (< 75 years)	33	16,795.1	0.20 (0.14–0.28)
Yes (≥ 75 years)	13	6658.3	0.20 (0.10–0.33)
Diabetes			
No	34	17,675.2	0.19 (0.13–0.27)
Yes	12	5778.2	0.21 (0.11–0.36)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 60: Incidence rate of noninfective liver disease associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	Rivaroxaban (N = 546)		
	Events n	Person-years	Incidence rate [b] (95% CI)
Noninfective liver disease [c]	**0**	**834.6**	**0.00 (0.00–0.44)**
Sex			
Male	0	449.1	0.00 (0.00–0.82)
Female	0	385.5	0.00 (0.00–0.96)
Age group			
≤ 49	0	38.9	0.00 (0.00–9.49)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	0	112.0	0.00 (0.00–3.29)
≥ 70–≤ 79	0	331.7	0.00 (0.00–1.11)
≥ 80–≤ 89	0	233.7	0.00 (0.00–1.58)
≥ 90	0	32.8	0.00 (0.00–11.25)
Renal function			
Normal	0	551.9	0.00 (0.00–0.67)
Impaired	0	282.7	0.00 (0.00–1.30)
Elderly			
No (< 75 years)	0	363.6	0.00 (0.00–1.01)
Yes (≥ 75 years)	0	471.1	0.00 (0.00–0.78)
Diabetes			
No	0	504.8	0.00 (0.00–0.73)
Yes	0	329.9	0.00 (0.00–1.12)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: 0 (0.0%) patients with noninfective liver disease had recent history of cancer

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 61: Incidence rate of DVT/PE associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
VTE	**268**	**175,660.0**	**0.15 (0.13–0.17)**
DVT	79	175,793.3	0.04 (0.04–0.06)
PE	190	175,731.6	0.11 (0.09–0.12)
Sex			
Male	127	89,674.6	0.14 (0.12–0.17)
Female	141	85,985.3	0.16 (0.14–0.19)
Age group			
≤ 49	3	2595.6	0.12 (0.02–0.34)
≥ 50–≤ 59	14	11,369.0	0.12 (0.07–0.21)
≥ 60–≤ 69	51	36,201.1	0.14 (0.10–0.19)
≥ 70–≤ 79	112	80,366.7	0.14 (0.11–0.17)
≥ 80–≤ 89	74	40,003.8	0.18 (0.15–0.23)
≥ 90	14	5123.8	0.27 (0.15–0.46)
Renal function			
Normal	169	132,283.0	0.13 (0.11–0.15)
Impaired	99	43,376.9	0.23 (0.19–0.28)
Elderly			
No (< 75 years)	118	88,931.5	0.13 (0.11–0.16)
Yes (≥ 75 years)	150	86,728.5	0.17 (0.15–0.20)
Diabetes			
No	149	108,224.7	0.14 (0.12–0.16)
Yes	119	67,435.2	0.18 (0.15–0.21)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; SPAF, stroke prevention in nonvalvular atrial fibrillation; VTE, venous thromboembolism

Annex 2.2 Table 62: Incidence rate of DVT/PE associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
VTE	**1503**	**174,084.8**	**0.86 (0.82–0.91)**
DVT [c]	1330	174,207.1	0.76 (0.72–0.81)
PE	190	175,731.6	0.11 (0.09–0.12)
Sex			
Male	732	88,901.5	0.82 (0.76–0.89)
Female	771	85,183.3	0.91 (0.84–0.97)
Age group			
≤ 49	32	2563.9	1.25 (0.85–1.76)
≥ 50–≤ 59	104	11,242.7	0.93 (0.76–1.12)
≥ 60–≤ 69	269	35,869.8	0.75 (0.66–0.85)
≥ 70–≤ 79	620	79,724.1	0.78 (0.72–0.84)
≥ 80–≤ 89	401	39,608.4	1.01 (0.92–1.12)
≥ 90	77	5075.9	1.52 (1.20–1.90)
Renal function			
Normal	1036	131,238.2	0.79 (0.74–0.84)
Impaired	467	42,846.6	1.09 (0.99–1.19)
Elderly			
No (< 75 years)	692	88,132.2	0.79 (0.73–0.85)
Yes (≥ 75 years)	811	85,952.6	0.94 (0.88–1.01)
Diabetes			
No	889	107,267.6	0.83 (0.78–0.89)
Yes	614	66,817.2	0.92 (0.85–0.99)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: Hospital and outpatient diagnosis

CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; SPAF, stroke prevention in nonvalvular atrial fibrillation; VTE, venous thromboembolism

Annex 2.2 Table 63: Incidence rate of DVT/PE associated with first use of rivaroxaban (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
VTE	**529**	**22,984.7**	**2.30 (2.11–2.51)**
DVT	188	23,323.8	0.81 (0.69–0.93)
PE	347	23,127.0	1.50 (1.35–1.67)
Sex			
Male	261	10,917.1	2.39 (2.11–2.70)
Female	268	12,067.6	2.22 (1.96–2.50)
Age group			
≤ 49	159	4675.5	3.40 (2.89–3.97)
≥ 50–≤ 59	98	4306.6	2.28 (1.85–2.77)
≥ 60–≤ 69	100	4392.7	2.28 (1.85–2.77)
≥ 70–≤ 79	108	6227.1	1.73 (1.42–2.09)
≥ 80–≤ 89	52	2910.0	1.79 (1.33–2.34)
≥ 90	12	472.8	2.54 (1.31–4.43)
Renal function			
Normal	448	19,397.5	2.31 (2.10–2.53)
Impaired	81	3587.1	2.26 (1.79–2.81)
Elderly			
No (< 75 years)	411	16,432.5	2.50 (2.27–2.76)
Yes (≥ 75 years)	118	6552.1	1.80 (1.49–2.16)
Diabetes			
No	412	17,321.3	2.38 (2.15–2.62)
Yes	117	5663.3	2.07 (1.71–2.48)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; VTE-T, treatment and secondary prevention of VTE

Annex 2.2 Table 64: Incidence rate of DVT/PE associated with first use of rivaroxaban (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
VTE	**10,880**	**14,744.5**	**73.79 (72.41–75.19)**
DVT [c]	10,659	14,975.0	71.18 (69.83–72.54)
PE	347	23,127.0	1.50 (1.35–1.67)
Sex			
Male	5149	6752.6	76.25 (74.18–78.36)
Female	5731	7991.8	71.71 (69.87–73.59)
Age group			
≤ 49	3168	2792.6	113.44 (109.53–117.46)
≥ 50–≤ 59	2189	2632.4	83.16 (79.71–86.72)
≥ 60–≤ 69	1970	2735.0	72.03 (68.88–75.28)
≥ 70–≤ 79	2365	4176.5	56.63 (54.37–58.96)
≥ 80–≤ 89	1019	2071.0	49.20 (46.23–52.32)
≥ 90	169	337.0	50.14 (42.87–58.30)
Renal function			
Normal	9820	12,275.0	80.00 (78.43–81.60)
Impaired	1060	2469.5	42.92 (40.38–45.59)
Elderly			
No (< 75 years)	8508	10,198.1	83.43 (81.66–85.22)
Yes (≥ 75 years)	2372	4546.4	52.17 (50.09–54.32)
Diabetes			
No	8740	10,967.9	79.69 (78.03–81.38)
Yes	2140	3776.6	56.66 (54.29–59.12)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: Hospital and outpatient diagnosis

CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; VTE-T, treatment and secondary prevention of VTE

Annex 2.2 Table 65: Incidence rate of DVT/PE associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
VTE	**4**	**828.0**	**0.48 (0.13–1.24)**
DVT	2	830.9	0.24 (0.03–0.87)
PE	2	831.7	0.24 (0.03–0.87)
Sex			
Male	3	445.9	0.67 (0.14–1.97)
Female	1	382.1	0.26 (0.01–1.46)
Age group			
≤ 49	0	38.9	0.00 (0.00–9.49)
≥ 50–≤ 59	1	85.6	1.17 (0.03–6.51)
≥ 60–≤ 69	0	112.0	0.00 (0.00–3.29)
≥ 70–≤ 79	2	328.5	0.61 (0.07–2.20)
≥ 80–≤ 89	1	230.2	0.43 (0.01–2.42)
≥ 90	0	32.8	0.00 (0.00–11.25)
Renal function			
Normal	4	545.2	0.73 (0.20–1.88)
Impaired	0	282.7	0.00 (0.00–1.30)
Elderly			
No (< 75 years)	3	360.3	0.83 (0.17–2.43)
Yes (≥ 75 years)	1	467.7	0.21 (0.01–1.19)
Diabetes			
No	2	504.4	0.40 (0.05–1.43)
Yes	2	323.5	0.62 (0.07–2.23)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

Annex 2.2 Table 66: Incidence rate of DVT/PE associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
VTE	13	816.7	1.59 (0.85–2.72)
DVT [c]	11	819.6	1.34 (0.67–2.40)
PE	2	831.7	0.24 (0.03–0.87)
Sex			
Male	6	440.5	1.36 (0.50–2.96)
Female	7	376.1	1.86 (0.75–3.83)
Age group			
≤ 49	2	35.2	5.68 (0.69–20.52)
≥ 50–≤ 59	1	85.6	1.17 (0.03–6.51)
≥ 60–≤ 69	0	112.0	0.00 (0.00–3.29)
≥ 70–≤ 79	7	322.5	2.17 (0.87–4.47)
≥ 80–≤ 89	3	228.6	1.31 (0.27–3.83)
≥ 90	0	32.8	0.00 (0.00–11.25)
Renal function			
Normal	10	535.5	1.87 (0.90–3.43)
Impaired	3	281.2	1.07 (0.22–3.12)
Elderly			
No (< 75 years)	7	352.7	1.98 (0.80–4.09)
Yes (≥ 75 years)	6	464.0	1.29 (0.47–2.81)
Diabetes			
No	8	494.0	1.62 (0.70–3.19)
Yes	5	322.7	1.55 (0.50–3.62)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: Hospital and outpatient diagnosis

ACS, acute coronary syndrome; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

Annex 2.2 Table 67: Incidence rate of ischemic stroke associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Ischemic stroke	**1978**	**174,469.8**	**1.13 (1.08–1.18)**
Sex			
Male	950	89,092.7	1.07 (1.00–1.14)
Female	1028	85,377.0	1.20 (1.13–1.28)
Age group			
≤ 49	7	2588.1	0.27 (0.11–0.56)
≥ 50–≤ 59	44	11,367.9	0.39 (0.28–0.52)
≥ 60–≤ 69	240	36,074.5	0.67 (0.58–0.76)
≥ 70–≤ 79	804	79,832.7	1.01 (0.94–1.08)
≥ 80–≤ 89	770	39,536.4	1.95 (1.81–2.09)
≥ 90	113	5070.2	2.23 (1.84–2.68)
Renal function			
Normal	1281	131,530.5	0.97 (0.92–1.03)
Impaired	697	42,939.3	1.62 (1.50–1.75)
Elderly			
No (< 75 years)	609	88,618.1	0.69 (0.63–0.74)
Yes (≥ 75 years)	1369	85,851.7	1.59 (1.51–1.68)
Diabetes			
No	1014	107,622.3	0.94 (0.89–1.00)
Yes	964	66,847.4	1.44 (1.35–1.54)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 68: Incidence rate of ischemic stroke associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Ischemic stroke [c]	**2034**	**174,422.6**	**1.17 (1.12–1.22)**
Sex			
Male	972	89,068.5	1.09 (1.02–1.16)
Female	1062	85,354.1	1.24 (1.17–1.32)
Age group			
≤ 49	7	2588.1	0.27 (0.11–0.56)
≥ 50–≤ 59	44	11,367.9	0.39 (0.28–0.52)
≥ 60–≤ 69	242	36,072.4	0.67 (0.59–0.76)
≥ 70–≤ 79	829	79,809.3	1.04 (0.97–1.11)
≥ 80–≤ 89	795	39,515.7	2.01 (1.87–2.16)
≥ 90	117	5069.3	2.31 (1.91–2.77)
Renal function			
Normal	1317	131,504.1	1.00 (0.95–1.06)
Impaired	717	42,918.6	1.67 (1.55–1.80)
Elderly			
No (< 75 years)	623	88,605.1	0.70 (0.65–0.76)
Yes (≥ 75 years)	1411	85,817.6	1.64 (1.56–1.73)
Diabetes			
No	1048	107,593.3	0.97 (0.92–1.03)
Yes	986	66,829.3	1.48 (1.38–1.57)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: Including I64-, stroke not specified as hemorrhagic or ischemic

CI, confidence interval; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 69: Incidence rate of ischemic stroke associated with first use of rivaroxaban (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Ischemic stroke	**150**	**23,383.2**	**0.64 (0.54–0.75)**
Sex			
Male	68	11,135.1	0.61 (0.47–0.77)
Female	82	12,248.1	0.67 (0.53–0.83)
Age group			
≤ 49	8	4782.8	0.17 (0.07–0.33)
≥ 50–≤ 59	18	4384.8	0.41 (0.24–0.65)
≥ 60–≤ 69	27	4482.9	0.60 (0.40–0.88)
≥ 70–≤ 79	51	6328.2	0.81 (0.60–1.06)
≥ 80–≤ 89	40	2931.1	1.36 (0.97–1.86)
≥ 90	6	473.4	1.27 (0.47–2.76)
Renal function			
Normal	112	19,735.2	0.57 (0.47–0.68)
Impaired	38	3648.0	1.04 (0.74–1.43)
Elderly			
No (< 75 years)	78	16,765.8	0.47 (0.37–0.58)
Yes (≥ 75 years)	72	6617.4	1.09 (0.85–1.37)
Diabetes			
No	88	17,638.2	0.50 (0.40–0.61)
Yes	62	5745.0	1.08 (0.83–1.38)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 70: Incidence rate of ischemic stroke associated with first use of rivaroxaban (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Ischemic stroke [c]	**150**	**23,382.8**	**0.64 (0.54–0.75)**
Sex			
Male	68	11,134.7	0.61 (0.47–0.77)
Female	82	12,248.1	0.67 (0.53–0.83)
Age group			
≤ 49	8	4782.8	0.17 (0.07–0.33)
≥ 50–≤ 59	18	4384.8	0.41 (0.24–0.65)
≥ 60–≤ 69	27	4482.9	0.60 (0.40–0.88)
≥ 70–≤ 79	51	6327.8	0.81 (0.60–1.06)
≥ 80–≤ 89	40	2931.1	1.36 (0.97–1.86)
≥ 90	6	473.4	1.27 (0.47–2.76)
Renal function			
Normal	112	19,735.2	0.57 (0.47–0.68)
Impaired	38	3647.6	1.04 (0.74–1.43)
Elderly			
No (< 75 years)	78	16,765.8	0.47 (0.37–0.58)
Yes (≥ 75 years)	72	6617.0	1.09 (0.85–1.37)
Diabetes			
No	88	17,637.8	0.50 (0.40–0.61)
Yes	62	5745.0	1.08 (0.83–1.38)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: Including I64-, stroke not specified as hemorrhagic or ischemic

CI, confidence interval; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 71: Incidence rate of ischemic stroke associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Ischemic stroke	**12**	**825.9**	**1.45 (0.75–2.54)**
Sex			
Male	6	445.9	1.35 (0.49–2.93)
Female	6	380.0	1.58 (0.58–3.44)
Age group			
≤ 49	0	38.9	0.00 (0.00–9.49)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	1	112.0	0.89 (0.02–4.98)
≥ 70–≤ 79	6	327.7	1.83 (0.67–3.98)
≥ 80–≤ 89	5	228.9	2.18 (0.71–5.10)
≥ 90	0	32.8	0.00 (0.00–11.25)
Renal function			
Normal	6	546.2	1.10 (0.40–2.39)
Impaired	6	279.7	2.15 (0.79–4.67)
Elderly			
No (< 75 years)	4	362.3	1.10 (0.30–2.83)
Yes (≥ 75 years)	8	463.6	1.73 (0.75–3.40)
Diabetes			
No	9	498.5	1.81 (0.83–3.43)
Yes	3	327.4	0.92 (0.19–2.68)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 72: Incidence rate of ischemic stroke associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Ischemic stroke [c]	**13**	**825.9**	**1.57 (0.84–2.69)**
Sex			
Male	6	445.9	1.35 (0.49–2.93)
Female	7	380.0	1.84 (0.74–3.80)
Age group			
≤ 49	0	38.9	0.00 (0.00–9.49)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	1	112.0	0.89 (0.02–4.98)
≥ 70–≤ 79	6	327.7	1.83 (0.67–3.98)
≥ 80–≤ 89	6	228.9	2.62 (0.96–5.71)
≥ 90	0	32.8	0.00 (0.00–11.25)
Renal function			
Normal	6	546.2	1.10 (0.40–2.39)
Impaired	7	279.7	2.50 (1.01–5.16)
Elderly			
No (< 75 years)	4	362.3	1.10 (0.30–2.83)
Yes (≥ 75 years)	9	463.5	1.94 (0.89–3.69)
Diabetes			
No	9	498.5	1.81 (0.83–3.43)
Yes	4	327.4	1.22 (0.33–3.13)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

c: Including I64-, stroke not specified as hemorrhagic or ischemic

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 73: Incidence rate of myocardial infarction associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Myocardial infarction	**1376**	**175,091.2**	**0.79 (0.74–0.83)**
Sex			
Male	829	89,332.5	0.93 (0.87–0.99)
Female	547	85,758.7	0.64 (0.59–0.69)
Age group			
≤ 49	4	2594.2	0.15 (0.04–0.39)
≥ 50–≤ 59	45	11,357.4	0.40 (0.29–0.53)
≥ 60–≤ 69	179	36,148.8	0.50 (0.43–0.57)
≥ 70–≤ 79	596	80,083.4	0.74 (0.69–0.81)
≥ 80–≤ 89	475	39,805.3	1.19 (1.09–1.31)
≥ 90	77	5102.1	1.51 (1.19–1.89)
Renal function			
Normal	829	131,962.6	0.63 (0.59–0.67)
Impaired	547	43,128.6	1.27 (1.16–1.38)
Elderly			
No (< 75 years)	476	88,744.8	0.54 (0.49–0.59)
Yes (≥ 75 years)	900	86,346.3	1.04 (0.98–1.11)
Diabetes			
No	665	107,975.9	0.62 (0.57–0.66)
Yes	711	67,115.3	1.06 (0.98–1.14)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 74: Incidence rate of myocardial infarction associated with first use of rivaroxaban (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
Myocardial infarction	**113**	**23,416.3**	**0.48 (0.40–0.58)**
Sex			
Male	67	11,130.2	0.60 (0.47–0.76)
Female	46	12,286.1	0.37 (0.27–0.50)
Age group			
≤ 49	3	4786.0	0.06 (0.01–0.18)
≥ 50–≤ 59	8	4394.6	0.18 (0.08–0.36)
≥ 60–≤ 69	20	4485.1	0.45 (0.27–0.69)
≥ 70–≤ 79	41	6336.7	0.65 (0.46–0.88)
≥ 80–≤ 89	34	2941.4	1.16 (0.80–1.62)
≥ 90	7	472.5	1.48 (0.60–3.05)
Renal function			
Normal	68	19,765.7	0.34 (0.27–0.44)
Impaired	45	3650.6	1.23 (0.90–1.65)
Elderly			
No (< 75 years)	42	16,785.4	0.25 (0.18–0.34)
Yes (≥ 75 years)	71	6631.0	1.07 (0.84–1.35)
Diabetes			
No	70	17,652.9	0.40 (0.31–0.50)
Yes	43	5763.4	0.75 (0.54–1.00)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 75: Incidence rate of myocardial infarction associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	Rivaroxaban (N = 546)		
	Events n	Person-years	Incidence rate [b] (95% CI)
Myocardial infarction	**42**	**796.0**	**5.28 (3.80–7.13)**
Sex			
Male	24	430.8	5.57 (3.57–8.29)
Female	18	365.2	4.93 (2.92–7.79)
Age group			
≤ 49	1	37.8	2.64 (0.07–14.72)
≥ 50–≤ 59	4	82.8	4.83 (1.32–12.36)
≥ 60–≤ 69	3	107.5	2.79 (0.58–8.15)
≥ 70–≤ 79	11	316.8	3.47 (1.73–6.21)
≥ 80–≤ 89	16	221.1	7.24 (4.14–11.75)
≥ 90	7	29.9	23.43 (9.42–48.27)
Renal function			
Normal	22	531.1	4.14 (2.60–6.27)
Impaired	20	264.9	7.55 (4.61–11.66)
Elderly			
No (< 75 years)	11	349.6	3.15 (1.57–5.63)
Yes (≥ 75 years)	31	446.4	6.95 (4.72–9.86)
Diabetes			
No	21	493.9	4.25 (2.63–6.50)
Yes	21	302.0	6.95 (4.30–10.63)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 76: Incidence rate of all-cause mortality associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	Rivaroxaban (N = 127,743)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
All-cause mortality	**10,694**	**175,865.0**	**6.08 (5.97–6.20)**
Sex			
Male	5167	89,782.5	5.76 (5.60–5.91)
Female	5527	86,082.5	6.42 (6.25–6.59)
Age group			
≤ 49	30	2598.2	1.15 (0.78–1.65)
≥ 50–≤ 59	146	11,393.9	1.28 (1.08–1.51)
≥ 60–≤ 69	837	36,248.6	2.31 (2.16–2.47)
≥ 70–≤ 79	3227	80,448.5	4.01 (3.87–4.15)
≥ 80–≤ 89	4933	40,045.9	12.32 (11.98–12.67)
≥ 90	1521	5129.9	29.65 (28.18–31.18)
Renal function			
Normal	5493	132,422.9	4.15 (4.04–4.26)
Impaired	5201	43,442.1	11.97 (11.65–12.30)
Elderly			
No (< 75 years)	2211	89,050.6	2.48 (2.38–2.59)
Yes (≥ 75 years)	8483	86,814.4	9.77 (9.56–9.98)
Diabetes			
No	5108	108,356.3	4.71 (4.59–4.85)
Yes	5586	67,508.7	8.27 (8.06–8.49)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 77: Incidence rate of all-cause mortality associated with first use of rivaroxaban (first episode of treatment [a]) – VTE-T without recent history of cancer

	Rivaroxaban (N = 25,914)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
All-cause mortality	**766**	**23,473.6**	**3.26 (3.04–3.50)**
Sex			
Male	268	11,170.3	2.40 (2.12–2.70)
Female	498	12,303.2	4.05 (3.70–4.42)
Age group			
≤ 49	18	4786.9	0.38 (0.22–0.59)
≥ 50–≤ 59	37	4398.5	0.84 (0.59–1.16)
≥ 60–≤ 69	68	4497.8	1.51 (1.17–1.92)
≥ 70–≤ 79	179	6362.0	2.81 (2.42–3.26)
≥ 80–≤ 89	340	2952.6	11.52 (10.32–12.81)
≥ 90	124	475.8	26.06 (21.67–31.07)
Renal function			
Normal	473	19,794.9	2.39 (2.18–2.61)
Impaired	293	3678.7	7.96 (7.08–8.93)
Elderly			
No (< 75 years)	199	16,812.7	1.18 (1.02–1.36)
Yes (≥ 75 years)	567	6660.9	8.51 (7.83–9.24)
Diabetes			
No	470	17,690.7	2.66 (2.42–2.91)
Yes	296	5782.9	5.12 (4.55–5.74)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

CI, confidence interval; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 78: Incidence rate of all-cause mortality associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	Rivaroxaban (N = 546)		
	Events n	**Person-years**	**Incidence rate [b] (95% CI)**
All-cause mortality	**75**	**834.6**	**8.99 (7.07–11.26)**
Sex			
Male	35	449.1	7.79 (5.43–10.84)
Female	40	385.5	10.38 (7.41–14.13)
Age group			
≤ 49	1	38.9	2.57 (0.07–14.33)
≥ 50–≤ 59	0	85.6	0.00 (0.00–4.31)
≥ 60–≤ 69	4	112.0	3.57 (0.97–9.15)
≥ 70–≤ 79	26	331.7	7.84 (5.12–11.48)
≥ 80–≤ 89	32	233.7	13.70 (9.37–19.33)
≥ 90	12	32.8	36.60 (18.91–63.94)
Renal function			
Normal	31	551.9	5.62 (3.82–7.97)
Impaired	44	282.7	15.56 (11.31–20.89)
Elderly			
No (< 75 years)	13	363.6	3.58 (1.90–6.11)
Yes (≥ 75 years)	62	471.1	13.16 (10.09–16.87)
Diabetes			
No	33	504.8	6.54 (4.50–9.18)
Yes	42	329.9	12.73 (9.18–17.21)

a: Patients will be censored at whichever comes first of treatment switching/discontinuation (30-day grace period), occurrence of the outcome of interest, date of last available information, end of study period or death

b: Per 100 person-years

ACS, acute coronary syndrome; CI, confidence interval

Annex 2.2 Table 79: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with intracranial bleeding – SPAF cohort at start date

	Controls N = 39,881		Cases of ICB N = 3995			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	20,758	52.0	2080	52.1	NA	NA
Female	19,123	48.0	1915	47.9	NA	NA
Age at index date						
≤ 49 (ref)	97	0.2	10	0.3	NA	NA
≥ 50–≤ 59	509	1.3	54	1.4	1.40	0.16–12.22
≥ 60–≤ 69	3036	7.6	301	7.5	0.67	0.06–7.76
≥ 70–≤ 79	15,335	38.5	1533	38.4	0.67	0.06–8.11
≥ 80–≤ 89	17,190	43.1	1719	43.0	0.69	0.06–8.37
≥ 90	3714	9.3	378	9.5	0.75	0.06–9.28
Calendar year (year of index date)						
2011–2012 (ref)	1444	3.6	145	3.6	NA	NA
2013–2014	10,739	26.9	1076	26.9	NA	NA
2015–2016	18,318	45.9	1835	45.9	NA	NA
2017–2018	9380	23.5	939	23.5	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	18,249	45.8	1384	34.6	NA	NA
1	11,203	28.1	1163	29.1	1.43	1.32–1.56
≥ 2	10,429	26.2	1448	36.2	1.94	1.79–2.10
Obesity diagnosis [c]						
No (ref)	24,727	62.0	2523	63.2	NA	NA
Yes	15,154	38.0	1472	36.8	0.95	0.89–1.02
Diagnosis indicating alcohol abuse [c]						
No (ref)	37,680	94.5	3631	90.9	NA	NA
Yes	2201	5.5	364	9.1	1.75	1.55–1.97

Deprivation index of place of residence						
Quintile 1 [d]	10,179	25.5	1061	26.6	1.05	0.95–1.15
Quintile 2	8444	21.2	840	21.0	1.00	0.90–1.10
Quintile 3 (ref)	9486	23.8	950	23.8	NA	NA
Quintile 4	6392	16.0	624	15.6	0.98	0.88–1.09
Quintile 5 [e]	5148	12.9	505	12.6	0.98	0.88–1.10
Unknown	232	0.6	15	0.4	0.65	0.38–1.10
Polypharmacy [f]						
< 5 (ref)	27,906	70.0	2562	64.1	NA	NA
5–9	11,562	29.0	1374	34.4	1.31	1.22–1.40
≥ 10	413	1.0	59	1.5	1.59	1.21–2.10

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; ICB, intracranial bleeding; NA, not applicable; OR, odds ratio; ref, reference group; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 80: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with intracranial bleeding – SPAF cohort at start date

	Controls N = 39,881		Cases of ICB N = 3995			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	1212	3.0	1090	27.3	11.85	10.79–13.00
GI bleeding	8518	21.4	903	22.6	1.08	1.00–1.16
UG bleeding	9320	23.4	971	24.3	1.05	0.98–1.14
Coronary artery disease	25,533	64.0	2605	65.2	1.05	0.98–1.13
Myocardial infarction	7529	18.9	833	20.9	1.13	1.05–1.23
Heart failure	23,954	60.1	2570	64.3	1.21	1.13–1.29
Ischemic stroke	7865	19.7	1187	29.7	1.74	1.61–1.87
Transient ischemic attack	5557	13.9	682	17.1	1.28	1.17–1.39
DVT/PE	3063	7.7	313	7.8	1.02	0.91–1.16
Renal failure	13,954	35.0	1589	39.8	1.24	1.16–1.33
Depression	17,911	44.9	2001	50.1	1.25	1.17–1.33
Hypertension	38,437	96.4	3894	97.5	1.46	1.19–1.79
Hyperlipidemia	30,105	75.5	3014	75.4	1.00	0.93–1.08
Diabetes	16,781	42.1	1802	45.1	1.13	1.06–1.21
Asthma	6416	16.1	591	14.8	0.91	0.83–0.99
COPD	11,070	27.8	1092	27.3	0.98	0.91–1.05
Cancer	13,028	32.7	1400	35.0	1.12	1.04–1.20
Risk scores: CHA_2DS_2VASc score at index date						
0–1 (ref)	465	1.2	19	0.5	NA	NA
2	1440	3.6	81	2.0	1.81	1.07–3.06
3	3696	9.3	287	7.2	3.05	1.84–5.05
4	6621	16.6	573	14.3	3.77	2.28–6.23
5	8518	21.4	829	20.8	4.47	2.70–7.40
≥ 6	19,141	48.0	2206	55.2	5.57	3.37–9.20
Risk scores: HAS-BLED score at index date						
0–1 (ref)	897	2.2	37	0.9	NA	NA
2	5553	13.9	297	7.4	1.66	1.15–2.38
3	11,998	30.1	975	24.4	2.65	1.86–3.78
≥ 4	21,433	53.7	2686	67.2	4.18	2.94–5.96

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period

c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; ICB, intracranial bleeding; NA, not applicable; OR, odds ratio; ref, reference group; PE, pulmonary embolism; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

Annex 2.2 Table 81: Current use [a] of medications among cases [b] and controls and association with intracranial bleeding – SPAF cohort at start date

	Controls N = 39,881		Cases of ICB N = 3995			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	2919	7.3	406	10.2	1.44	1.29–1.61
Parenteral anticoagulants	1239	3.1	191	4.8	1.59	1.36–1.87
Other oral anticoagulants	2143	5.4	163	4.1	0.74	0.63–0.88
Proton pump inhibitors	12,954	32.5	1454	36.4	1.19	1.11–1.28
NSAIDs	1806	4.5	205	5.1	1.14	0.98–1.32
SSRIs	1181	3.0	216	5.4	1.87	1.62–2.18
Oral steroids	1480	3.7	149	3.7	1.01	0.85–1.20
Antibiotics	732	1.8	121	3.0	1.68	1.38–2.04
Lipid-lowering medications	10,885	27.3	1104	27.6	1.02	0.95–1.10

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the respective drug in the year before

CI, confidence interval; ICB, intracranial bleeding; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SPAF, stroke prevention in nonvalvular atrial fibrillation; SSRI, selective serotonin reuptake inhibitor

Annex 2.2 Table 82: Relative risk of intracranial bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – SPAF cohort at start date

	Controls N = 39,881		Cases of ICB [a] N = 3995		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	4487	11.3	325	8.1	NA	NA	NA	NA
Current use (0–30 days before index date)	16,217	40.7	1452	36.3	1.28	1.12–1.45	1.32	1.15–1.51
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	5667	14.2	548	13.7	1.37	1.19–1.59	1.20	1.01–1.41
20 mg	10,550	26.5	904	22.6	1.22	1.07–1.40	1.41	1.21–1.63
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	2	0.0	2	0.1	14.44	2.03–102.86	7.35	0.73–73.92
10 mg	419	1.1	35	0.9	1.19	0.83–1.72	1.11	0.75–1.63
15 mg	6129	15.4	584	14.6	1.36	1.17–1.57	1.28	1.09–1.50
20 mg	9648	24.2	826	20.7	1.22	1.06–1.40	1.35	1.16–1.56
Combination 15 + 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
multiple	19	0.0	5	0.1	3.89	1.44–10.49	4.60	1.58–13.39
Event date during first treatment episode								
Yes	10,362	26.0	894	22.4	1.23	1.07–1.41	1.31	1.13–1.52
No	5855	14.7	558	14.0	1.34	1.16–1.54	1.32	1.14–1.54
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	690	1.7	60	1.5	1.28	0.87–1.89	1.29	0.85–1.96
31–180	2692	6.8	218	5.5	1.14	0.92–1.42	1.19	0.94–1.50
> 180	6980	17.5	616	15.4	1.25	1.08–1.44	1.34	1.15–1.56
SOC recency								
Nonuse (ref)	4487	11.3	325	8.1	NA	NA	NA	NA
Current use (0–30 days before index date)	10,771	27.0	1235	30.9	1.65	1.44–1.88	1.85	1.61–2.14
Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	532	1.3	55	1.4	1.47	0.99–2.17	1.67	1.10–2.54
31–180	2016	5.1	219	5.5	1.66	1.34–2.07	1.92	1.52–2.42
> 180	6330	15.9	609	15.2	1.35	1.17–1.56	1.57	1.35–1.83

a: Cases ascertained during complete follow-up period
b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report.

d: If event date during treatment episode

CI, confidence interval; ICB, intracranial bleeding; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 83: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with intracranial bleeding – VTE-T without recent history of cancer at start date

	Controls N = 3481		Cases of ICB N = 360			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	1641	47.1	171	47.5	NA	NA
Female	1840	52.9	189	52.5	NA	NA
Age at index date						
≤ 49 (ref)	116	3.3	13	3.6	NA	NA
≥ 50–≤ 59	359	10.3	36	10.0	1.59	0.09–27.25
≥ 60–≤ 69	352	10.1	37	10.3	1.94	0.06–64.44
≥ 70–≤ 79	1239	35.6	123	34.2	2.24	0.05–97.71
≥ 80–≤ 89	1174	33.7	124	34.4	4.39	0.09–208.56
≥ 90	241	6.9	27	7.5	4.73	0.08–274.36
Calendar year (year of index date)						
2011–2012 (ref)	126	3.6	13	3.6	NA	NA
2013–2014	901	25.9	94	26.1	NA	NA
2015–2016	1605	46.1	166	46.1	NA	NA
2017–2018	849	24.4	87	24.2	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	1713	49.2	111	30.8	NA	NA
1	1006	28.9	115	31.9	2.03	1.53–2.71
≥ 2	762	21.9	134	37.2	3.24	2.43–4.32
Obesity diagnosis [c]						
No (ref)	2174	62.5	235	65.3	NA	NA
Yes	1307	37.5	125	34.7	0.86	0.68–1.09
Diagnosis indicating alcohol abuse [c]						
No (ref)	3318	95.3	319	88.6	NA	NA
Yes	163	4.7	41	11.4	2.62	1.81–3.77

Deprivation index of place of residence						
Quintile 1 [d]	951	27.3	93	25.8	0.98	0.71–1.34
Quintile 2	712	20.5	83	23.1	1.18	0.85–1.62
Quintile 3 (ref)	806	23.2	85	23.6	NA	NA
Quintile 4	535	15.4	57	15.8	1.06	0.74–1.52
Quintile 5 [e]	447	12.8	40	11.1	0.86	0.58–1.27
Unknown	30	0.9	2	0.6	0.66	0.16–2.83
Polypharmacy [f]						
< 5 (ref)	2550	73.3	248	68.9	NA	NA
5–9	905	26.0	109	30.3	1.25	0.97–1.60
≥ 10	26	0.7	3	0.8	1.24	0.37–4.14

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; ICB, intracranial bleeding; NA, not applicable; OR, odds ratio; ref, reference group; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 84: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with intracranial bleeding – VTE-T without recent history of cancer at start date

	Controls N = 3481		Cases of ICB N = 360			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	94	2.7	106	29.4	14.98	10.85–20.69
GI bleeding	633	18.2	78	21.7	1.27	0.97–1.65
UG bleeding	734	21.1	86	23.9	1.20	0.92–1.56
Coronary artery disease	1364	39.2	167	46.4	1.41	1.13–1.78
Myocardial infarction	362	10.4	41	11.4	1.13	0.80–1.59
Heart failure	1322	38.0	156	43.3	1.28	1.01–1.62
Ischemic stroke	365	10.5	75	20.8	2.31	1.74–3.05
Transient ischemic attack	312	9.0	54	15.0	1.84	1.33–2.53
Atrial fibrillation	227	6.5	34	9.4	1.47	1.00–2.17
Renal failure	956	27.5	108	30.0	1.17	0.91–1.51
Depression	1651	47.4	196	54.4	1.36	1.08–1.70
Hypertension	2921	83.9	316	87.8	1.49	1.04–2.14
Hyperlipidemia	2361	67.8	244	67.8	1.01	0.80–1.29
Diabetes	1138	32.7	118	32.8	1.00	0.79–1.27
Asthma	658	18.9	73	20.3	1.10	0.84–1.45
COPD	903	25.9	112	31.1	1.29	1.01–1.64
Cancer	632	18.2	75	20.8	1.23	0.93–1.62

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; ICB, intracranial bleeding; OR, odds ratio; UG, urogenital; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 85: Current use [a] of medications among cases [b] and controls and association with intracranial bleeding – VTE-T without recent history of cancer at start date

	Controls N = 3481		Cases of ICB N = 360			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	226	6.5	32	8.9	1.42	0.96–2.10
Parenteral anticoagulants	144	4.1	29	8.1	2.15	1.39–3.33
Other oral anticoagulants	102	2.9	6	1.7	0.56	0.24–1.29
Proton pump inhibitors	1146	32.9	134	37.2	1.22	0.97–1.54
NSAIDs	197	5.7	26	7.2	1.30	0.84–1.99
SSRIs	162	4.7	26	7.2	1.64	1.06–2.52
Oral steroids	181	5.2	18	5.0	0.96	0.58–1.58
Antibiotics	85	2.4	12	3.3	1.32	0.71–2.45
Lipid-lowering medications	577	16.6	64	17.8	1.11	0.83–1.48

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the respective drug in the year before

CI, confidence interval; ICB, intracranial bleeding; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 86: Relative risk of intracranial bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – VTE-T without recent history of cancer at start date

	Controls N = 3481		Cases of ICB [a] N = 360		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	891	25.6	62	17.2	NA	NA	NA	NA
Current use (0–30 days before index date)	965	27.7	111	30.8	1.92	1.34–2.74	1.73	1.16–2.58
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	264	7.6	32	8.9	2.01	1.25–3.24	1.45	0.81–2.61
20 mg	701	20.1	79	21.9	1.88	1.29–2.75	1.85	1.20–2.85
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	0	0.0	0	0.0	NA	NA	NA	NA
10 mg	19	0.5	5	1.4	3.90	1.39–10.95	3.20	0.99–10.35
15 mg	243	7.0	32	8.9	2.17	1.34–3.51	1.71	0.99–2.94
20 mg	667	19.2	69	19.2	1.73	1.17–2.55	1.64	1.06–2.54
Combination 15 + 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
multiple	36	1.0	5	1.4	2.80	0.97–8.10	3.00	0.87–10.38
Event date during first treatment episode								
Yes	627	18.0	65	18.1	1.75	1.16–2.65	1.50	0.94–2.39
No	338	9.7	46	12.8	2.12	1.40–3.21	1.99	1.26–3.15
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	63	1.8	8	2.2	3.17	0.93–10.77	2.34	0.63–8.78
31–180	218	6.3	23	6.4	2.24	1.17–4.30	1.88	0.92–3.85
> 180	346	9.9	34	9.4	1.52	0.95–2.43	1.31	0.77–2.23
SOC recency								
Nonuse (ref)	891	25.6	62	17.2	NA	NA	NA	NA
Current use (0–30 days before index date)	740	21.3	109	30.3	2.50	1.74–3.59	2.42	1.62–3.61
Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	64	1.8	7	1.9	2.01	0.60–6.76	2.39	0.63–9.09
31–180	214	6.1	25	6.9	2.26	1.16–4.39	2.30	1.11–4.79
> 180	349	10.0	50	13.9	2.19	1.45–3.33	2.13	1.34–3.39

a: Cases ascertained during complete follow-up period

b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report.
d: If event date during treatment episode
CI, confidence interval; ICB, intracranial bleeding; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 87: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with gastrointestinal bleeding – SPAF cohort at start date

	Controls N = 97,347		Cases of GI bleeding N = 9769			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	49,346	50.7	4949	50.7	NA	NA
Female	48,001	49.3	4820	49.3	NA	NA
Age at index date						
≤ 49 (ref)	256	0.3	30	0.3	NA	NA
≥ 50–≤ 59	1820	1.9	182	1.9	1.80	0.42–7.70
≥ 60–≤ 69	8729	9.0	880	9.0	2.25	0.48–10.50
≥ 70–≤ 79	37,279	38.3	3704	37.9	2.24	0.47–10.64
≥ 80–≤ 89	40,639	41.7	4080	41.8	2.52	0.53–12.04
≥ 90	8624	8.9	893	9.1	2.80	0.58–13.52
Calendar year (year of index date)						
2011–2012 (ref)	5233	5.4	527	5.4	NA	NA
2013–2014	29,364	30.2	2945	30.1	NA	NA
2015–2016	43,287	44.5	4339	44.4	NA	NA
2017–2018	19,463	20.0	1958	20.0	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	42,443	43.6	2555	26.2	NA	NA
1	29,080	29.9	2683	27.5	1.67	1.58–1.77
≥ 2	25,824	26.5	4531	46.4	3.24	3.08–3.42
Obesity diagnosis [c]						
No (ref)	60,281	61.9	5448	55.8	NA	NA
Yes	37,066	38.1	4321	44.2	1.30	1.25–1.36
Diagnosis indicating alcohol abuse [c]						
No (ref)	92,100	94.6	8682	88.9	NA	NA
Yes	5247	5.4	1087	11.1	2.26	2.11–2.43

Deprivation index of place of residence						
Quintile 1 [d]	25,014	25.7	2565	26.3	1.02	0.96–1.09
Quintile 2	20,273	20.8	1990	20.4	0.98	0.92–1.04
Quintile 3 (ref)	23,146	23.8	2334	23.9	NA	NA
Quintile 4	15,526	15.9	1577	16.1	1.01	0.95–1.08
Quintile 5 [e]	12,819	13.2	1248	12.8	0.97	0.90–1.04
Unknown	569	0.6	55	0.6	0.96	0.73–1.27
Polypharmacy [f]						
< 5 (ref)	67,163	69.0	5223	53.5	NA	NA
5–9	29,106	29.9	4289	43.9	1.94	1.86–2.03
≥ 10	1078	1.1	257	2.6	3.20	2.78–3.68

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; GI, gastrointestinal; NA, not applicable; OR, odds ratio; ref, reference group; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 88: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with gastrointestinal bleeding – SPAF cohort at start date

	Controls N = 97,347		Cases of GI bleeding N = 9769			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	3497	3.6	442	4.5	1.27	1.15–1.41
GI bleeding	18,188	18.7	4712	48.2	4.08	3.90–4.26
UG bleeding	21,989	22.6	2447	25.0	1.15	1.09–1.20
Coronary artery disease	61,645	63.3	6958	71.2	1.45	1.38–1.52
Myocardial infarction	18,170	18.7	2552	26.1	1.56	1.48–1.64
Heart failure	57,309	58.9	7106	72.7	1.92	1.84–2.02
Ischemic stroke	18,937	19.5	2248	23.0	1.24	1.18–1.30
Transient ischemic attack	13,547	13.9	1408	14.4	1.04	0.98–1.11
DVT/PE	7662	7.9	941	9.6	1.25	1.16–1.34
Renal failure	33,348	34.3	4780	48.9	1.90	1.82–1.99
Depression	43,469	44.7	4905	50.2	1.27	1.22–1.32
Hypertension	93,632	96.2	9577	98.0	2.02	1.75–2.35
Hyperlipidemia	72,723	74.7	7553	77.3	1.16	1.10–1.22
Diabetes	41,268	42.4	4850	49.6	1.35	1.29–1.41
Asthma	15,809	16.2	1799	18.4	1.16	1.10–1.23
COPD	26,908	27.6	3513	36.0	1.48	1.41–1.54
Cancer	31,401	32.3	3649	37.4	1.26	1.21–1.32
Risk scores: CHA_2DS_2VASc score at index date						
0 –1(ref)	1406	1.4	77	0.8	NA	NA
2	3844	3.9	188	1.9	1.23	0.93–1.64
3	9333	9.6	640	6.6	2.22	1.70–2.90
4	16,232	16.7	1262	12.9	2.90	2.22–3.79
5	20,856	21.4	1982	20.3	3.86	2.96–5.05
≥ 6	45,676	46.9	5620	57.5	5.39	4.13–7.03

Risk scores: HAS-BLED score at index date						
0 –1 (ref)	2675	2.7	70	0.7	NA	NA
2	14,441	14.8	570	5.8	2.34	1.80–3.04
3	29,569	30.4	2029	20.8	4.55	3.51–5.88
≥ 4	50,662	52.0	7100	72.7	9.69	7.50–12.53

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; NA, not applicable; OR, odds ratio; ref, reference group; PE, pulmonary embolism; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

Annex 2.2 Table 89: Current use [a] of medications among cases [b] and controls and association with gastrointestinal bleeding – SPAF cohort at start date

	Controls N = 97,347		Cases of GI bleeding N = 9769			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	7583	7.8	1597	16.3	2.37	2.23–2.51
Parenteral anticoagulants	3809	3.9	852	8.7	2.47	2.28–2.68
Other oral anticoagulants	4843	5.0	534	5.5	1.11	1.01–1.21
Proton pump inhibitors	31,424	32.3	4707	48.2	1.97	1.89–2.05
NSAIDs	4459	4.6	912	9.3	2.15	1.99–2.32
SSRIs	3111	3.2	468	4.8	1.53	1.38–1.69
Oral steroids	3736	3.8	736	7.5	2.05	1.88–2.22
Antibiotics	1848	1.9	403	4.1	2.22	1.99–2.48
Lipid-lowering medications	26,197	26.9	2959	30.3	1.19	1.13–1.24

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the drug in the year before

CI, confidence interval; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SPAF, stroke prevention in nonvalvular atrial fibrillation; SSRI, selective serotonin reuptake inhibitor

Annex 2.2 Table 90: Relative risk of gastrointestinal bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – SPAF cohort at start date

	Controls N = 97,347		Cases of GI bleeding [a] N = 9769		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	9350	9.6	739	7.6	NA	NA	NA	NA
Current use (0–30 days before index date)	40,734	41.8	4508	46.1	1.47	1.35–1.61	1.72	1.57–1.88
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	13,712	14.1	2143	21.9	2.08	1.90–2.28	1.71	1.54–1.89
20 mg	27,022	27.8	2365	24.2	1.15	1.05–1.26	1.73	1.57–1.91
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	10	0.0	0	0.0	NA	NA	NA	NA
10 mg	1103	1.1	157	1.6	1.94	1.61–2.34	1.79	1.47–2.18
15 mg	15,208	15.6	1929	19.7	1.71	1.56–1.88	1.73	1.56–1.90
20 mg	24,345	25.0	2409	24.7	1.31	1.20–1.43	1.71	1.55–1.88
Combination 15 + 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
multiple	68	0.1	13	0.1	2.69	1.47–4.91	2.39	1.26–4.52
Event date during first treatment episode								
Yes	28,099	28.9	2842	29.1	1.31	1.20–1.44	1.62	1.47–1.78
No	12,635	13.0	1666	17.1	1.69	1.54–1.86	1.84	1.67–2.03
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	4111	4.2	399	4.1	1.24	1.04–1.48	1.47	1.22–1.78
31–180	8149	8.4	802	8.2	1.26	1.10–1.43	1.50	1.31–1.73
> 180	15,839	16.3	1641	16.8	1.34	1.22–1.47	1.66	1.50–1.83
SOC recency								
Nonuse (ref)	9350	9.6	739	7.6	NA	NA	NA	NA
Current use (0–30 days before index date)	27,757	28.5	2500	25.6	1.19	1.09–1.30	1.43	1.30–1.57
Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	3172	3.3	299	3.1	1.45	1.21–1.73	1.59	1.32–1.91
31–180	5884	6.0	505	5.2	1.21	1.06–1.40	1.46	1.26–1.69
> 180	14,575	15.0	1110	11.4	0.97	0.88–1.08	1.26	1.14–1.40

a: Cases ascertained during complete follow-up period

b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report
d: If event date during treatment episode
CI, confidence interval; GI, gastrointestinal; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 91: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with gastrointestinal bleeding – VTE-T without recent history of cancer at start date

	Controls N = 10,484		Cases of GI bleeding N = 1080			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	3933	37.5	407	37.7	NA	NA
Female	6551	62.5	673	62.3	NA	NA
Age at index date						
≤ 49 (ref)	572	5.5	59	5.5	NA	NA
≥ 50–≤ 59	838	8.0	89	8.2	2.11	0.53–8.37
≥ 60–≤ 69	1246	11.9	128	11.9	2.96	0.52–16.88
≥ 70–≤ 79	3455	33.0	356	33.0	3.41	0.50–23.35
≥ 80–≤ 89	3491	33.3	355	32.9	2.83	0.39–20.80
≥ 90	882	8.4	93	8.6	2.53	0.32–20.19
Calendar year (year of index date)						
2011–2012 (ref)	637	6.1	66	6.1	NA	NA
2013–2014	3116	29.7	321	29.7	NA	NA
2015–2016	4605	43.9	475	44.0	NA	NA
2017–2018	2126	20.3	218	20.2	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	4685	44.7	279	25.8	NA	NA
1	3344	31.9	315	29.2	1.95	1.63–2.33
≥ 2	2455	23.4	486	45.0	4.23	3.57–5.03
Obesity diagnosis [c]						
No (ref)	6484	61.8	619	57.3	NA	NA
Yes	4000	38.2	461	42.7	1.22	1.07–1.39
Diagnosis indicating alcohol abuse [c]						
No (ref)	10,003	95.4	972	90.0	NA	NA
Yes	481	4.6	108	10.0	2.33	1.86–2.91

Deprivation index of place of residence						
Quintile 1 [d]	2759	26.3	296	27.4	1.17	0.98–1.41
Quintile 2	2202	21.0	218	20.2	1.08	0.89–1.32
Quintile 3 (ref)	2453	23.4	237	21.9	NA	NA
Quintile 4	1604	15.3	178	16.5	1.21	0.98–1.48
Quintile 5 [e]	1384	13.2	146	13.5	1.10	0.88–1.36
Unknown	82	0.8	5	0.5	0.64	0.26–1.61
Polypharmacy [f]						
< 5 (ref)	7593	72.4	641	59.4	NA	NA
5–9	2815	26.9	421	39.0	1.84	1.61–2.11
≥ 10	76	0.7	18	1.7	3.00	1.77–5.08

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; GI, gastrointestinal; NA, not applicable; OR, odds ratio; ref, reference group; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 92: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with gastrointestinal bleeding – VTE-T without recent history of cancer at start date

	Controls N = 10,484		Cases of GI bleeding N = 1080			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	294	2.8	41	3.8	1.36	0.98–1.90
GI bleeding	1798	17.1	503	46.6	4.34	3.80–4.96
UG bleeding	2255	21.5	255	23.6	1.13	0.97–1.32
Coronary artery disease	4243	40.5	535	49.5	1.50	1.31–1.71
Myocardial infarction	1068	10.2	173	16.0	1.71	1.43–2.04
Heart failure	3998	38.1	546	50.6	1.82	1.59–2.09
Ischemic stroke	1040	9.9	193	17.9	2.01	1.70–2.39
Transient ischemic attack	918	8.8	144	13.3	1.62	1.34–1.96
Atrial fibrillation	676	6.4	97	9.0	1.45	1.15–1.82
Renal failure	2886	27.5	414	38.3	1.76	1.53–2.02
Depression	5119	48.8	614	56.9	1.41	1.24–1.61
Hypertension	8730	83.3	968	89.6	2.01	1.60–2.52
Hyperlipidemia	7096	67.7	757	70.1	1.16	1.01–1.34
Diabetes	3383	32.3	419	38.8	1.35	1.18–1.54
Asthma	1899	18.1	236	21.9	1.26	1.08–1.46
COPD	2605	24.8	369	34.2	1.58	1.38–1.80
Cancer	1909	18.2	218	20.2	1.14	0.98–1.34

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; OR, odds ratio; UG, urogenital; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 93: Current use [a] of medications among cases [b] and controls and association with gastrointestinal bleeding – VTE-T without recent history of cancer at start date

	Controls N = 10,484		Cases of GI bleeding N = 1080			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	677	6.5	120	11.1	1.82	1.47–2.24
Parenteral anticoagulants	595	5.7	115	10.6	2.18	1.73–2.76
Other oral anticoagulants	197	1.9	29	2.7	1.48	1.00–2.21
Proton pump inhibitors	3635	34.7	553	51.2	2.04	1.80–2.33
NSAIDs	596	5.7	111	10.3	1.90	1.53–2.35
SSRIs	410	3.9	81	7.5	2.02	1.58–2.59
Oral steroids	577	5.5	110	10.2	1.98	1.59–2.45
Antibiotics	203	1.9	49	4.5	2.40	1.74–3.30
Lipid-lowering medications	1736	16.6	212	19.6	1.25	1.06–1.46

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the drug in the year before

CI, confidence interval; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 94: Relative risk of gastrointestinal bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – VTE-T without recent history of cancer at start date

	Controls N = 10,484		Cases of GI bleeding [a] N = 1080		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	2575	24.6	176	16.3	NA	NA	NA	NA
Current use (0–30 days before index date)	3152	30.1	395	36.6	2.42	1.96–2.98	2.24	1.79–2.82
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	875	8.3	152	14.1	3.26	2.54–4.19	2.37	1.77–3.17
20 mg	2277	21.7	243	22.5	2.04	1.63–2.57	2.17	1.69–2.80
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	0	0.0	0	0.0	NA	NA	NA	NA
10 mg	64	0.6	8	0.7	2.30	1.08–4.93	2.23	1.00–4.97
15 mg	861	8.2	141	13.1	3.27	2.52–4.25	2.79	2.10–3.70
20 mg	2044	19.5	227	21.0	2.09	1.67–2.63	2.02	1.58–2.58
Combination 15 + 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
multiple	183	1.7	19	1.8	2.34	1.37–3.99	2.28	1.30–3.99
Event date during first treatment episode								
Yes	2247	21.4	261	24.2	2.34	1.84–2.98	2.28	1.76–2.95
No	905	8.6	134	12.4	2.50	1.96–3.20	2.20	1.69–2.87
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	605	5.8	70	6.5	3.10	1.96–4.91	3.07	1.89–5.00
31–180	821	7.8	78	7.2	1.95	1.34–2.83	1.82	1.22–2.71
> 180	821	7.8	113	10.5	2.36	1.80–3.10	2.32	1.74–3.11
SOC recency								
Nonuse (ref)	2575	24.6	176	16.3	NA	NA	NA	NA
Current use (0–30 days before index date)	2565	24.5	296	27.4	2.18	1.75–2.71	2.24	1.76–2.84
Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	530	5.1	45	4.2	1.68	1.05–2.68	1.55	0.96–2.53
31–180	731	7.0	79	7.3	2.57	1.75–3.77	2.44	1.62–3.68
> 180	955	9.1	114	10.6	1.96	1.51–2.55	2.26	1.71–3.00

a: Cases ascertained during complete follow-up period

b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report.
d: If event date during treatment episode
CI, confidence interval; GI, gastrointestinal; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 95: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with urogenital bleeding – SPAF cohort at start date

	Controls N = 27,604		Cases of UG bleeding N = 2774			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	17,214	62.4	1725	62.2	NA	NA
Female	10,390	37.6	1049	37.8	NA	NA
Age at index date						
≤ 49 (ref)	331	1.2	42	1.5	NA	NA
≥ 50–≤ 59	1117	4.0	111	4.0	0.78	0.23–2.62
≥ 60–≤ 69	2916	10.6	294	10.6	0.88	0.22–3.59
≥ 70–≤ 79	10,892	39.5	1077	38.8	0.84	0.19–3.68
≥ 80–≤ 89	10,449	37.9	1054	38.0	1.01	0.23–4.57
≥ 90	1899	6.9	196	7.1	1.12	0.24–5.30
Calendar year (year of index date)						
2011–2012 (ref)	1195	4.3	121	4.4	NA	NA
2013–2014	7929	28.7	796	28.7	NA	NA
2015–2016	12,102	43.8	1215	43.8	NA	NA
2017–2018	6378	23.1	642	23.1	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	12,367	44.8	669	24.1	NA	NA
1	8085	29.3	834	30.1	2.09	1.88–2.33
≥ 2	7152	25.9	1271	45.8	3.67	3.31–4.07
Obesity diagnosis [c]						
No (ref)	16,971	61.5	1540	55.5	NA	NA
Yes	10,633	38.5	1234	44.5	1.29	1.19–1.40
Diagnosis indicating alcohol abuse [c]						
No (ref)	25,980	94.1	2590	93.4	NA	NA
Yes	1624	5.9	184	6.6	1.14	0.97–1.34

Deprivation index of place of residence						
Quintile 1 [d]	6914	25.0	614	22.1	0.87	0.77–0.97
Quintile 2	5790	21.0	588	21.2	0.99	0.88–1.11
Quintile 3 (ref)	6534	23.7	672	24.2	NA	NA
Quintile 4	4406	16.0	484	17.4	1.07	0.95–1.22
Quintile 5 [e]	3828	13.9	407	14.7	1.04	0.91–1.18
Unknown	132	0.5	9	0.3	0.67	0.34–1.32
Polypharmacy [f]						
< 5 (ref)	19,102	69.2	1393	50.2	NA	NA
5–9	8217	29.8	1259	45.4	2.15	1.98–2.33
≥ 10	285	1.0	122	4.4	6.04	4.84–7.53

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

Annex 2.2 Table 96: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with urogenital bleeding – SPAF cohort at start date

	Controls N = 27,604		Cases of UG bleeding N = 2774			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	1003	3.6	135	4.9	1.36	1.13–1.64
GI bleeding	5505	19.9	664	23.9	1.27	1.16–1.39
UG bleeding	6747	24.4	1930	69.6	7.50	6.87–8.19
Coronary artery disease	17,436	63.2	1903	68.6	1.30	1.19–1.41
Myocardial infarction	5418	19.6	638	23.0	1.23	1.12–1.36
Heart failure	15,728	57.0	1856	66.9	1.58	1.45–1.72
Ischemic stroke	5172	18.7	700	25.2	1.47	1.34–1.61
Transient ischemic attack	3804	13.8	454	16.4	1.23	1.11–1.37
DVT/PE	2024	7.3	231	8.3	1.14	0.99–1.31
Renal failure	9476	34.3	1187	42.8	1.48	1.36–1.61
Depression	11,703	42.4	1344	48.4	1.29	1.19–1.40
Hypertension	26,316	95.3	2698	97.3	1.82	1.43–2.31
Hyperlipidemia	20,441	74.1	2089	75.3	1.08	0.98–1.18
Diabetes	11,453	41.5	1336	48.2	1.32	1.22–1.43
Asthma	4526	16.4	438	15.8	0.95	0.86–1.06
COPD	7758	28.1	838	30.2	1.11	1.02–1.21
Cancer	9150	33.1	1291	46.5	1.80	1.67–1.96
Risk scores: CHA_2DS_2VASc score at index date						
0–1 (ref)	544	2.0	20	0.7	NA	NA
2	1515	5.5	129	4.7	2.80	1.71–4.61
3	3371	12.2	265	9.6	3.08	1.89–5.02
4	4905	17.8	389	14.0	3.43	2.11–5.60
5	5901	21.4	575	20.7	4.52	2.77–7.37
≥ 6	11,368	41.2	1396	50.3	5.99	3.68–9.75
Risk scores: HAS-BLED score at index date						
0–1 (ref)	1119	4.1	26	0.9	NA	NA
2	4352	15.8	223	8.0	3.18	2.09–4.83
3	8000	29.0	697	25.1	6.43	4.26–9.71
≥ 4	14,133	51.2	1828	65.9	10.33	6.84–15.61

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period

c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; NA, not applicable; OR, odds ratio; ref, reference group; PE, pulmonary embolism; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

Annex 2.2 Table 97: Current use [a] of medications among cases [b] and controls and association with urogenital bleeding – SPAF cohort at start date

	Controls N = 27,604		Cases of UG bleeding N = 2774			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	2159	7.8	320	11.5	1.55	1.37–1.76
Parenteral anticoagulants	1095	4.0	616	22.2	7.60	6.78–8.53
Other oral anticoagulants	1436	5.2	157	5.7	1.10	0.92–1.30
Proton pump inhibitors	8659	31.4	1071	38.6	1.38	1.27–1.49
NSAIDs	1272	4.6	120	4.3	0.94	0.77–1.13
SSRIs	783	2.8	137	4.9	1.78	1.48–2.14
Oral steroids	1052	3.8	142	5.1	1.36	1.14–1.63
Antibiotics	499	1.8	261	9.4	5.64	4.82–6.60
Lipid-lowering medications	7650	27.7	820	29.6	1.10	1.01–1.20

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the drug in the year before

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

Annex 2.2 Table 98: Relative risk of urogenital bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – SPAF cohort at start date

	Controls N = 27,604		Cases of UG bleeding [a] N = 2774		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	3044	11.0	223	8.0	NA	NA	NA	NA
Current use (0–30 days before index date)	11,340	41.1	1280	46.1	1.64	1.41–1.92	1.69	1.43–2.00
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	3812	13.8	547	19.7	2.09	1.76–2.48	1.80	1.48–2.18
20 mg	7528	27.3	733	26.4	1.40	1.19–1.65	1.61	1.34–1.94
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	4	0.0	0	0.0	NA	NA	NA	NA
10 mg	278	1.0	40	1.4	2.15	1.49–3.09	2.02	1.35–3.02
15 mg	3784	13.7	491	17.7	1.91	1.60–2.27	1.79	1.48–2.16
20 mg	7257	26.3	744	26.8	1.48	1.26–1.75	1.62	1.35–1.93
Combination 15 + 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
multiple	17	0.1	5	0.2	4.51	1.64–12.36	4.19	1.38–12.74
Event date during first treatment episode								
Yes	7727	28.0	806	29.1	1.49	1.27–1.77	1.61	1.34–1.93
No	3613	13.1	474	17.1	1.83	1.55–2.17	1.79	1.49–2.15
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	1059	3.8	102	3.7	1.34	0.95–1.89	1.33	0.92–1.93
31–180	2253	8.2	232	8.4	1.49	1.17–1.91	1.60	1.22–2.09
> 180	4415	16.0	472	17.0	1.51	1.27–1.79	1.64	1.36–1.98
SOC recency								
Nonuse (ref)	3044	11.0	223	8.0	NA	NA	NA	NA
Current use (0–30 days before index date)	7819	28.3	714	25.7	1.32	1.12–1.55	1.45	1.21–1.73
Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	771	2.8	71	2.6	1.53	1.08–2.17	1.73	1.19–2.52
31–180	1646	6.0	159	5.7	1.62	1.25–2.09	1.85	1.40–2.43
> 180	4233	15.3	329	11.9	1.09	0.91–1.30	1.25	1.03–1.53

a: Cases ascertained during complete follow-up period

b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report
d: If event date during treatment episode
CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

Annex 2.2 Table 99: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with urogenital bleeding – VTE-T without recent history of cancer at start date

	Controls N = 4571		Cases of UG bleeding N = 465			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	1033	22.6	105	22.6	NA	NA
Female	3538	77.4	360	77.4	NA	NA
Age at index date						
≤ 49 (ref)	1716	37.5	177	38.1	NA	NA
≥ 50–≤ 59	892	19.5	89	19.1	0.93	0.47–1.82
≥ 60–≤ 69	511	11.2	51	11.0	1.30	0.21–8.26
≥ 70–≤ 79	631	13.8	63	13.5	2.94	0.25–34.94
≥ 80–≤ 89	719	15.7	73	15.7	4.44	0.30–65.47
≥ 90	102	2.2	12	2.6	6.44	0.26–161.41
Calendar year (year of index date)						
2011–2012 (ref)	291	6.4	30	6.5	NA	NA
2013–2014	1452	31.8	147	31.6	NA	NA
2015–2016	1960	42.9	200	43.0	NA	NA
2017–2018	868	19.0	88	18.9	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	2172	47.5	138	29.7	NA	NA
1	1409	30.8	155	33.3	2.10	1.62–2.73
≥ 2	990	21.7	172	37.0	3.47	2.66–4.51
Obesity diagnosis [c]						
No (ref)	2725	59.6	235	50.5	NA	NA
Yes	1846	40.4	230	49.5	1.44	1.19–1.74
Diagnosis indicating alcohol abuse [c]						
No (ref)	4383	95.9	446	95.9	NA	NA
Yes	188	4.1	19	4.1	1.01	0.62–1.63

Deprivation index of place of residence						
Quintile 1 [d]	1126	24.6	98	21.1	0.94	0.71–1.26
Quintile 2	928	20.3	79	17.0	0.94	0.69–1.27
Quintile 3 (ref)	1118	24.5	104	22.4	NA	NA
Quintile 4	741	16.2	93	20.0	1.36	1.01–1.83
Quintile 5 [e]	635	13.9	87	18.7	1.47	1.08–2.00
Unknown	23	0.5	4	0.9	1.87	0.63–5.54
Polypharmacy [f]						
< 5 (ref)	3425	74.9	294	63.2	NA	NA
5–9	1114	24.4	164	35.3	1.81	1.46–2.23
≥ 10	32	0.7	7	1.5	2.72	1.18–6.24

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; UG, urogenital; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 100: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with urogenital bleeding – VTE-T without recent history of cancer at start date

	Controls N = 4571		Cases of UG bleeding N = 465			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	73	1.6	14	3.0	1.95	1.09–3.49
GI bleeding	616	13.5	70	15.1	1.17	0.89–1.53
UG bleeding	2018	44.1	382	82.2	8.33	6.36–10.90
Coronary artery disease	1050	23.0	126	27.1	1.33	1.04–1.70
Myocardial infarction	243	5.3	24	5.2	0.99	0.63–1.54
Heart failure	971	21.2	117	25.2	1.31	1.03–1.69
Ischemic stroke	254	5.6	35	7.5	1.40	0.96–2.05
Transient ischemic attack	225	4.9	33	7.1	1.53	1.04–2.26
Atrial fibrillation	161	3.5	20	4.3	1.23	0.75–2.03
Renal failure	688	15.1	94	20.2	1.57	1.20–2.06
Depression	2314	50.6	261	56.1	1.27	1.04–1.54
Hypertension	2722	59.5	318	68.4	1.71	1.35–2.17
Hyperlipidemia	2179	47.7	206	44.3	0.85	0.69–1.06
Diabetes	942	20.6	113	24.3	1.26	0.99–1.60
Asthma	921	20.1	113	24.3	1.29	1.03–1.62
COPD	846	18.5	94	20.2	1.12	0.87–1.43
Cancer	548	12.0	95	20.4	1.98	1.54–2.54

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; OR, odds ratio; ref, reference group; UG, urogenital; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 101: Current use [a] of medications among cases [b] and controls and association with urogenital bleeding – VTE-T without recent history of cancer at start date

	Controls N = 4571		Cases of UG bleeding N = 465			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	145	3.2	22	4.7	1.54	0.96–2.48
Parenteral anticoagulants	319	7.0	97	20.9	4.39	3.32–5.82
Other oral anticoagulants	72	1.6	9	1.9	1.23	0.61–2.49
Proton pump inhibitors	1199	26.2	161	34.6	1.54	1.25–1.90
NSAIDs	282	6.2	27	5.8	0.94	0.62–1.41
SSRIs	214	4.7	28	6.0	1.32	0.88–1.98
Oral steroids	231	5.1	28	6.0	1.22	0.81–1.84
Antibiotics	82	1.8	28	6.0	3.46	2.22–5.38
Lipid-lowering medications	448	9.8	40	8.6	0.87	0.61–1.23

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the drug in the year before

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; UG, urogenital; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 102: Relative risk of urogenital bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – VTE-T without recent history of cancer at start date

	Controls N = 4571		Cases of UG bleeding [a] N = 465		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	1046	22.9	70	15.1	NA	NA	NA	NA
Current use (0–30 days before index date)	1415	31.0	210	45.2	3.55	2.51–5.03	3.02	2.07–4.41
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	222	4.9	37	8.0	3.63	2.27–5.80	2.06	1.16–3.67
20 mg	1193	26.1	173	37.2	3.53	2.47–5.06	3.33	2.25–4.94
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	1	0.0	0	0.0	NA	NA	NA	NA
10 mg	25	0.5	3	0.6	2.97	0.85–10.34	3.18	0.83–12.27
15 mg	318	7.0	53	11.4	4.25	2.71–6.66	3.28	2.00–5.38
20 mg	953	20.8	140	30.1	3.38	2.35–4.84	2.95	2.00–4.36
Combination 15 + 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
multiple	118	2.6	14	3.0	3.63	1.85–7.15	3.04	1.48–6.27
Event date during first treatment episode								
Yes	1095	24.0	152	32.7	3.57	2.43–5.23	3.19	2.10–4.84
No	320	7.0	58	12.5	3.54	2.37–5.27	2.83	1.83–4.38
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	309	6.8	42	9.0	6.51	3.04–13.95	5.85	2.55–13.39
31–180	443	9.7	50	10.8	2.92	1.70–5.02	2.56	1.43–4.57
> 180	343	7.5	60	12.9	3.48	2.27–5.34	3.17	1.99–5.04
SOC recency								
Nonuse (ref)	1046	22.9	70	15.1	NA	NA	NA	NA
Current use (0–30 days before index date)	1085	23.7	108	23.2	2.22	1.54–3.20	1.79	1.20–2.68
Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	227	5.0	14	3.0	1.32	0.61–2.85	0.99	0.43–2.27
31–180	391	8.6	28	6.0	1.60	0.88–2.90	1.19	0.63–2.24
> 180	329	7.2	44	9.5	2.38	1.56–3.64	2.20	1.39–3.48

a: Cases ascertained during complete follow-up period

b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report.
d: If event date during treatment episode
CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; UG, urogenital; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 103: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with other bleeding – SPAF cohort at start date

	Controls N = 49,129		Cases of other bleeding N = 4924			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	25,963	52.8	2600	52.8	NA	NA
Female	23,166	47.2	2324	47.2	NA	NA
Age at index date						
≤ 49 (ref)	202	0.4	24	0.5	NA	NA
≥ 50–≤ 59	1172	2.4	119	2.4	0.85	0.13–5.49
≥ 60–≤ 69	5839	11.9	578	11.7	0.74	0.10–5.34
≥ 70–≤ 79	20,827	42.4	2068	42.0	0.83	0.11–6.13
≥ 80–≤ 89	18,035	36.7	1804	36.6	0.99	0.13–7.35
≥ 90	3054	6.2	331	6.7	1.58	0.21–11.98
Calendar year (year of index date)						
2011–2012 (ref)	3258	6.6	327	6.6	NA	NA
2013–2014	15,783	32.1	1582	32.1	NA	NA
2015–2016	21,402	43.6	2146	43.6	NA	NA
2017–2018	8686	17.7	869	17.6	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	21,132	43.0	1351	27.4	NA	NA
1	14,579	29.7	1391	28.2	1.61	1.48–1.74
≥ 2	13,418	27.3	2182	44.3	2.78	2.58–3.00
Obesity diagnosis [c]						
No (ref)	29,748	60.6	2760	56.1	NA	NA
Yes	19,381	39.4	2164	43.9	1.21	1.14–1.29
Diagnosis indicating alcohol abuse [c]						
No (ref)	46,325	94.3	4483	91.0	NA	NA
Yes	2804	5.7	441	9.0	1.65	1.48–1.84
Deprivation index of place of residence						
Quintile 1 [d]	12,377	25.2	1113	22.6	0.91	0.83–0.99
Quintile 2	10,126	20.6	1030	20.9	1.03	0.94–1.12
Quintile 3 (ref)	11,646	23.7	1154	23.4	NA	NA
Quintile 4	7991	16.3	831	16.9	1.05	0.96–1.15
Quintile 5 [e]	6729	13.7	756	15.4	1.14	1.03–1.25
Unknown	260	0.5	40	0.8	1.56	1.11–2.18

Polypharmacy [f]						
< 5	33,820	68.8	2613	53.1	NA	NA
5–9	14,709	29.9	2193	44.5	1.97	1.85–2.09
≥ 10	600	1.2	118	2.4	2.61	2.13–3.20

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 104: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with other bleeding – SPAF cohort at start date

	Controls N = 49,129		Cases of other bleeding N = 4924			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	1803	3.7	205	4.2	1.14	0.99–1.32
GI bleeding	9723	19.8	1304	26.5	1.47	1.37–1.57
UG bleeding	11,003	22.4	1266	25.7	1.20	1.12–1.28
Coronary artery disease	30,953	63.0	3450	70.1	1.39	1.30–1.48
Myocardial infarction	8948	18.2	1195	24.3	1.45	1.36–1.56
Heart failure	28,127	57.3	3382	68.7	1.68	1.58–1.80
Ischemic stroke	9168	18.7	974	19.8	1.08	1.00–1.16
Transient ischemic attack	6521	13.3	667	13.5	1.02	0.94–1.12
DVT/PE	3818	7.8	444	9.0	1.18	1.06–1.30
Renal failure	15,944	32.5	2155	43.8	1.67	1.57–1.77
Depression	21,763	44.3	2388	48.5	1.20	1.13–1.27
Hypertension	47,056	95.8	4824	98.0	2.16	1.76–2.65
Hyperlipidemia	36,640	74.6	3816	77.5	1.18	1.10–1.26
Diabetes	20,597	41.9	2321	47.1	1.24	1.17–1.32
Asthma	7933	16.1	941	19.1	1.23	1.14–1.32
COPD	13,417	27.3	1632	33.1	1.32	1.24–1.41
Cancer	15,604	31.8	1793	36.4	1.24	1.17–1.32
Risk scores: CHA_2DS_2VASc score at index date						
0–1 (ref)	991	2.0	46	0.9	NA	NA
2	2465	5.0	159	3.2	1.81	1.28–2.57
3	5331	10.9	391	7.9	2.47	1.76–3.46
4	8490	17.3	752	15.3	3.36	2.40–4.70
5	10,329	21.0	1070	21.7	4.21	3.00–5.89
≥ 6	21,523	43.8	2506	50.9	5.00	3.58–7.00
Risk scores: HAS-BLED score at index date						
0–1 (ref)	1667	3.4	51	1.0	NA	NA
2	7819	15.9	350	7.1	2.07	1.52–2.82
3	14,879	30.3	1191	24.2	4.07	3.01–5.50
≥ 4	24,764	50.4	3332	67.7	7.13	5.29–9.62

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period

c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; GI, gastrointestinal; NA, not applicable; OR, odds ratio; ref, reference group; PE, pulmonary embolism; SPAF, stroke prevention in nonvalvular atrial fibrillation; UG, urogenital

Annex 2.2 Table 105: Current use [a] of medications among cases [b] and controls and association with other bleeding – SPAF cohort at start date

	Controls N = 49,129		Cases of other bleeding N = 4924			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	3838	7.8	751	15.3	2.18	2.00–2.38
Parenteral anticoagulants	2002	4.1	542	11.0	3.08	2.77–3.41
Other oral anticoagulants	2299	4.7	181	3.7	0.77	0.66–0.90
Proton pump inhibitors	15,814	32.2	2111	42.9	1.59	1.50–1.69
NSAIDs	2398	4.9	355	7.2	1.52	1.35–1.70
SSRIs	1505	3.1	154	3.1	1.02	0.86–1.21
Oral steroids	1832	3.7	278	5.6	1.55	1.36–1.76
Antibiotics	856	1.7	248	5.0	2.97	2.57–3.43
Lipid-lowering medications	13,321	27.1	1554	31.6	1.24	1.17–1.33

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the drug in the year before

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 106: Relative risk of other bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – SPAF cohort at start date

	Controls N = 49,129		Cases of other bleeding [a] N = 4924		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	4689	9.5	250	5.1	NA	NA	NA	NA
Current use (0–30 days before index date)	20,172	41.1	1782	36.2	1.79	1.55–2.06	1.92	1.66–2.22
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	6417	13.1	727	14.8	2.28	1.95–2.65	1.77	1.51–2.08
20 mg	13,755	28.0	1055	21.4	1.55	1.34–1.80	2.05	1.75–2.39
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	10	0.0	0	0.0	NA	NA	NA	NA
10 mg	517	1.1	47	1.0	1.89	1.36–2.63	1.73	1.24–2.42
15 mg	6824	13.9	713	14.5	2.12	1.81–2.47	2.02	1.73–2.36
20 mg	12,779	26.0	1018	20.7	1.61	1.39–1.86	1.86	1.60–2.17
Combination 15 + 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
multiple	42	0.1	4	0.1	2.10	0.75–5.93	2.01	0.70–5.78
Event date during first treatment episode								
Yes	13,962	28.4	1156	23.5	1.68	1.45–1.95	1.89	1.62–2.20
No	6210	12.6	626	12.7	1.95	1.68–2.28	1.96	1.68–2.29
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	2091	4.3	164	3.3	1.71	1.32–2.20	1.91	1.47–2.48
31–180	4088	8.3	318	6.5	1.62	1.32–1.97	1.74	1.42–2.14
> 180	7783	15.8	674	13.7	1.69	1.45–1.97	1.93	1.65–2.26
SOC recency								
Nonuse (ref)	4689	9.5	250	5.1	NA	NA	NA	NA
Current use (0–30 days before index date)	14,479	29.5	1867	37.9	2.66	2.31–3.07	2.84	2.46–3.28

Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	1710	3.5	219	4.4	3.35	2.60–4.32	3.29	2.54–4.26
31–180	3177	6.5	380	7.7	2.81	2.30–3.43	3.01	2.46–3.69
> 180	7523	15.3	861	17.5	2.24	1.93–2.60	2.53	2.17–2.95

a: Cases ascertained during complete follow-up period
b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report
d: If event date during treatment episode
CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; SPAF, stroke prevention in nonvalvular atrial fibrillation

Annex 2.2 Table 107: Demographics, lifestyle factors and healthcare utilization prior to or on the index date among cases [a] and controls and association with other bleeding – VTE-T without recent history of cancer at start date

	Controls N = 5065		Cases of other bleeding N = 520			
	n	%	n	%	OR [b]	95% CI
Sex						
Male (ref)	2110	41.7	218	41.9	NA	NA
Female	2955	58.3	302	58.1	NA	NA
Age at index date						
≤ 49 (ref)	438	8.6	45	8.7	NA	NA
≥ 50–≤ 59	594	11.7	61	11.7	1.59	0.25–9.93
≥ 60–≤ 69	736	14.5	73	14.0	2.01	0.20–20.41
≥ 70–≤ 79	1733	34.2	180	34.6	2.91	0.25–34.36
≥ 80–≤ 89	1308	25.8	134	25.8	2.08	0.15–27.93
≥ 90	256	5.1	27	5.2	2.17	0.14–34.49
Calendar year (year of index date)						
2011–2012 (ref)	453	8.9	47	9.0	NA	NA
2013–2014	1831	36.2	190	36.5	NA	NA
2015–2016	1959	38.7	200	38.5	NA	NA
2017–2018	822	16.2	83	16.0	NA	NA
Hospitalization in the 1 year prior to index date						
None (ref)	2136	42.2	132	25.4	NA	NA
1	1695	33.5	168	32.3	1.88	1.46–2.42
≥ 2	1234	24.4	220	42.3	3.40	2.66–4.35
Obesity diagnosis [c]						
No (ref)	3137	61.9	283	54.4	NA	NA
Yes	1928	38.1	237	45.6	1.39	1.15–1.67
Diagnosis indicating alcohol abuse [c]						
No (ref)	4817	95.1	468	90.0	NA	NA
Yes	248	4.9	52	10.0	2.23	1.62–3.08
Deprivation index of place of residence						
Quintile 1 [d]	1312	25.9	112	21.5	0.91	0.69–1.21
Quintile 2	1085	21.4	114	21.9	1.12	0.85–1.48
Quintile 3 (ref)	1157	22.8	114	21.9	NA	NA
Quintile 4	841	16.6	110	21.2	1.38	1.05–1.83
Quintile 5 [e]	641	12.7	65	12.5	1.06	0.77–1.46
Unknown	29	0.6	5	1.0	1.83	0.69–4.85

Polypharmacy [f]						
< 5	3631	71.7	305	58.7	NA	NA
5–9	1397	27.6	205	39.4	1.83	1.51–2.22
≥ 10	37	0.7	10	1.9	3.47	1.68–7.18

a: Cases ascertained during complete follow-up period
b: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: Any time prior to index date
d: Lowest degree of deprivation/highest socioeconomic status
e: Highest degree of deprivation/lowest socioeconomic status
f: Number of individual ATC codes; in the year before index date

ATC, Anatomical Therapeutic Chemical (Classification System); CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 108: Comorbidities, past medical events [a] and risk scores among cases and controls among cases [b] and controls and association with other bleeding – VTE-T without recent history of cancer at start date

	Controls N = 5065		Cases of other bleeding N = 520			
	n	%	n	%	OR [c]	95% CI
Medical history any time prior to index date						
Intracranial bleeding	128	2.5	17	3.3	1.26	0.75–2.12
GI bleeding	863	17.0	138	26.5	1.80	1.46–2.23
UG bleeding	1111	21.9	131	25.2	1.25	1.00–1.56
Coronary artery disease	1848	36.5	248	47.7	1.71	1.40–2.07
Myocardial infarction	484	9.6	80	15.4	1.79	1.38–2.34
Heart failure	1589	31.4	232	44.6	1.94	1.59–2.37
Ischemic stroke	467	9.2	62	11.9	1.34	1.01–1.79
Transient ischemic attack	411	8.1	53	10.2	1.29	0.95–1.76
Atrial fibrillation	255	5.0	50	9.6	2.11	1.52–2.94
Renal failure	1162	22.9	192	36.9	2.21	1.79–2.72
Depression	2337	46.1	261	50.2	1.20	1.00–1.45
Hypertension	3983	78.6	436	83.8	1.56	1.18–2.06
Hyperlipidemia	3189	63.0	350	67.3	1.26	1.02–1.54
Diabetes	1528	30.2	192	36.9	1.39	1.14–1.69
Asthma	951	18.8	107	20.6	1.12	0.89–1.40
COPD	1186	23.4	166	31.9	1.56	1.28–1.90
Cancer	809	16.0	102	19.6	1.31	1.03–1.66

a: Based on all the information available in the database prior to index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
CI, confidence interval; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; OR, odds ratio; ref, reference group; UG, urogenital; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 109: Current use [a] of medications among cases [b] and controls and association with other bleeding – VTE-T without recent history of cancer at start date

	Controls N = 5065		Cases of other bleeding N = 520			
	n	%	n	%	OR [c]	95% CI
Medications of interest prescribed/dispensed up to 90 days before or on the start date						
Antiplatelets	293	5.8	56	10.8	2.01	1.48–2.72
Parenteral anticoagulants	361	7.1	85	16.3	3.14	2.35–4.19
Other oral anticoagulants	93	1.8	12	2.3	1.25	0.67–2.31
Proton pump inhibitors	1622	32.0	243	46.7	1.94	1.61–2.34
NSAIDs	323	6.4	48	9.2	1.52	1.10–2.10
SSRIs	169	3.3	23	4.4	1.35	0.86–2.11
Oral steroids	282	5.6	56	10.8	2.04	1.50–2.76
Antibiotics	111	2.2	31	6.0	2.88	1.90–4.35
Lipid-lowering medications	716	14.1	89	17.1	1.27	0.99–1.62

a: Defined as end of supply overlapping the index date
b: Cases ascertained during complete follow-up period
c: OR adjusted for matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date) – the reference category is nonuse of the drug in the year before

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 2.2 Table 110: Relative risk of other bleeding in users of rivaroxaban or SOC associated with recency of use, daily dose and duration of use – VTE-T without recent history of cancer at start date

	Controls N = 5065		Cases of other bleeding [a] N = 520		OR 1 [b]		OR 2 [c]	
	n	%	n	%	OR	95% CI	OR	95% CI
Rivaroxaban recency								
Nonuse (ref)	1033	20.4	46	8.8	NA	NA	NA	NA
Current use (0–30 days before index date)	1610	31.8	150	28.8	3.26	2.23–4.78	3.02	2.03–4.48
Rivaroxaban assumed daily dose among current users (ref = nonuse)								
≤ 10 mg	0	0.0	0	0.0	NA	NA	NA	NA
15 mg	361	7.1	58	11.2	5.33	3.42–8.28	3.51	2.17–5.67
20 mg	1249	24.7	92	17.7	2.56	1.70–3.84	2.76	1.80–4.24
> 20 mg	0	0.0	0	0.0	NA	NA	NA	NA
Rivaroxaban–tablet strength among current users (ref = nonuse)								
2,5 mg	0	0.0	0	0.0	NA	NA	NA	NA
10 mg	35	0.7	3	0.6	3.23	0.95–11.06	2.54	0.71–9.03
15 mg	406	8.0	50	9.6	4.52	2.85–7.17	3.84	2.39–6.18
20 mg	1043	20.6	90	17.3	2.93	1.96–4.39	2.81	1.85–4.27
Combination 15 + 20 mg	1	0.0	0	0.0	NA	NA	NA	NA
multiple	125	2.5	7	1.3	2.16	0.91–5.11	1.89	0.78–4.57
Event date during first treatment episode								
Yes	1204	23.8	101	19.4	3.09	2.04–4.68	3.00	1.95–4.61
No	406	8.0	49	9.4	3.51	2.27–5.44	3.04	1.93–4.79
Time since first dispensing (i.e. cohort entry) among current users of Rivaroxaban (ref = nonuse) [d]								
Up to 30	359	7.1	18	3.5	1.57	0.79–3.13	1.54	0.76–3.14
31–180	493	9.7	29	5.6	1.88	1.05–3.38	1.86	1.02–3.39
> 180	352	6.9	54	10.4	4.59	2.93–7.19	4.41	2.77–7.03
SOC recency								
Nonuse (ref)	1033	20.4	46	8.8	NA	NA	NA	NA
Current use (0–30 days before index date)	1419	28.0	227	43.7	6.00	4.12–8.75	5.85	3.95–8.65

Time since first dispensing (i.e. cohort entry) among current users of SOC (ref = nonuse)								
Up to 30	374	7.4	56	10.8	11.89	6.06–23.31	11.00	5.50–22.00
31–180	441	8.7	57	11.0	5.79	3.37–9.96	4.98	2.85–8.72
> 180	425	8.4	73	14.0	5.03	3.30–7.65	5.19	3.35–8.03

a: Cases ascertained during complete follow-up period
b: OR adjusted by matching variables (age at index date, sex, statutory health insurance provider and calendar year of index date)
c: OR adjusted for the variables specified in the report
d: If event date during treatment episode
CI, confidence interval; NA, not applicable; OR, odds ratio; ref, reference group; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Annex 3 Signature Pages

Signature Page – Principal Investigator

Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
Study type / Study phase	Observational post-authorization safety study (PASS) Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS11145
Medicinal product	Xarelto®
Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

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

Print Name: Dr. Tania Schink

Date, Signature: _____, _____

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Signature Page – OS Conduct Responsible

Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
Study type / Study phase	Observational post-authorization safety study (PASS) Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS11145
Medicinal product	Xarelto®
Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

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

Print Name: Yanina Lenz

Date, Signature: _____, _____

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Signature Page – OS Safety Lead / PV Country Head

Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
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Medicinal product	Xarelto®
Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

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

Print Name: Tomasz Dyszynski

Date, Signature: _____, _____

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Signature Page – OS Medical Expert

Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
Study type / Study phase	Observational post-authorization safety study (PASS) Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS11145
Medicinal product	Xarelto®
Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

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

Print Name: Samuel Fatoba

Date, Signature: _____, _____

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Signature Page – OS Statistician

Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
Study type / Study phase	Observational post-authorization safety study (PASS) Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS11145
Medicinal product	Xarelto®
Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

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

Print Name: Martin Homering

Date, Signature: _____, _____

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Signature Page – OS Epidemiologist

Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
Study type / Study phase	Observational post-authorization safety study (PASS) Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS11145
Medicinal product	Xarelto®
Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

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

Print Name: Gunnar Brobert

Date, Signature: _____, _____

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Signature Page – Regulatory Affairs responsible/MAH contact person

Title	Pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in Germany (EU PAS Register No. ENCePP/SDPP/11145)
Report version and date	V1.0 26 NOV 2020
IMPACT study number	16159
Study type / Study phase	Observational post-authorization safety study (PASS) Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS11145
Medicinal product	Xarelto®
Reference therapy	Phenprocoumon
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

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

Print Name: Christine Tarenz

Date, Signature: _____, _____

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