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

Acronym/Title	Final study report comprising the pharmacoepidemiological study program of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden
Report version and date	V1.0, 26 NOV 2020
IMPACT study number	UK: 16647 Germany: 16159 The Netherlands: 16646 Sweden: 17543
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	UK: EUPAS11299 Germany: EUPAS11145 The Netherlands: EUPAS11141 Sweden: EUPAS9895
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
Reference therapy	UK: warfarin Germany: phenprocoumon The Netherlands: acenocoumarol or phenprocoumon Sweden: warfarin
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany

Research question and objectives	This post-authorization observational study was designed to assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in first-time users of rivaroxaban and first-time users of standard of care (SOC) in routine clinical practice. The primary objectives were: • to provide a description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed 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 or referral to a specialist from primary care for three bleeding events (primary safety outcomes): (a) intracranial hemorrhage, (b) gastrointestinal bleeding and (c) urogenital bleeding among users of rivaroxaban in comparison with individuals receiving current 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 (deep vein thrombosis/pulmonary embolism, 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.
Country(-ies) of study	UK, Germany, Netherlands, Sweden
Author	UK – Principal investigators: PPD PPD *Spain*

Germany – Principal investigator: PPD

PPD

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Netherlands – Principal investigator: PPD

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1. Abstract

Acronym/Title	Final study report comprising the pharmacoepidemiological study program of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden
Report version and date	V1.0, 26 NOV 2020
Authors	UK: PPD Spain Germany: PPD Germany Netherlands: PPD Netherlands Sweden: PPD Sweden
IMPACT study number	UK: 16647 Germany: 16159 The Netherlands: 16646 Sweden: 17543
Keywords	UK, Germany, Sweden, Netherlands, rivaroxaban, vitamin K antagonists, safety, effectiveness, atrial fibrillation, venous thromboembolism, acute coronary syndrome
Rationale and background	Rivaroxaban 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 program 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 standard of care anticoagulants (hereafter referred to as SOC).

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	All patients with incident exposure to rivaroxaban or SOC during the enrollment period.
Subjects and study size, including dropouts	After application of the inclusion and exclusion criteria, the following first-time users of rivaroxaban/SOC were identified in each study. Sweden: rivaroxaban, 58,974; SOC, 121,908 UK: rivaroxaban, 24,953; SOC, 25,346 Germany: rivaroxaban, 265,584; SOC, 172,727 Netherlands (overall): rivaroxaban, 23,670; SOC, 85,112 Netherlands (subcohort with available general practitioner data): rivaroxaban, 5641; SOC, 18,918
Variables and data sources	Detailed descriptive variables were captured relating to demographics, healthcare resource utilization, lifestyle characteristics, mediations, medical history and renal function. The data sources used for these studies included the IQVIA Medical Research Data-UK (IMRD-UK) database in the UK, the German Pharmacoepidemiological Research Database (GePaRD), the PHARMO Database Network in the Netherlands and the Swedish Health Registers.
Results	For SPAF, the majority of patients were prescribed 20 mg once daily, while the remainder were prescribed 15 mg. Almost all patients who received rivaroxaban for TKR/THR were prescribed 10 mg once daily. For VTE-T, patients were predominantly prescribed either 15 mg or 20 mg, with 15 mg being more common than 20 mg in Sweden, the Netherlands and Germany. In the ACS cohort, which was very limited in size across all studies, few patients were prescribed the 2.5 mg tablet. For SPAF, unadjusted incidence rates of intracranial and other bleeding were lower for rivaroxaban users than SOC users, whereas unadjusted incidence rates of gastrointestinal bleeding and urogenital bleeding were higher, although there were some minor deviations from this trend in the individual countries. For VTE-T, unadjusted incidence rates of intracranial and other bleeding were lower for rivaroxaban users than SOC users in Sweden and Germany, but unadjusted incidence rates of urogenital bleeding were higher. Unadjusted incidence rates of gastrointestinal bleeding

	were higher among rivaroxaban users than SOC users in all countries. There were few bleeding events among rivaroxaban users for the ACS indication. In the nested case-control analysis, current use of rivaroxaban for SPAF was associated with a similar risk of intracranial bleeding and urogenital bleeding as nonuse in the UK, the Netherlands and Sweden. Current use of rivaroxaban was associated with a higher risk of gastrointestinal bleeding relative to nonuse in all countries except Sweden. Current use of rivaroxaban was associated with a higher risk of other bleeding relative to nonuse in Germany and the UK, but not in the Netherlands or Sweden. For VTE-T, current use of rivaroxaban conferred a similar risk of intracranial bleeding as nonuse in Sweden or the UK, but a higher risk in Germany. Current use of rivaroxaban was associated with a higher risk of gastrointestinal bleeding relative to nonuse in all countries except the Netherlands. Current use of rivaroxaban was associated with a higher risk of urogenital and other bleeding relative to nonuse in Germany and Sweden, but not in the UK or the Netherlands.
Discussion	Based on the characteristics of first prescription/dispensation, dose posology (UK, Netherlands) and tablet strengths (Germany, Sweden) were broadly in line with the dose recommendations for each indication except for ACS. 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 for the SOC cohorts in the UK, Sweden and Germany. The safety and effectiveness profile of rivaroxaban for SPAF and VTE-T in these real-world populations 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
Names and affiliations of	UK: PPD

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2. List of abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
ALT	Alanine transaminase
AP	Alkaline phosphatase
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
bid	Twice daily
BMI	Body mass index
CAD	Coronary artery disease
CEIFE	Centre for Pharmacoepidemiological Research
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CYP3A4	Cytochrome P450 3A4
DSD	Data strategy document
DVT	Deep vein thrombosis
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GEP	Good Epidemiological Practice
GePaRD	The German Pharmacoepidemiological Research Database
GFR	Glomerular filtration rate
GI	Gastrointestinal
GP	General practitioner
GPP	Good Pharmacoepidemiology Practice
GPS	Good Practice of Secondary Data Analysis
h/o	History of
ICD	International Classification of Diseases
ICD-10-GM	International Statistical Classification of Diseases and Related Health Problems 10th revision, German Modification
IEC	Independent Ethics Committee
IMRD-UK	IQVIA Medical Research Data-UK

INR	International normalized ratio
ITT	Intent-to-treat
LISA	Longitudinal integrated database for health insurance and labor market studies
MAH	Marketing Authorization Holder
n/a	Not applicable
NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
od	Once daily
OMOP-CDM	Observational Medical Outcomes Partnership Common Data Model
OR	Odds ratio
OS	Observational Study
OTC	Over the counter
PAD	Peripheral artery disease
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCP	Primary care provider
PE	Pulmonary embolism
PG-P	P-glycoprotein
PPI	Proton pump inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Person Responsible for Pharmacovigilance
RCT	Randomized controlled trial
SAP	Statistical Analysis Plan
SHI	Statutory health insurance provider
SOC	Standard of care
SPAF	Prevention of stroke and systemic embolism in nonvalvular atrial fibrillation
SSRI	Selective serotonin reuptake inhibitor
STEMI	ST-elevation myocardial infarction
THIN	The Health Improvement Network
THR	Total hip replacement
TIA	Transient ischemic attack
TKR	Total knee replacement
UG	Urogenital
UNL	Upper limit of normal

UK	United Kingdom
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
VTE-T	Treatment and secondary prevention of venous thromboembolism
WHO	World Health Organization

3. Investigators

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4. Other responsible parties

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Contact details of the responsible parties are available upon request.

5. Milestones

Table 5–1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection [a]	UK: Q4 2011	01 JAN 2012	
	Germany: Q1 2012	09 DEC 2011	
	Netherlands: Q1 2012	09 DEC 2011	
	Sweden: Q4 2011	09 DEC 2011	
End of data collection [a]	31 DEC 2018	31 DEC 2018 (UK, Sweden, Netherlands) 31 Dec 2017 (Germany)	
Registration in the EU PAS register	After PRAC approval	UK: 01 OCT 2015	
		Germany: 30 SEP 2015	
		Netherlands: 01 OCT 2015	
		Sweden: 01 OCT 2015	
Study progress reports	NOV 2014–2019	NOV 2014–2019	
Interim report 1	Q4 2015	Q4 2015	Data collection until 31 DEC 2013 (Germany, the Netherlands) or 02 SEP 2014 (Sweden, UK)
Interim report 2	Q4 2017	Q4 2017	Data collection until 31 MAY 2015 (UK), 31 DEC 2014 (Germany), 31 DEC 2015 (The Netherlands) or 31 DEC 2016 (Sweden)
Final report of study results	Q4 2020	Q4 2020	Data collection until 31 DEC 2017 (Germany) or 31 DEC 2018 (UK, Sweden, Netherlands)

a: Dates relate to the study period within each of the secondary data sources
EU PAS, European Union Post-Authorisation Studies; PRAC, Pharmacovigilance Risk Assessment Committee

6. Rationale and background

Rivaroxaban, a direct factor Xa inhibitor, is licensed for multiple indications (1).

- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective knee replacement (TKR) surgery or hip replacement (THR) surgery; hereafter referred to as TKR/THR. The recommended dose is 10 mg once daily (od) for 35 days following THR surgery and 14 days following TKR surgery.
- The treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients; hereafter referred to as VTE-T. The recommended dose is 15 mg rivaroxaban 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 of 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack (TIA); hereafter referred to as SPAF. 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).
- Coadministered 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; hereafter referred to as ACS. The recommended dose is rivaroxaban 2.5 mg bid.
- Coadministered with ASA for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) 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 on 23 AUG 2018 and is therefore outside the enrollment period of this study.

Consistent with other oral anticoagulants, clinical studies of rivaroxaban identified hemorrhage as an important safety outcome (2–8). In randomized controlled trials, rivaroxaban demonstrated superior or noninferior efficacy to standard therapy for each indication and had an acceptable safety profile (2–8). In patients with VTE, rivaroxaban was associated with a lower rate of major bleeding than in those who received enoxaparin followed by warfarin or acenocoumarol (8). Overall rates of major bleeding were similar for rivaroxaban and warfarin in patients with AF; however, rivaroxaban was associated with a higher rate of gastrointestinal bleeding and a lower rate of intracranial and fatal bleeding than warfarin (4). In patients with ACS, the addition of rivaroxaban to dual antiplatelet therapy increased the rate of major bleeding and intracranial hemorrhage, but did not increase the risk of fatal bleeding, compared with dual antiplatelet therapy alone (6).

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 four studies conducted in parallel with common objectives; individual reports for each study can be found in Annex 2.1 Individual study reports.

7. Research question and objectives

These studies 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 prescribed or dispensed oral rivaroxaban for the first time in comparison with those who are prescribed SOC for the first time, and to 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, (a) intracranial hemorrhage, (b) gastrointestinal bleeding and (c) urogenital bleeding, among users of rivaroxaban (for VTE-T, SPAF and ACS) in comparison with individuals receiving current SOC.

7.2 Secondary objectives

- To study the occurrence of hospitalization for bleeding events not specified as primary safety outcomes ("other bleeding") 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 and myocardial infarction).
- To study all-cause mortality.
- To conduct subgroup analysis of safety and effectiveness outcomes in populations of special interest, including elderly patients, patients with decreased renal function and patients with cardiovascular comorbidities.

8. Amendments and updates

Major amendments occurred owing to label expansion or to enable capture of additional data as requested by the Pharmacovigilance Risk Assessment Committee (PRAC). A detailed description of amendments can be found in Annex 2.1 Individual study reports.

9. Research methods

9.1 Study design

This study used a cohort design to assess patterns of rivaroxaban utilization and to estimate incidences of safety and effectiveness outcomes during the first episode of treatment. The enrollment period began on 09 DEC 2011 (Germany, Netherlands and Sweden) or 01 JAN 2012 (UK) and continued until 31 DEC 2016 (Germany) or 31 DEC 2017 (UK, Netherlands and Sweden). The observation period ended on 31 DEC 2017 (Germany) or 31 DEC 2018 (UK, Netherlands and Sweden). The start date was defined as the date of first prescription or dispensation for rivaroxaban or SOC during the enrollment period. The index date was defined as the date of the outcome of interest, and therefore differed for each outcome.

It was originally planned for the studies to be conducted separately. In order to conduct the analyses in parallel and discuss the results in a comparative manner, as requested by the European Medicines Agency (EMA), a data strategy document was developed to promote harmonization of the analytical approaches used by the studies. However, some differences in the data collection and analysis remain owing to inherent differences in the prescribing environments of the respective countries, as well as the specific characteristics of the data sources.

Some changes from the analytical approaches described in the individual study protocols were agreed by the investigators, owing to the limitations of the data sources.

- Safety and effectiveness outcomes were not directly compared between rivaroxaban users and SOC users because residual confounding, resulting from selective prescribing of rivaroxaban and SOC to different groups of patients, could not be fully eliminated during statistical analyses. There is a lack of detailed information regarding the clinical reasons why rivaroxaban, a new class of drug, may be prescribed over vitamin K antagonists (VKAs), which have been on the market for more than 50 years. Furthermore, several other non-VKA oral anticoagulants (NOACs) became available and were increasingly prescribed over the last several years, so factors influencing the decision to prescribe rivaroxaban or a VKA may have evolved during the course of the study. Any comparative analyses between rivaroxaban and SOC could, therefore, produce misleading results. Consequently, an alternative approach was agreed by all the investigators. The incidence rates of safety and effectiveness outcomes during the first episode of treatment were calculated for rivaroxaban users and SOC users. Additionally, a nested case-control analysis was conducted in users of rivaroxaban and SOC to estimate risk of safety outcomes during complete follow-up associated with recency of use, daily dose and treatment duration, after adjustment for risk factors. The investigators believe that combining these two analysis strategies will produce the most meaningful results based on the observational data sets used as secondary data sources.
- No SOC group was defined for the ACS indication. There is wide variation in the treatments that may be prescribed for prevention of atherothrombosis after an ACS, including several potential combinations of antiplatelet therapies; as such, it was not possible to identify an SOC that could be applied reliably. Instead, all analyses were conducted in the cohort of first-time users of rivaroxaban, which is the main focus of this program. Furthermore, analyses were limited by the small sample size of the rivaroxaban cohort and the heterogeneity of patients.
- A bleeding event had to be associated with hospitalization to be included as an outcome; bleeding events necessitating referral to a specialist, which were originally

planned to be included by the UK study, were not included because they are not captured by all the databases and could lead to misclassification of serious bleeding events.

- The VTE-T indication was stratified into subcohorts of patients with and without a recent history of cancer. The outcomes analysis was conducted only in patients without a recent history of cancer, owing to: the different standards of care for patients with VTE compared with for those with cancer-associated thrombosis; the heterogeneity of patients with cancer; and the higher risk of thromboembolic events and bleeding in patients with cancer than in those without (9). There is also an increased risk of thromboembolic events associated with more advanced cancer forms, such as metastatic cancer, and certain types of cancer therapies that were not individually assessed within this study.

9.2 Setting

All studies used a population-based healthcare database containing data from patients based in a European country of interest (Table 9–1).

Table 9–1: Data sources

Country	Data source
UK	IQVIA Medical Research Data-UK (IMRD-UK) [a]
Germany	The German Pharmacoepidemiological Research Database (GePaRD)
Netherlands	PHARMO Database Network
Sweden	The Swedish national health registers

a: Formerly known as The Health Improvement Network (THIN)

9.3 Subjects

9.3.1 Eligibility

Inclusion in the study required incident exposure to rivaroxaban or SOC (collectively referred to as ‘study drugs’) during the enrollment period.

Patients were excluded if they:

- were younger than 2 years of age
- had any record of being prescribed their study drug prior to the date of cohort entry (i.e. previous rivaroxaban use among patients in the rivaroxaban cohort and previous SOC use among patients in the SOC cohort)
- qualified as members of both the rivaroxaban and SOC cohorts on the same day
- had less than 12 months of baseline data
- were older than the upper age limit defined by each study (UK, 89 years; Sweden, 108 years; Germany, 100 years; Netherlands, no upper age limit applied).

Although rivaroxaban was only approved for use ‘in adults’ during the study enrollment period, children and adolescents were not excluded from the program because the aim was to describe patterns of real-world rivaroxaban use.

If a patient qualified as a user of both rivaroxaban and SOC during the enrollment period, she/he was assigned only to the cohort of the study drug first dispensed during the enrollment period.

For SPAF and the 'VTE-T without a recent history of cancer' subcohort, SOC was the most widely used VKA(s) in each of the respective countries (Table 9–2

Table 9–2). Parenteral anticoagulants administered for bridging in treatment of acute VTE were not included in the definition of SOC. No SOC was defined for the 'VTE-T with a recent history of cancer' subcohort and these patients were not included in the safety and effectiveness outcomes analysis. TKR/THR was not included in the safety and effectiveness outcomes analysis because this was outside the scope of the program.

Table 9–2: SOC for SPAF and VTE-T by country

	SPAF and VTE-T (subcohort without a recent history of cancer)
UK	Warfarin
Germany	Phenprocoumon
Netherlands	Acenocoumarol or phenprocoumon
Sweden	Warfarin

SOC, standard of care; SPAF, prevention of stroke and systemic embolism in nonvalvular atrial fibrillation; VTE-T, treatment and secondary prevention of venous thromboembolism

Many patients with ACS (ST-elevation myocardial infarction [STEMI], non-STEMI [NSTEMI] and unstable angina) also have a history of ischemic heart disease, for which platelet inhibition is standard treatment; thus, exclusion of patients with prior use of platelet inhibitors would likely have resulted in the exclusion of the majority of typical patients with ACS. Consequently, patients with ACS who had used one or more platelet inhibitor before cohort entry were eligible to enter the study. The ACS cohort consists of first-time users of rivaroxaban with or without prevalent or incident aspirin, clopidogrel or multiple antiplatelet therapies. No SOC group was defined for this indication; all analyses were conducted in the cohort of rivaroxaban users.

9.3.2 Assignment of indication

The following criteria were used to assign first-time users of study drugs to an indication.

- SPAF: diagnostic code for AF (excluding mitral stenosis and mechanical heart valves) any time before the start date and up to 15 days after.
- VTE-T: diagnostic code for DVT/PE from 90 days before the start date to up to 15 days after.
- Owing to the different standards of care for cancer- and non-cancer-associated thrombosis and the heterogeneity of patients with cancer, the VTE-T indication was further stratified into subcohorts of patients with or without a recent history of cancer based on a diagnosis of cancer from 3 years before the start date to up to 1 month after.
- TKR/THR: code for a relevant surgical procedure (i.e. elective total or partial knee or hip replacement) from 60 days before the start date to up to 15 days after.

- ACS: diagnostic code for STEMI, NSTEMI or unstable angina (or procedure code for coronary vascularization in the UK) from 30 days before the start date to up to 15 days after.
- Unknown: any user that could not be assigned to any of the above indications.

The start date was defined as the date of first prescription or dispensation for rivaroxaban or SOC during the enrollment period. In Germany, indications were ascertained before and on the start date only (i.e. not up to 15 days after the start date), except for the TKR/THR indication.

In the UK and Germany, an 'Other' indication was defined which included specific incidences of off-label use (e.g. stroke prevention in valvular AF). In Sweden, use of study drugs outside of the defined indications above was included in a combined 'Other/Unknown' category. In the Netherlands, dosing was used as a proxy to assign rivaroxaban users to an indication among patients with no relevant diagnoses.

In cases of multiple potential indications (i.e. diagnoses relating to more than one indication within the respective time windows), study-specific strategies were used to assign patients to a single indication; these are described in Annex 2.1 Individual study reports.

9.3.3 Cohort analysis

Unadjusted incidence rates of safety and effectiveness outcomes during the first episode of treatment were calculated for first-time users of rivaroxaban and SOC assigned to SPAF and the 'VTE-T without a recent history of cancer' subcohort, and first-time users of rivaroxaban assigned to ACS.

9.3.4 Nested case-control analysis

Controls for each outcome were sampled using the two pooled cohorts of first-time users of rivaroxaban and SOC. Cases and controls were matched within each main indication (SPAF and the 'VTE-T without a recent history of cancer' subcohort). Selection of controls was performed by individual or frequency matching and matched on age at the index date or year of birth, sex and calendar year, as well as statutory health insurance providers (SHI) in Germany, using risk-set sampling. Further details of the nested case-control methods are described in the individual study reports (Annex 2.1 Individual study reports).

9.3.5 Follow-up and censoring

Patients were censored at (whichever came first of):

- time of first occurrence of the safety or effectiveness outcome of interest
- time of death
- end of observation time
- disenrollment from the database.

For the cohort analysis, which was restricted to the first episode of treatment, patients were also censored at treatment switching/discontinuation.

9.3.6 Exposure time

The drug exposure time for an individual patient was captured from the date of first prescription or dispensation of rivaroxaban or SOC until censoring.

In Germany, information on the prescribed dose or duration was not available, so the duration of supply with rivaroxaban and SOC had to be estimated from the data as described in the individual study report (Annex 2.1 Individual study reports).

9.3.7 Switching

A switch was defined as the prescription of an alternative oral anticoagulant (NOAC or VKA) within 30 days of the end of supply of the study drug. Prescription of a parenteral anticoagulant, a local or systemic enzyme or an antiplatelet, did not constitute a switch.

9.3.8 Discontinuation

Continuous drug exposure was defined as use of a study drug up to the end of the prescription supply with a 30-day grace period. A gap of more than 30 days after the end of supply without a subsequent prescription for an oral anticoagulant was considered to be discontinuation of treatment.

In Sweden, it was not possible to determine exactly when a study drug was discontinued based on dispensation data except when a switch was made, in which case the dispensation date of the other drug was considered to mark the end of exposure to the first drug. In other cases, the end of exposure to rivaroxaban was defined as a gap greater than 30 days between the end of supply after one dispensation and the beginning of the subsequent one. The end of exposure to SOC was calculated from refill interval information as described in the individual study report (Annex 2.1 Individual study reports).

In Germany, rivaroxaban discontinuation was defined as a gap of greater than 30 days between the end of one dispensation and the beginning of the subsequent one, or greater than four times the number of defined daily doses of the current dispensation of SOC. Further information can be found in the individual study report (Annex 2.1 Individual study reports).

9.3.9 Subgroups

The cohort analyses were also conducted in subgroups of first-time users of rivaroxaban:

- with normal or near normal renal function versus renal impairment
- aged 75 years or older versus younger than 75 years
- with diabetes mellitus versus no diabetes mellitus.

9.4 Variables

9.4.1 Drug utilization

Characteristics of first prescription/dispensation, including tablet strength, dose frequency per day (based on posology, when available), daily dose and duration of the first episode of use were described for rivaroxaban users only, stratified by indication (SPAF, ‘VTE-T with recent

history of cancer' subcohort, 'VTE-T without a recent history of cancer' subcohort, TKR/THR and ACS). Dose posology was not available in Sweden or Germany.

Additionally, patterns of rivaroxaban use, including switching and discontinuation, during the first year of treatment were described for the SPAF indication.

9.4.2 General characteristics

Patient characteristics were described for each indication (SPAF and 'VTE-T without a recent history of cancer' subcohort [rivaroxaban and SOC users], 'VTE-T with a recent history of cancer' subcohort [rivaroxaban users only], TKR/THR [rivaroxaban users only] and ACS [rivaroxaban users only]) at the start date and were stratified by calendar year.

For SPAF and VTE-T, users were categorized as naive or non-naive according to their previous use of any oral anticoagulant any time prior to the start date other than their respective study drug. Naive patients were defined as those with no previous prescription/dispensation of any other oral anticoagulant drug recorded before the start date.

9.4.3 Healthcare resource utilization

Healthcare resource utilization was described for each indication (SPAF and 'VTE-T without a recent history of cancer' subcohort [rivaroxaban and SOC users], 'VTE-T with a recent history of cancer' subcohort [rivaroxaban users only] and ACS [rivaroxaban users only]). In all countries, the number of hospitalizations in the year before and the year after the start date were described. The number of contacts with a general practitioner (GP) in the year prior to the start date was also described in the UK and the Netherlands. In the Netherlands, these contacts included office visits, home visits, phone consultations and email consultations. In Sweden, the number of open care visits was instead described, owing to the available information in the Swedish registers. No information on GP contacts or open care visits was presented for Germany because the number of coded encounters is not meaningful.

9.4.4 Lifestyle characteristics

Lifestyle characteristics were described for each indication (SPAF and 'VTE-T without a recent history of cancer' subcohort [rivaroxaban and SOC users], 'VTE-T with a recent history of cancer' subcohort [rivaroxaban users only] and ACS [rivaroxaban users only]).

Reported lifestyle characteristics were based on available information in each of the data sources. In the UK and the Netherlands, information on body mass index (BMI), smoking status and alcohol consumption was available, whereas in Germany and Sweden, obesity and alcohol abuse had to be ascertained from diagnostic codes. In Sweden, information on smoking was also ascertained from diagnostic codes. Socioeconomic status was ascertained using methods specific to each of the databases, and was reported using categories in the UK, the Netherlands and Germany. In Sweden, several socioeconomic variables were individually reported including educational level, disposable income, living alone and born abroad.

9.4.5 Medications of interest

Medications of interest were described for each indication (SPAF and 'VTE-T without a recent history of cancer' subcohort [rivaroxaban and SOC users], 'VTE-T with a recent history of cancer' subcohort [rivaroxaban cohort users] and ACS [rivaroxaban users only]).

Polypharmacy was defined as the number of medications (based on individual World Health Organization [WHO] Anatomical Therapeutic Chemical [ATC] codes) prescribed/dispensed in the 30 days prior to the start date (UK), 3 months prior to the start date (Netherlands) or the year prior to the start date (Germany). It was not feasible to calculate polypharmacy in Sweden. Prior use of medications of interest up to 90 days before or on the start date were also described. Drug classes of interest included:

- antiplatelet drugs
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- antiarrhythmic drugs
- antihypertensive agents
- diuretics
- statins
- antidiabetic agents (metformin, insulin, dipeptidyl peptidase-4 inhibitors, sodium–glucose co-transporter-2 inhibitors, sulfonylureas)
- oral steroids
- proton pump inhibitors
- selective serotonin reuptake inhibitors
- antibiotics
- strong inhibitors of either cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-GP)
- strong CYP3A4 inducers.

In the UK and the Netherlands, antihypertensives were described as a single drug class, whereas in Sweden, antihypertensive agents were described separately using the following categories: beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers and dihydropyridine calcium-channel blockers. In Germany, antihypertensive agents were described for the overall drug class and stratified by subtype.

9.4.6 Medical history

Past medical events and comorbidities of interest ascertained any time prior to the start date were described for each indication (SPAF and 'VTE-T without a recent history of cancer' subcohort [rivaroxaban and SOC users], 'VTE-T with a recent history of cancer' subcohort [rivaroxaban users only] and ACS [rivaroxaban users only]). The frailty of patients was also measured using the electronic frailty index in the UK and the Charlson comorbidity index in Germany, Sweden and the Netherlands (10, 11).

Past medical events and comorbidities of interest included:

- intracranial bleeding (intracerebral, other)
- gastrointestinal bleeding
- urogenital bleeding
- ischemic stroke

- TIA
- VTE (DVT, PE)
- myocardial infarction
- hypertension
- AF
- heart failure
- CAD
- PAD
- hyperlipidemia
- diabetes
- liver disease
- chronic obstructive pulmonary disorder
- asthma
- cancer
- dementia
- depression.

9.4.7 Risk scores

CHA_2DS_2-VASc and modified HAS-BLED scores were calculated as specified in Table 9–3 and Table 9–4, respectively, for the SPAF indication only using information most recently recorded before or on the start date.

The CHA_2DS_2-VASc score estimates stroke risk in patients with nonvalvular AF. As CHA_2DS_2-VASc score increases, the rate of thromboembolic events increases. Scores of 0, 1, and 2 or more are considered to indicate a low risk, intermediate risk and high risk of thromboembolic events, respectively (12).

The HAS-BLED score was calculated based on the presence of bleeding risk factors. Scores range from 0 to 9, with a score of 3 or more indicating a high risk of bleeding. In these studies, HAS-BLED scores were calculated without labile international normalized ratio (INR).

Table 9–3: CHA_2DS_2-VASc criteria

	CHA_2DS_2-VASc criteria	**Score**
C	Congestive heart failure or left ventricle dysfunction	1
H	Hypertension	1
A_2	Age ≥ 75 years	2
D	Diabetes mellitus	1
S_2	Stroke/transient ischemic attack	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age 65–74 years	1
Sc	Female [a]	1
Total score		0–9

a: If no other risk factors are present, female sex scores 0

Table 9–4. Modified HAS-BLED score [a]

	HAS-BLED criteria	Score
H	Uncontrolled hypertension (systolic blood pressure > 160 mmHg) [b]	1
A	Abnormal renal or liver function	
	Renal: chronic dialysis, renal transplant, serum creatinine ≥ 2.3 mg/dL (200 µmol/L) [c]	1
	Liver: cirrhosis, bilirubin > 2 x UNL with AST/ALT/AP > 3 x UNL [d]	1
S	Previous stroke	1
B	Bleeding history or predisposition (anemia)	1
L	Labile INR (therapeutic time in range < 60%) [a]	–
E	Elderly (> 65 years)	1
D	Drugs or alcohol	
	Drugs: other antiplatelet agents or NSAIDs	1
	Alcohol: more than eight drinks per week [e]	1
Total score		0–8

a: Labile INR is not captured in any of the studies
b: In Germany, diagnosis of hypertension
c: Serum creatinine levels not available in Germany
d: In Germany and Sweden, based on diagnoses
e: Diagnoses indicating alcohol abuse in Germany and Sweden
ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; UNL, upper limit of normal

9.4.8 Renal function

Renal function was described for each indication (SPAF and 'VTE-T without a recent history of cancer' subcohort [rivaroxaban and SOC users], 'VTE-T with a recent history of cancer' subcohort [rivaroxaban users only] and ACS [rivaroxaban users only]). Renal function was ascertained using methods specific to the data sources. In the UK, renal function was categorized based on estimated glomerular filtration rate (eGFR) values recorded in the year prior to the start date. In the Netherlands, renal function was based on the eGFR recorded by the GP. In Germany, renal disease was determined based on the presence of diagnostic codes for chronic kidney disease and procedure codes for dialysis, with renal impairment defined as chronic kidney disease stage 3 or higher, or dialysis. In Sweden, renal function was estimated indirectly because the laboratory values required to estimate individual glomerular filtration rate (GFR) are not recorded in the Swedish Patient register. Instead, an algorithm that predicts likely GFR value from diagnostic values and medication dispensation data was used (13). In Sweden, renal disease was also determined based on the presence of diagnostic codes for chronic kidney disease.

9.4.9 Pregnancy and pregnancy outcomes

If available, information on pregnancies and pregnancy outcomes during follow-up were reported for first-time users of rivaroxaban, irrespective of indication. In Germany, pregnancies in female patients aged 11–50 years were identified and dated using an established algorithm (14, 15). In the UK, pregnancies were ascertained among female patients aged 11–50 years for up to 270 days before the start date until the end of the follow-up period. Information on pregnancy and pregnancy outcomes was not available in the Netherlands.

It should be noted that the pregnancies described do not necessarily represent exposure of a fetus to rivaroxaban, as the mother may have terminated treatment with rivaroxaban prior to the start of the pregnancy.

9.4.10 Safety and effectiveness outcomes

Analyses of all safety and effectiveness outcomes were conducted in first-time users of rivaroxaban and SOC assigned to SPAF and the 'VTE-T without a recent history of cancer' subcohort and in first-time users of rivaroxaban assigned to ACS. Outcomes were not analyzed in the 'VTE-T with a recent history of cancer' subcohort owing to the heterogeneity of patients with cancer, differences in cancer therapies that may impact the risk of thromboembolic events and the different SOC anticoagulants for cancer-associated thrombosis compared with VTE.

The definitions of outcomes were harmonized as much as possible for the purpose of this analysis; however, some minor differences remained among the studies. Sets/versions of codes for individual studies to define these outcomes of interest are attached to individual study reports (Annex 2.1 Individual study reports).

In Germany, the main hospital discharge diagnosis was used to identify outcome events since this code indicates the reason for hospitalization, although an additional analysis was conducted for DVT/PE including both outpatient and hospital diagnoses. In the UK, only diagnoses considered to be the main reason for admission were included as outcome events. In the Netherlands, outcomes were based on both primary and secondary codes associated with hospital admissions. In Sweden, analyses were restricted to principal diagnoses given at discharge from hospital (restrictive definition); however, for some outcomes of interest, all principal and secondary diagnoses given in hospital or in open care (inclusive definition) were also analyzed and described, based on previous validation work in Swedish registers.

In the UK study, anonymized profiles of patients with each outcome event, including any free-text comments related to the event, were manually reviewed because validation studies have demonstrated that the incidence rates of gastrointestinal bleeding, urogenital bleeding and VTE identified using Read codes are overestimated in the absence of manual profile review (16, 17). A separate validation study conducted using the Swedish registers has demonstrated high sensitivity (85.5%) and specificity (95.9%) for the detection of major bleeding events associated with hospitalization (18). In Germany, the main hospital discharge diagnoses used for outcome events were assumed to have a high validity because they are based on all information captured during the hospital stay, including laboratory tests and imaging results. Furthermore, these diagnoses are the basis for reimbursement and, therefore, are subject to inspections.

9.4.10.1 Intracranial hemorrhage

In all studies, intracranial hemorrhage was defined as hospitalization with a diagnosis of intracerebral hemorrhage, subarachnoid hemorrhage or subdural hematoma. In the Netherlands, the diagnosis was associated with computed tomography, magnetic resonance imaging or x-ray angiography, or an appropriate therapeutic procedure. Cases were defined via chart review since therapeutic procedures are not captured by the PHARMO database. In the UK, manual profile review was used to assign the file case status.

9.4.10.2 Gastrointestinal bleeding

Gastrointestinal bleeding was defined as hospitalization for bleeding originating in the upper or lower gastrointestinal tract (more specifically, in the esophagus, stomach, duodenum, jejunum, ileum, colon or rectum). For upper gastrointestinal bleeding, lesion types include erosion, gastritis, duodenitis or peptic (gastric or duodenal) ulcer. Lesions related to cancer were excluded in the Netherlands. In the UK, manual profile review was used to assign the file case status.

9.4.10.3 Urogenital bleeding

Urogenital bleeding was defined as hospitalization for bleeding originating in the urogenital tract. In the UK, manual profile review was used to assign the file case status.

9.4.10.4 Other bleeding

Other bleeding was defined as hospitalization for bleeding occurring at a site other than the sites included in the primary safety outcomes.

9.4.10.5 Noninfective liver disease

Noninfective liver disease was defined as hospitalization for alcoholic liver disease, toxic liver disease, chronic hepatitis, liver fibrosis and cirrhosis, and other inflammatory liver diseases.

Because some cases of noninfective liver disease may be associated with cancer, the number of patients with noninfective liver disease and a recent history of cancer (defined as a diagnosis of cancer from 3 years before the start date to up to 1 month after) was also reported.

9.4.10.6 Effectiveness outcomes

Effectiveness outcomes were defined as a diagnosis of DVT/PE, ischemic stroke or myocardial infarction. Within the data sources used, it is challenging to distinguish recurrent events (e.g. DVT/PE in the VTE-T cohort, myocardial infarction in the ACS cohort) from outpatient follow-up visits occurring after an indication event because these are recorded using the same diagnostic codes. For this reason, effectiveness outcomes were restricted to events necessitating hospitalization. This restriction is unlikely to underestimate the number of myocardial infarction events because these are typically treated in hospital. However, because a substantial proportion of patients with DVT are treated in outpatient care, DVT events requiring hospitalization should not be considered to be a complete measure of effectiveness. Instead, we focused on the most severe forms of DVT (i.e. hospitalized cases), owing to methodological reasons related to the analysis of secondary data.

9.4.10.7 All-cause mortality

- In the UK, automated computer searches for mortality were performed based on Read codes, death certification and registration status of the patient in the IMRD-UK database.

- In the Netherlands, date of death is available from the PHARMO Database Network and was confirmed through linkage with the Dutch central bureau of genealogy.
- In Germany, death was identified by the reason for either ending insurance or discharge from hospital.
- In Sweden, the Cause of Death Register was used for determination of all-cause and cause-specific mortality.

9.5 Data sources and measurement

9.5.1 UK

The data source for the UK study was the IQVIA Medical Research Data-UK (IMRD-UK) database, formerly known as The Health Improvement Network, which was established in 2002. IMRD-UK includes information on over 3 million patients, covering ~6% of the UK population. Data that have been systematically recorded by participating primary care providers (PCPs) as part of routine patient care are anonymized and sent to IMRD-UK for use in research projects. The computerized information includes demographics, details of PCP visits, referrals to specialists and hospital admissions (including diagnostic and treatment information), results of laboratory tests and free-text notes. Prescriptions issued by the PCP are recorded electronically and the indication can be ascertained by reviewing the patient's clinical history. The Read classification is used to code specific diagnoses as reasons for each consultation (19, 20), and a drug dictionary based on data from the Multilex classification is used to record prescriptions (21). IMRD-UK has been extensively validated for use in pharmacoepidemiology (22), and has been used successfully in studies of bleeding risk (23–31).

9.5.2 Germany

The data source for the German study was the GePaRD, which includes claims data from four SHIs. GePaRD currently includes information on the 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 (32, 33).

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 (including 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 certainty of the diagnosis. 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 (34, 35). 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 International

Statistical Classification of Diseases and Related Health Problems 10th Revision, German Modification (ICD-10-GM) with at least four digits; diagnostic and surgical/medical procedures are coded using the Operations and Procedures Coding System, 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 WHO 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, although there are a few exceptions for expensive drugs such as monoclonal antibodies. Outpatient drug data include the dates of the prescription and dispensation, 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 defined daily dose and further pharmaceutical information (e.g. route of administration) is linked to GePaRD. If laboratory 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 laboratory 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 recorded in the database if the person was treated for this condition. Socioeconomic status 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.

The GePaRD has been used successfully to study hemorrhagic complications of drug treatment (36–39) and also to evaluate the use of rivaroxaban during a time when it was only approved for the orthopedic indication (40).

9.5.3 The Netherlands

In the Netherlands, data were obtained from the PHARMO Database Network. This population-based network of healthcare databases combines data from different primary and secondary healthcare settings. These different data sources, including data from general practices, inpatient and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, the pathology registry and the perinatal registry, are linked on a patient level through validated algorithms. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymization of the data are performed by STIZON. STIZON is an independent, ISO/IEC 27001-certified foundation that acts as a Trusted Third Party between the data sources and the PHARMO Institute. Detailed information on the methodology and validation of the used record linkage method has been published (41–43).

The longitudinal nature of the PHARMO Database Network system enables the follow-up of more than 9 million residents of a well-defined population in the Netherlands for an average of 12 years. Currently, the PHARMO Database Network covers over 6 million active persons out of 17 million inhabitants of the Netherlands. The data collection period, catchment area and overlap between data sources differ. All electronic patient records in the PHARMO

Database Network include information on age, sex, socioeconomic status and mortality. Other information available is dependent on the specific data source. The PHARMO Database Network has been used in previous studies of anticoagulant use and bleeding risk (44–47).

To address the objectives of the present study, data were used from the Out-patient Pharmacy Database, the General Practitioner Database and the Hospitalisation Database.

9.5.3.1 Out-patient Pharmacy Database

The Out-patient Pharmacy Database comprises GP- or specialist-prescribed healthcare products dispensed by the outpatient pharmacy. The dispensation records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensations are coded according to the WHO ATC Classification System (48). Outpatient pharmacy data cover a catchment area representing 4.2 million residents (~25% of the Dutch population).

9.5.3.2 General Practitioner Database

The General Practitioner Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses, symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO ATC Classification System (48). Diagnoses and symptoms are coded according to the International Classification of Primary Care (49), which can be mapped to International Classification of Diseases ICD codes, but can also be entered as free text. GP data cover a catchment area representing 3.2 million residents (~20% of the Dutch population).

9.5.3.3 Hospitalisation Database

The Hospitalisation Database comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required (i.e. inpatient records) from the Dutch Hospital Data Foundation (50). The records include information on hospital admission and discharge dates, discharge diagnoses and procedures. Diagnoses are coded according to the ICD codes (51) and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures (3), which links to the Dutch Healthcare Authority (NZa) declaration codes (52) and the Dutch Classification of Procedures (53). The Dutch Hospital Data Foundation collects hospitalization records from nearly all hospitals in the Netherlands. Currently, PHARMO has access to data from over 80% of hospitals in the Netherlands going back as far as 1998.

9.5.4 Sweden

The data sources for the Swedish study were the National Drug Register, the National Patient Register, the National Cause of Death Register and the longitudinal integrated database for health insurance and labor market studies (LISA). These registers cover the entire population of Sweden (~10 million lives). Data from these registers were cross-matched with the use of the unique 10-digit civic registration numbers that are used in all contacts within the

healthcare system and in contacts with authorities in Sweden. Such numbers are given to all residents in Sweden, irrespective of citizenship.

The registers, except the LISA register, are maintained by a governmental agency: the National Board of Health and Welfare. The LISA register is maintained by Statistics Sweden, another governmental agency. After cross-matching, the civic registration numbers were replaced by anonymous numbers before the data was made available to protect the personal integrity of patient data. Nevertheless, this anonymized information is considered to be sensitive and the handling of such data is strictly regulated by Swedish law. Access to data requires permission by the regional Ethics committee.

9.5.4.1 The National Drug Register

The National Drug Register stores details about every prescription dispensed from a pharmacy in Sweden since 01 JUL 2005. The Drug Register is almost complete because all pharmacies in the country are required to participate by law, and information is transferred electronically whenever a drug is dispensed.

The register does not contain information about prescriptions that have been issued but not dispensed and about drugs used by patients during hospital stays, although patients in long-term care and in community care are included. The register does not include information on nonprescribed (i.e. OTC) drugs.

9.5.4.2 The National Patient Register

The National Patient Register carries detailed information about all hospitalizations throughout Sweden since 1987, going back as far as 1964 for some regions. Information about outpatient visits to hospital-affiliated open clinics was added in 2001. While the Patient Register is hospital-based, it is not limited to hospitalization, and there are more registrations for open clinic visits than for hospitalizations. For example, in a data set including all patients with a clinical diagnosis of AF in Sweden (2005–2013), there were approximately 420,000 unique individuals with 3.2 million hospitalizations and 11.3 million outpatient visits providing diagnostic codes.

9.5.4.3 The National Cause of Death Register

The Cause of Death Register was used for determination of all-cause and cause-specific mortality. Information from this register also provides data about dates of deaths needed for determination of individual time at risk during follow-up. The register carries one "underlying" and up to 48 contributory causes of death. The distinction between what is an underlying and a contributory cause, and between what is mode of death and cause of death is not understood in the same way by all doctors. According to one validation study, 23% of alleged underlying causes of death were incorrect (54).

9.5.4.4 The LISA Register

The LISA register is a longitudinal database for studies of health insurance utilization and labor market conditions. It contains detailed information about educational level, economic conditions, periods of unemployment, type of work etc., and provides additional information

about socioeconomic conditions at baseline that may have an impact on health and thus on outcome.

9.6 Bias

Since all data recording was independent of patients' memories or agreement to participate, patient nonresponse or recall bias are nonexistent. The potential for misclassification of indication exists because the assignment depends on the proper and accurate recording of the condition in the database.

9.7 Study size

This study includes all eligible first-time users of rivaroxaban and first-time users of SOC during the enrollment period based on available data, dependent on the data sources.

9.8 Data transformation

Details of data transformation can be found in Annex 2.1 Individual study reports.

9.9 Statistical methods

9.9.1 Main summary measures

Descriptive statistics (e.g. frequencies, means, medians, standard deviations, interquartile ranges etc.) were used to quantify variables relating to drug utilization and patient characteristics.

9.9.2 Main statistical methods

9.9.2.1 Cohort analysis

The incidence rates of safety and effectiveness outcomes were computed using the person–time contribution of the study drugs. Patients were censored at whichever came first of treatment switching/discontinuation (30-day grace period), first occurrence of the outcome of interest, date of last available information, end of study period or death. Unadjusted incidence rates and 95% confidence intervals were computed as the number of events per 100 person-years for each outcome of interest during the first episode of treatment.

For bleeding outcomes, incidence rates were reported for rivaroxaban users and SOC users assigned to the SPAF indication and the 'VTE-T without a recent history of cancer' subcohort, and incidence rates were reported for the rivaroxaban users assigned to ACS. For effectiveness outcomes (DVT/PE, ischemic stroke and myocardial infarction), all-cause mortality and noninfective liver disease, incidence rates were reported for rivaroxaban users assigned to SPAF, the 'VTE-T without a recent history of cancer' subcohort and ACS.

In the Netherlands, the cohort analysis was conducted in the subcohort with available GP data.

9.9.2.2 Nested case-control analysis

Nested case-control analyses were conducted to assess the impact of current use of rivaroxaban/SOC, dose and treatment duration on the risk of bleeding (intracranial hemorrhage, gastrointestinal bleeding, urogenital bleeding and other bleeding) after adjustment for bleeding risk factors that were identified as the first step of the analysis. These analyses were conducted in rivaroxaban users and SOC users assigned to the SPAF indication and the 'VTE-T without a recent history of cancer' subcohort. The nested case-control analysis included all cases occurring during complete follow-up, irrespective of the treatment episode.

The index date was defined as the date of the outcome of interest and, therefore, differed for each outcome. Recency was estimated before the index date, using date of outcome occurrence for cases and an assigned date for controls; this was the same date as the matched case for individual matching and a random date for frequency matching.

In these analyses, outcomes for current users were contrasted with those of nonusers; however, exposure was defined differently between the studies.

- In Sweden, current users were defined as patients who had filled a prescription for a study drug within the 4 months before the index date, and nonusers were defined as patients who had not been dispensed any oral anticoagulant (whether NOAC or VKA) within the 4 months before the index date. Patients who received an anticoagulant other than a study drug were excluded from this analysis. Consequently, rivaroxaban and SOC users were compared with the same group of nonusers.
- In Germany, exposure at the index date was categorized as 'current use of rivaroxaban without current use of SOC', 'current use of SOC without current use of rivaroxaban', 'nonuse of rivaroxaban and nonuse of SOC in the year before' and 'other'. Current use was defined as end of supply up to 30 days before or on the index date, and nonuse was defined as end of supply of rivaroxaban or SOC more than 365 days before the index date or no supply ever before the index date. Consequently, rivaroxaban and SOC users were compared with the same group of nonusers.
- In the UK and the Netherlands, current use for each study drug was defined as end of supply up to 30 days before or on the index date, and nonuse was defined as end of supply of the respective study drug (irrespective of use of other oral anticoagulants) more than 365 days before the index date or no supply ever before the index date. Consequently, rivaroxaban and SOC current use were compared with nonusers of their respective drug.

Unconditional or conditional logistic regression analyses were used to estimate odds ratios (ORs), depending on whether frequency or individual matching was used for selection of controls. In the UK and the Netherlands, use of SOC and use of rivaroxaban were included as independent variables in the adjusted model and, consequently, were mutually adjusted for exposure history of the two study drugs. The full logistic regression models are included in the appendices of the individual study reports (Annex 2.1 Individual study reports).

In the Netherlands, the nested case-control analysis was conducted in the subcohort with available GP data.

9.9.3 Missing values

No data imputation strategies were performed.

9.9.4 Sensitivity analyses

In Germany, the following sensitivity analyses were conducted for the cohort analysis.

- To avoid overestimation and to increase the specificity of detection of DVT events, only events requiring hospitalization were used in the main analysis. In a sensitivity analysis, outpatient diagnoses were also included in the outcome definition.
- Usually, ischemic strokes are coded with the ICD-10-GM code I63 ("cerebral infarction"). In a sensitivity analysis, the code I64 ("stroke not specified as hemorrhagic or ischemic") was also included in the outcome definition.

In Sweden, outcome events included in the cohort analysis were restricted to principal diagnoses given at discharge from hospital (restrictive definition); however, for some outcomes of interest, all principal and secondary diagnoses given in hospital or in open care (inclusive definition) were also analyzed.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

This study was conducted according to the Guidelines for Good Pharmacoepidemiology Practice (GPP), Good Practice of Secondary Data Analysis (GPS), Good Epidemiological Practice (GEP) and the European Network of Centers in Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (55–58).

10. Results

10.1 Participants

The German study had the largest cohort of eligible patients, encompassing 265,584 rivaroxaban users and 172,727 SOC users, followed by the Swedish study with 58,974 rivaroxaban users and 121,908 SOC users. In the UK study, there were 24,953 and 25,346 users of rivaroxaban and SOC, respectively. The Dutch study included an overall cohort and a subcohort with available GP data: there were 23,670 rivaroxaban users, of which 5641 had available GP data, and 85,112 SOC users, of which 18,918 had available GP data (Table 10–1). Within this combined report, descriptive results for the Dutch study are described for the subcohort with available GP data, except for medications of interest, which are described for the overall cohort.

The proportion of rivaroxaban users who could be assigned to an indication ranged from 75.0% in Sweden to 99.8% in the Netherlands. SPAF was the most common indication among rivaroxaban users in all countries, ranging from 32.8% of rivaroxaban users in Sweden to 51.6% of rivaroxaban users in the Netherlands. The second most common indication was VTE-T in the UK, Germany (excluding 'Other') and Sweden, and TKR/THR in the Netherlands. Very few rivaroxaban users were assigned to the ACS indication: 88 (0.4%) in the UK, 192 (0.3%) in Sweden, 27 (< 0.5%) in the Netherlands and 546 (0.2%) in Germany.

In the UK and Germany, specific cases of off-label use (e.g. valvular AF) were assigned to an 'Other' indication category, whereas in Sweden, use of rivaroxaban that did not fulfill the criteria for any of the specified indications was included within a combined 'Other/Unknown' category. The 'Other' category accounted for 8.7% of rivaroxaban users in the UK and 17.2% of rivaroxaban users in Germany. The proportion of rivaroxaban users with unknown indication was lower in the Netherlands than in the other countries because dosing information was used as a proxy to assign patients to one of the indications.

Among rivaroxaban users for SPAF, median time at risk during first episode of treatment and total available follow-up time, respectively, were 382 and 721 days in the UK, 318 and 1035 days in Sweden, 468 and 738 days in the Netherlands, and 303 and 1077 days in Germany. Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, median time at risk during first episode of treatment and total available follow-up time, respectively, were 112 and 770.5 days in the UK, 233 and 1086 days in Sweden, 216 and 515 days in the Netherlands, and 207 and 1033 days in Germany. For both SPAF and the 'VTE-T without a recent history of cancer' subcohort, median time at risk during the first episode of treatment and median total available follow-up time were longer for SOC users than for rivaroxaban users in the UK, Sweden and Germany. In the Netherlands, median total follow-up time was longer for SOC users than rivaroxaban users, whereas median time at risk during first episode of treatment was not. Among users of rivaroxaban for ACS, median time at risk during first episode of treatment ranged from 207.5 days in the UK to 394 days in Germany.

Table 10–1: Cohort definition: first-time users of study drugs

	UK				Netherlands (GP subcohort)				Germany				Sweden			
	Rivaroxaban N = 24,953		SOC N = 25,346		Rivaroxaban N = 5641		SOC [a] N = 18,218		Rivaroxaban N = 265,584		SOC N = 172,727		Rivaroxaban N = 58,974		SOC N = 121,908	
Indication	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
SPAF	12,929	51.8	15,475	61.1	2909	51.6	9123	50.1	127,743	48.1	88,655	51.3	19,338	32.8	64,505	52.9
VTE-T	6486	26.0	-	-	645	11.4	-	-	31,112	11.7	-	-	13,813	23.4	-	-
Subcohort without h/o cancer [b]	*5680*	*22.8*	*4636*	*18.3*	*586*	*10.4*	*2617*	*14.4*	*25,914*	*9.8*	*20,502*	*11.9*	*12,557*	*21.3*	*18,087*	*16.6*
Subcohort with h/o cancer [c]	*806*	*3.2*	*-*	*-*	*59*	*1.0*	*-*	*-*	*5198*	*2.0*	*-*	*-*	*1256*	*2.1*	*-*	*-*
TKR/THR	504	2.0	-	-	2050	36.3	-	-	30,079	11.3	-	-	10,906	18.5	-	-
ACS	88	0.4	-	-	27	< 0.5	-	-	546	0.2	-	-	192	0.3	-	-
Other	2166	8.7	-	-	-	-	-	-	45,714	17.2	-	-	-	-	-	-
Total with assigned indication	22,173	88.9	22,882 [c]	90.3	5631	99.8	11,740	64.4	235,194	88.6	157,535	91.2	44,249	75.0	82,597	67.8
Unknown indication [d]	2780	11.1	2464	9.7	10	< 0.5	6478	35.6	30,390	11.4	15,192	8.8	14,725	25.0	39,311	32.2

a: Excluding 700 patients (3.7%) with 'VTE-T with a recent history of cancer', TKR/THR or ACS
b: Recent history of cancer was defined as a diagnosis of cancer from 3 years before the start date to up to 1 month after
c: Including 2771 patients (10.9%) with 'VTE-T with a recent history of cancer', TKR/THR, ACS or 'Other' indication
d: Including patients without any indication recorded

ACS, acute coronary syndrome; GP, general practitioner; h/o, history of; SOC, standard of care; SPAF, prevention of stroke and systemic embolism in nonvalvular atrial fibrillation; THR, total hip replacement; TKR, total knee replacement; VTE-T, treatment and secondary prevention of venous thromboembolism

10.2 Descriptive data

10.2.1 Characteristics of first prescription/dispensation and first continuous treatment episode

For SPAF, most patients were prescribed a rivaroxaban tablet strength of either 20 mg or 15 mg. In the UK and the Netherlands, where dose posology was available, most patients were administered rivaroxaban once daily, resulting in a daily dose of 20 mg or 15 mg. This is consistent with dose recommendations for the SPAF indication for patients with normal renal function and mild-to-moderate renal impairment, respectively. The first episode of treatment lasted 365 days or longer for 38.2–62.9% of rivaroxaban users.

Within the VTE-T indication, rivaroxaban users were typically prescribed either the 15 mg or 20 mg tablet. The 15 mg tablet was prescribed to a greater proportion of patients than the 20 mg tablet in the Netherlands, Germany and Sweden, whereas the 20 mg tablet was more common in the UK, regardless of subcohort. In the 'VTE-T without a recent history of cancer' subcohort, 17.0% of rivaroxaban users received a prescription for multiple tablet strengths in Germany compared with only 1.7% of patients in the Netherlands. Similarly, in the 'VTE-T with a recent history of cancer' subcohort, 13.0% and 3.4% of rivaroxaban users received multiple tablet strengths in Germany and the Netherlands, respectively. In both VTE-T subcohorts, most patients were prescribed rivaroxaban once daily in the UK, whereas twice daily was more common in the Netherlands. Consequently, the most common daily dose was 20 mg in the UK and 30 mg in the Netherlands. It is challenging to define posology for this indication, however, because the label recommendations are to administer 15 mg twice daily for the first three weeks, followed by 20 mg or 15 mg once daily for 6 months, depending on renal function. Furthermore, in some countries, starter packs are available that provide the multiple tablet strengths necessary for the initiation of treatment. In Sweden, Germany and the Netherlands, over three-quarters of rivaroxaban users were treated for longer than 90 days, whereas the duration of the first treatment episode was variable in the UK. The duration of the first treatment episode was similar among VTE-T patients with and without a recent history of cancer.

Most users of rivaroxaban who underwent TKR/THR were prescribed the 10 mg tablet. In the UK and the Netherlands, almost all patients were prescribed rivaroxaban once daily, resulting in a daily dose of 10 mg, in line with dose recommendations for this indication. Most patients received rivaroxaban for 1–30 days in the UK, 31–60 days in Germany and Sweden and 61–90 days in the Netherlands.

Only 0.5–14.8% of users of rivaroxaban for ACS received the 2.5 mg tablet. Instead, most patients received either the 20 mg or 15 mg tablet strengths, which could indicate a misclassification of indication for some patients assigned to this cohort. In the hierarchy used for assignment of indication in cases of multiple potential indications, however, ACS was given a lower priority than SPAF, VTE-T and TKR/THR. Furthermore, in the UK, all patients assigned to the ACS cohort were validated by manual review to ensure that they did not have another potential indication for treatment. In the UK and the Netherlands, only 8 patients (9.1%) and 2 patients (7.4%), respectively, received the recommended 5 mg daily dose (i.e. 2.5 mg bid). The duration of the first episode of treatment was most commonly 365 days or longer, except in Sweden where a slightly greater proportion were treated for 181–365 days.

In all countries, 60.0–74.0% of patients with SPAF were continuously treated with rivaroxaban during the first year of treatment. Most patients who reinitiated treatment with an oral anticoagulant after discontinuation of rivaroxaban were again prescribed rivaroxaban. Of

those who discontinued rivaroxaban, 8.9–28.6% did not reinitiate oral anticoagulation in the first year of treatment.

10.2.2 Characteristics of the study cohort

For the SPAF indication, there was a greater proportion of male patients than female patients among both rivaroxaban and SOC users. The median age was PPD for rivaroxaban users and PPD for SOC users. The proportion of patients who were naive to oral anticoagulation at the start date was higher for SOC users than for rivaroxaban users. Among rivaroxaban users, the proportion of naive users increased over time in the UK, the Netherlands and Germany. Based on the calendar year of first prescription, uptake of rivaroxaban increased over the enrollment period up to 2015 or 2016, with a corresponding decrease in use of SOC.

Within the VTE-T indication, the male-to-female ratio differed between the countries and the subcohorts. For the 'VTE-T without a recent history of cancer' subcohort, there was an approximately equal ratio of male patients to female patients for both the rivaroxaban and SOC cohorts in the UK and Sweden, whereas there was a slightly higher proportion of female patients in the Netherlands and Germany. Among users of rivaroxaban in the 'VTE-T with a recent history of cancer' subcohort, there was a higher proportion of female patients than male patients in the UK, Germany and the Netherlands, whereas in Sweden, the male-to-female ratio was equal. The median age of patients in the 'VTE-T without a recent history of cancer' subcohort ranged from PPD for rivaroxaban users and from PPD for SOC users, whereas median age was slightly higher among rivaroxaban users in the 'VTE-T with a recent history of cancer' subcohort PPD The proportion of patients who were naive to oral anticoagulation at the start date was higher for SOC users than for rivaroxaban users. Among rivaroxaban users, the proportion of naive users increased over time in the UK and Germany. Uptake of rivaroxaban generally increased over time, while use of SOC decreased.

Among users of rivaroxaban who underwent TKR/THR, a greater proportion were female than male. The median age of patients ranged from PPD Uptake of rivaroxaban was consistent for this indication across the study enrollment period.

Among users of rivaroxaban for ACS, patients were predominantly male with a median age of PPD The indication was approved in 2013; however, uptake of rivaroxaban for ACS remained consistently low throughout the enrollment period in all countries included in this study. Patients prescribed a daily dose of more than 10 mg were older than those prescribed less than 10 mg (median age, PPD in the UK. This trend was also observed in Germany, where patients prescribed the 2.5 mg tablet had a median age of PPD compared with PPD for those prescribed a 10 mg tablet or higher.

10.2.3 Healthcare resource utilization

For the SPAF indication, a greater proportion of rivaroxaban users than SOC users were hospitalized in the year before the start date in the UK, whereas in the Netherlands and Sweden, a greater proportion of SOC users were hospitalized. In the year after the start date, the proportion of patients who were hospitalized at least once decreased relative to the year before among both rivaroxaban users and SOC users. In the year prior to the start date, 54.0% of rivaroxaban users and 42.0% of SOC users had 20 or more contacts with a GP in the UK, whereas over half of rivaroxaban users and SOC users had 0–4 contacts in the Netherlands. In Sweden, most rivaroxaban and SOC users had 0–4 open care visits in the year before the start date.

Among users of rivaroxaban assigned to the 'VTE-T without a recent history of cancer' subcohort, a greater proportion of SOC users than rivaroxaban users were hospitalized in the year prior to the start date. For the 'VTE-T with a recent history of cancer' subcohort, over half of the rivaroxaban users in Germany and a little under half of users in the UK, the Netherlands and Sweden were hospitalized twice or more in the year prior to the start date. In the year after the start date, the proportion of patients who were hospitalized decreased relative to the year before the start date for rivaroxaban users in both subcohorts and for SOC users. In the year prior to the start date, most users of rivaroxaban and SOC in the 'VTE-T without a recent history of cancer' subcohort in the UK had at least 10 contacts with a GP, whereas over half of patients in the Netherlands had 0–4 contacts with a GP. In Sweden, around three-quarters of rivaroxaban users and SOC users in the 'VTE-T without a recent history of cancer' subcohort had 0–4 open care visits in the year prior to the start date. The number of GP or open care contacts was higher among rivaroxaban users with a recent history of cancer than those without a recent history of cancer. In the UK, 65.8% of rivaroxaban users in the 'VTE-T with a recent history of cancer' subcohort had 20 or more contacts with a GP in the year prior to the start date. In the Netherlands, most users had 5–9 contacts (40.7%) or 0–4 contacts (35.6%) with a GP in the year prior to the start date. In Sweden, 35.7% of rivaroxaban users had 5–9 open care visits in the year prior to the start date, followed by 0–4 visits (33.5%) and 10–19 visits (24.0%).

Most rivaroxaban users with ACS were hospitalized at least once in the year prior to the start date. The proportion of patients who were hospitalized decreased in the year after the start date relative to the year before. In THIN, most rivaroxaban users had at least 10 contacts with a GP in the year before the start date. In contrast, almost all rivaroxaban users in the Netherlands had 0–9 visits. Most rivaroxaban users (72.9%) had 0–4 open care visits in Sweden. In the UK, patients prescribed a daily dose of less than 10 mg had fewer hospitalizations and contacts with a GP than those prescribed 10 mg or more. Similarly, in Germany, patients prescribed a 10 mg tablet or higher were more often hospitalized twice or more in the year after the start date compared with those prescribed the 2.5 mg tablet (39.5% vs 20.8%).

10.2.4 Lifestyle characteristics

Among rivaroxaban users and SOC users for SPAF, median BMI was within the obese range for the UK and the Netherlands. BMI information was available for almost all patients (> 95%) in the rivaroxaban and SOC cohorts in the UK, but only half of the SOC cohort and 58.6% of the rivaroxaban cohort in the Netherlands. In Germany, 38.5% of rivaroxaban users and 39.3% of SOC users had a diagnosis of obesity, whereas in Sweden, a code for obesity was only used for 4.9% of rivaroxaban users and 4.9% of SOC users. Almost all patients were nonsmokers or ex-smokers in the UK. Among patients with available information on smoking in the Netherlands, the majority were either nonsmokers or ex-smokers. Only 2.5% of rivaroxaban users and 2.2% of SOC users had a diagnostic code indicative of smoking in Sweden, although this may be an underestimation since codes for smoking are rarely used in clinical practice. In the UK and the Netherlands, most patients reported some alcohol consumption, but excessive consumption was not commonly reported. Alcohol abuse was rare in Germany and Sweden for users of either study drug. Socioeconomic index was similar between rivaroxaban users and SOC users in the UK and the Netherlands. In Germany, a greater proportion of rivaroxaban users than SOC users were in the least-deprived socioeconomic category. In Sweden, a greater proportion of rivaroxaban users than SOC users had a university-level education, and rivaroxaban users also had higher median disposable

income than SOC users; however, a greater proportion of rivaroxaban users than SOC users lived alone.

For the 'VTE-T without a recent history of cancer' subcohort, median BMI was PPD for both rivaroxaban users and SOC users in the UK. Median BMI was slightly higher in the Netherlands, and was similar between rivaroxaban users PPD and SOC users PPD In Germany, 35.5% of rivaroxaban users and 36.5% of SOC users had diagnosed obesity. In Sweden, a diagnosis of obesity was reported for 4.5% and 4.7% of rivaroxaban and SOC users, respectively. In the UK, the proportion of ex-smokers and nonsmokers was similar between the study drugs, although the proportion of smokers was slightly higher among rivaroxaban users (19.8%) than among SOC users (17.8%). In the Netherlands, the proportion of smokers was lower for rivaroxaban users than for SOC users among those with an available smoking status. The proportion of smokers was similar for rivaroxaban users (1.9%) and SOC users (2.0%) in Sweden. In all countries, excessive alcohol consumption or alcohol abuse was slightly more common among rivaroxaban users than SOC users. Light-to-moderate alcohol consumption was also higher among rivaroxaban users than SOC users in the Netherlands, but not in the UK. In Germany, a greater proportion of rivaroxaban users than SOC users were in the least deprived socioeconomic category. Similarly, in Sweden, rivaroxaban users had a higher median disposable income than SOC users, and a greater proportion of rivaroxaban users than SOC users were educated to university level (28.0% vs 24.5%). The reverse was observed in the UK, with a higher proportion of SOC users than rivaroxaban users in the least deprived socioeconomic category. In the Netherlands, the proportion of SOC users and rivaroxaban users in the 'middle' socioeconomic index category was similar, although a greater proportion of rivaroxaban users than SOC users were in the 'high' socioeconomic index category.

Among rivaroxaban users in the 'VTE-T with a recent history of cancer' subcohort, median BMI was PPD in the UK and PPD in the Netherlands. In Germany and Sweden, the proportion of patients diagnosed as obese was 35.8% and 3.6%, respectively. The proportion of smokers included 1.9%, 6.8% and 12.0% of patients in Sweden, the Netherlands and the UK, respectively. Excessive alcohol consumption or alcohol abuse was uncommon in all countries. The proportion of patients in the least deprived socioeconomic category was 23.3% in the UK and 27.9% in Germany. In the Netherlands, 30.5% of patients were in the 'high' socioeconomic category and 27.8% of patients were educated to university level in Sweden.

Among rivaroxaban users for ACS, median BMI was PPD in the UK and PPD in the Netherlands. The proportion of patients diagnosed with obesity was 33.9% in Germany and 7.8% in Sweden. The proportion of smokers was 19.3% in the UK, 7.4% in the Netherlands and 4.7% in Sweden. Excessive alcohol consumption or alcohol abuse was reported for 4.2% of patients in Germany, 2.3% in the UK (≥ 42 units per week) and 1.6% in Sweden. Excessive alcohol consumption was not reported for any patients in the Netherlands; however, there was a large proportion of patients for whom no information on alcohol consumption was available. The proportion of patients in the least deprived socioeconomic category was 28.4% in the UK, 14.8% in the Netherlands and 29.7% in Germany, although these categories were calculated using different methods. In Sweden, 14.6% of patients were educated to university level and half of the cohort lived alone. In the UK, the proportion of patients in the least deprived socioeconomic category and the proportion of nonsmokers were higher among those who received a rivaroxaban daily dose of less than 10 mg than among those who received 10 mg or more, although median BMI was higher among the low-dose than the higher-dose rivaroxaban users.

10.2.5 Medications of interest

Among users of rivaroxaban for SPAF, patients predominantly received 5–9 medications prior to the start date in the UK, the Netherlands and Germany. The proportion of patients who received 10 or more medications, however, was lower in Germany than in the UK and the Netherlands, despite a longer lookback period available for a more detailed analysis in Germany. Information on polypharmacy was not available in Sweden. Drug classes commonly prescribed to rivaroxaban users for SPAF in the 90 days prior to the start date include antihypertensives, diuretics, statins, antiplatelets and proton pump inhibitors (PPIs). Among rivaroxaban users, the use of antiplatelets ranged from 12.1% in Germany to 40.9% in the UK; however, a greater proportion of SOC users received antiplatelets than rivaroxaban users in all countries.

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, over half of patients in the Netherlands and Germany, and slightly less than half of patients in the UK, received fewer than five medications prior to the start date. Polypharmacy was higher among the 'VTE-T with a recent history of cancer' subcohort, with patients predominantly receiving 5–9 medications prior to the start date in the UK, the Netherlands and Germany. In Germany, however, only 7.5% of rivaroxaban users in the 'VTE-T with a recent history of cancer' subcohort were prescribed 10 or more medications compared with 27.5% of rivaroxaban users in both the UK and the Netherlands. In the 'VTE-T without a recent history of cancer' subcohort, use of drug classes of interest were generally similar between rivaroxaban users and SOC users. Antihypertensives and PPIs were among the most prescribed drug classes in the 90 days prior to the start date among rivaroxaban users for VTE-T, regardless of subcohort.

In the UK, over half of rivaroxaban users with ACS received 10 or more medications, whereas patients predominantly received 5–9 medications in Germany. In the Netherlands, 51.9% of patients received 5–9 medications and 41.8% received 10 or more. Rivaroxaban users more commonly received fewer than five medications in Germany (37.7%) than in the UK (8.0%) or the Netherlands (6.3%). Commonly prescribed drug classes in the 90 days prior to the start date included antihypertensives, antiplatelets, diuretics, statins and PPIs. In the UK, patients who received a daily dose of less than 10 mg had a lower degree of polypharmacy than those who received 10 mg or more (≥ 10 medications, 23.1% vs 66.7%). In Germany, only 4.2% of rivaroxaban users who received a tablet strength of 2.5 mg received 10 or more medications, compared with 17.4% of users who received a tablet strength of 10 mg or higher.

Among users of rivaroxaban with ACS, use of antiplatelet therapy in the year prior to the start date (not including the start date) was higher in the Netherlands (53.2%) and Sweden (62.0%) than in the UK (38.6%) or in Germany (36.4%); the most commonly prescribed antiplatelet was aspirin. In the month after or on the start date, the proportion of users who received antiplatelet therapy increased to 80.7% in the UK and 45.6% in Germany, whereas the proportion decreased to 49.4% in the Netherlands and 44.3% in Sweden. Use of antiplatelets in the month after or on the start date was higher among patients who received a daily dose of rivaroxaban of less than 10 mg compared with those who received more than 10 mg in the Netherlands and the UK. Similarly, in Germany, use of antiplatelets in the month after or on the start date was higher among patients who were prescribed a tablet strength of 2.5 mg (87.5%) compared with those prescribed a higher tablet strength (43.7%). The most common combination of antiplatelet medications was aspirin and clopidogrel in the UK, aspirin monotherapy in Sweden and clopidogrel monotherapy in the Netherlands and Germany.

The time from the ACS event to the start date differed between the countries. The majority of patients in the UK initiated treatment with rivaroxaban 16–30 days after the ACS event, whereas the most common time interval in Sweden was 1–7 days. In the Netherlands, a time interval of 1–7 days was reported for a third of patients, 8–15 days for another third of patients and, for the remainder, the reported interval was 16–30 days or unknown. In Germany, the interval between the ACS event and initiation of rivaroxaban treatment was most often either 8–15 days or 16–30 days. Patients prescribed a daily dose of rivaroxaban of less than 10 mg tended to have a shorter time interval between the ACS event and the start date than patients who received 10 mg or more in the UK. This trend was also observed in Germany among patients prescribed a tablet strength of 2.5 mg compared with those prescribed a higher tablet strength.

10.2.6 Medical history

Hypertension was common among users of rivaroxaban and SOC with SPAF, affecting over half of patients in the UK and Sweden, and more than three-quarters of patients in Germany and the Netherlands. Other common comorbidities in the SPAF cohorts included CAD, heart failure, hyperlipidemia, depression, cancer, asthma, chronic obstructive pulmonary disease (COPD) and diabetes, although the proportions of patients affected differed between the countries. The proportion of rivaroxaban users with hyperlipidemia (69.1%), CAD (51.9%), heart failure (48.8%) and diabetes (37.8%) in Germany, specifically, was higher than in the other countries. A history of intracranial, gastrointestinal or urogenital bleeding was more common among rivaroxaban users than among SOC users in Sweden, the UK and Germany, whereas the proportions were similar in the Netherlands. A history of ischemic stroke and TIA were more common among rivaroxaban users than SOC users in the UK and Germany.

Among users of rivaroxaban assigned to the 'VTE-T without a recent history of cancer' subcohort, the proportion of patients with hypertension ranged from 26.3% to 63.0%, with a trend for higher proportions among SOC users (31.1–66.0%) in all countries except the Netherlands. Only 5.9% of rivaroxaban users and 6.4% of SOC users had hyperlipidemia in Sweden, whereas hyperlipidemia affected over half of rivaroxaban and SOC users in Germany. Hyperlipidemia was also common in the Netherlands and in the UK but to a lesser extent than in Germany. The proportion of rivaroxaban users who had a VTE any time prior to the event necessitating treatment at the start date was 28.1% in Germany, 22.7% in the UK, 3.1% in the Netherlands and 10.6% in Sweden; the equivalent proportions for SOC users were lower in Germany, the Netherlands and the UK.

Hypertension was also common among users of rivaroxaban assigned to the 'VTE-T with a recent history of cancer' subcohort, ranging from 40.2% in Sweden to 78.0% in Germany. A substantial proportion of patients from this subcohort had a VTE at any time prior to the event necessitating treatment at the start date in Sweden (30.9%), the UK (20.1%) and Germany (33.6%). In contrast, only 5.1% had a prior VTE in the Netherlands. There were also differences between the countries in the proportion of patients with hyperlipidemia, with the highest being in Germany (61.0%), followed by the Netherlands (40.7%), the UK (21.1%) and Sweden (8.4%). The proportion of patients with diabetes ranged from 12.1% in Sweden to 30.4% in Germany. A history of bleeding was uncommon in Sweden, Germany and the Netherlands; however, in the UK, 16.0% and 18.1% of patients had a history of gastrointestinal bleeding and urogenital bleeding, respectively.

Over half of rivaroxaban users with ACS in the UK and Sweden and over three-quarters in the Netherlands and Germany had hypertension. Heart failure was common among patients in Germany (67.0%) and the Netherlands (48.1%), but less so in Sweden (26.0%) and the UK

(17.0%). Similarly, the proportion of patients with hyperlipidemia was high in Germany (85.9%) and the Netherlands (77.8%) compared with in the UK (28.4%) and Sweden (26.6%). The proportion of patients who had a myocardial infarction prior to the event necessitating treatment at the start date ranged from 22.9% in Sweden to 84.4% in Germany; however, in Germany, indication events were not excluded from this analysis. In Germany, patients who were prescribed the 2.5 mg tablet less commonly had comorbidities and past medical events than those who were prescribed the 10 mg tablet or higher, although the proportion with a history of myocardial infarction (prior to the event necessitating treatment) and asthma were higher. In the UK, however, several comorbidities and past medical events were more common among rivaroxaban users with a daily dose of less than 10 mg than those who received a daily dose of 10 mg or more, including a history of gastrointestinal and urogenital bleeding, hyperlipidemia, diabetes and depression.

10.2.7 Risk scores

CHA_2DS_2-VASc score and modified HAS-BLED score were calculated for the SPAF indication only.

Among users of rivaroxaban and SOC, the median CHA_2DS_2-VASc score was 3 in the UK, Sweden and the Netherlands, and 5 in Germany. The proportion of patients with each CHA_2DS_2-VASc score was similar between users of rivaroxaban and SOC in the UK, Germany and Sweden. There were minor differences in the Netherlands, with a greater proportion of rivaroxaban users than SOC users among CHA_2DS_2-VASc scores of 0–3. In the Netherlands, the mean CHA_2DS_2-VASc score was 3.3 for SOC users compared with 2.8 for rivaroxaban users.

Among users of rivaroxaban and SOC, the median HAS-BLED score was 3 in Germany, 2 in the UK and Sweden, and 1 in the Netherlands. In the UK, a greater proportion of rivaroxaban users than SOC users had a HAS-BLED score of 1 or 2. A similar trend was observed in the Netherlands for HAS-BLED scores of 0 and 1.

10.2.8 Renal function

For SPAF, the majority of rivaroxaban and SOC users had normal or near normal renal function. Although only a small proportion of patients had advanced renal impairment, there was a trend for advanced renal impairment to be more common among SOC users than rivaroxaban users.

For the ‘VTE-T without a recent history of cancer’ subcohort, most rivaroxaban and SOC users had normal or near normal renal function. A slightly greater proportion of SOC users than rivaroxaban users had intermediate or advanced renal failure.

The majority of rivaroxaban users with ‘VTE-T with a recent history of cancer’ and rivaroxaban users with ACS had normal or near normal renal function.

10.2.9 Pregnancy and pregnancy outcomes

In the UK, there were 80 pregnancies among rivaroxaban users, of which most resulted in a live birth (37.5%), an unknown outcome (32.9%) or a termination (25.0%); stillbirths (2.5%) and miscarriages (6.3%) were uncommon. Of the 296 pregnancies identified among users of rivaroxaban in Sweden, there were 179 deliveries (60.5%), 44 miscarriages (14.9%), 50

terminations (16.9%) and 23 unknown outcomes (7.8%). There were 778 pregnancies among rivaroxaban users in Germany, of which the majority resulted in live births (88.9%). There were only a small proportion of terminations (6.7%), ectopic pregnancies (3.0%), miscarriages (1.3%) and stillbirths (0.1%). Data on pregnancy and pregnancy outcomes were not available in the Netherlands.

10.3 Outcome data

10.3.1 Cohort analysis

The unadjusted incidence rates of bleeding outcomes during the first episode of treatment were determined for first-time users of rivaroxaban and SOC assigned to the SPAF indication and the 'VTE-T without a recent history of cancer' subcohort, and for first-time users of rivaroxaban assigned to ACS. The incidence rates of all other safety and effectiveness outcomes were determined for rivaroxaban users assigned to SPAF, the 'VTE-T without a recent history of cancer' subcohort and ACS. Outcomes were not analyzed in the 'VTE-T with a recent history of cancer' subcohort, owing to the heterogeneity of patients with cancer in terms of their cancer type, metastatic involvement and cancer therapies, as well as the different SOC anticoagulants for cancer-associated thrombosis compared with VTE.

The results of the cohort analysis are described in detail below, with full results available from the individual study reports (Annex 2.1 Individual study reports). A summary of the results for SPAF (Table 10–2, Table 10–3), VTE-T without a recent history of cancer (Table 10–4, Table 10–5) and ACS (Table 10–6, Table 10–7) are provided in Section 10.3.1.10.

10.3.1.1 Intracranial bleeding

10.3.1.1.1 SPAF

In the UK, the Netherlands, Germany and Sweden, the incidence rates of intracranial bleeding among rivaroxaban users were 0.25, 0.34, 0.53 and 0.63 events per 100 person-years, respectively. Among SOC users, the corresponding incidence rates were 0.30, 0.43, 0.49 and 0.80 events per 100 person-years.

Intracerebral bleeding was the most common bleeding subtype among rivaroxaban users, followed by subdural/extradural and subarachnoid bleeding (excluding unspecified bleeds). This trend was also observed for SOC users in Germany and the Netherlands; however, in the UK and Sweden, subdural/extradural bleeding was the most common bleeding subtype among SOC users, followed by intracerebral and subarachnoid bleeding.

The incidence rates of intracranial bleeding among rivaroxaban and SOC users were generally higher for male patients than for female patients, although the incidence rate was higher for female patients than for male patients among SOC users in the UK. There was a trend for higher incidence rates with advancing age for both rivaroxaban users and SOC users.

Among rivaroxaban users, the incidence rates of intracranial bleeding were higher for patients with renal impairment than for those with normal renal function, and for elderly patients than for patients aged 75 years or younger. The incidence rates were also higher among patients with diabetes than among those without diabetes in Germany, the Netherlands and Sweden.

10.3.1.1.2 VTE-T

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, the incidence rate of intracranial bleeding was 0.17, 0.41, 0.29 and 0.40 events per 100 person-years in the UK, the Netherlands, Germany and Sweden, respectively. Among SOC users, the corresponding incidence rates were 0.16, 0.16, 0.31 and 0.50 events per 100 person-years.

When stratified by bleeding subtype, the incidence rates were highest for intracerebral bleeding, followed by subdural/extradural and subarachnoid bleeding among rivaroxaban users in Germany, Sweden and the UK. In the Netherlands, the incidence rates of intracerebral and subarachnoid bleeding were the same, with no subdural/extradural bleeding events among rivaroxaban users. Among SOC users, bleeding subtypes differed between different countries, with intracerebral the most common in Germany, subarachnoid the most common in the Netherlands and subdural/extradural the most common in Sweden. In the UK, the incidence rates of the three bleeding subtypes were identical among SOC users.

Among rivaroxaban users, the incidence rates of intracranial bleeding were higher among female patients than among male patients in Germany and Sweden, whereas the incidence rate was higher among male patients than among female patients in the UK. In the Netherlands, the incidence rates were the same for male patients and female patients who received rivaroxaban. For SOC users, the incidence rates were higher among female patients than among male patients in Germany and the Netherlands but were higher among male patients in Sweden and the UK. There was a trend for higher incidence rates with advancing age for both rivaroxaban and SOC users.

Among rivaroxaban users, incidence rates of intracranial bleeding were higher for patients with renal impairment than for those with normal renal function, for elderly patients than for patients aged 75 years or younger, and for patients with diabetes than for those without.

10.3.1.1.3 ACS

There were very few intracranial bleeding events among rivaroxaban users with ACS, with only one event in the UK, one event in Sweden and two events in Germany. There were no intracranial bleeding events among ACS patients in the Netherlands. Owing to the low number of events, no trends could be identified with regard to age, sex and subgroups of interest.

10.3.1.2 Gastrointestinal bleeding

10.3.1.2.1 SPAF

The incidence rate of gastrointestinal bleeding among rivaroxaban users with SPAF was 1.72 events per 100 person-years in Germany, 1.30 events per 100 person-years in Sweden, 1.02 events per 100 person-years in the Netherlands and 0.49 events per 100 person-years in the UK. The corresponding incidence rates among SOC users were 1.15, 0.82, 1.42 and 0.3 events per 100 person-years, respectively.

Among rivaroxaban users, the incidence rates were higher for female patients than for male patients in Germany, the Netherlands and Sweden, although incidence rates were similar between the sexes for SOC users. The incidence rate of gastrointestinal bleeding increased with advancing age for both rivaroxaban users and SOC users. Among users of rivaroxaban, the incidence rate of gastrointestinal bleeding was higher for elderly patients than for nonelderly patients and for patients with diabetes than for patients without. In the UK,

Sweden and Germany, the incidence rates of gastrointestinal bleeding were higher for patients with renal impairment than for those with normal or near normal renal function, but in the Netherlands, there were too few events in patients with renal impairment for meaningful interpretation.

10.3.1.2.2 VTE-T

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, the incidence rates of gastrointestinal bleeding were 1.13 (Germany), 0.62 (Netherlands), 0.92 (Sweden) and 0.58 (UK) events per 100 person-years. The corresponding incidence rates for SOC users were 0.94, 0.49, 0.71 and 0.37 events per 100 person-years, respectively.

In the Netherlands, there were only three gastrointestinal bleeding events among rivaroxaban users and nine among SOC users, which precludes identification of trends with regard to age, sex and subgroups of interest. In the remaining countries, the incidence rates of gastrointestinal bleeding were higher among female patients than among male patients for both rivaroxaban and SOC users. Incidence rates increased with advancing age, although this trend was less apparent in the UK than in Sweden and Germany, which may be due to the lower number of events included in the analysis.

Among users of rivaroxaban, the incidence rates of gastrointestinal bleeding were higher for patients with renal impairment than for those with normal or near normal renal function, for elderly patients than for nonelderly patients and for patients with diabetes than for those without.

10.3.1.2.3 ACS

Among rivaroxaban users with ACS, there were only two gastrointestinal bleeding events in the Netherlands, five in Sweden, and one in the UK; therefore, no trends could be observed with regard to age, sex or subgroups of interest in these countries. In Germany, there were 29 gastrointestinal bleeding events, corresponding to an incidence rate of 3.55 events per 100 person-years. The incidence rate was higher for male patients than for female patients, and it increased with advancing age. The incidence rate of gastrointestinal bleeding was higher for patients with renal impairment than for those with normal or near normal renal function, for elderly patients than for nonelderly patients and for patients without diabetes than for those with diabetes.

10.3.1.3 Urogenital bleeding

10.3.1.3.1 SPAF

Among rivaroxaban users for SPAF, the incidence rates of urogenital bleeding were similar between the countries: 0.54 events per 100 person-years in Sweden, 0.48 events per 100 person-years in Germany, 0.34 events per 100 person-years in the Netherlands and 0.27 events per 100 person-years in the UK. The equivalent incidence rates among SOC users were 0.41, 0.34, 0.42 and 0.24 events per 100 person-years, respectively. The incidence rates of urogenital bleeding were higher for male patients than for female patients among rivaroxaban users and SOC users, and the incidence rates tended to increase with advancing age.

Among rivaroxaban users, the incidence rates of urogenital bleeding were higher for patients with renal impairment than for those with normal or near normal renal function, for elderly patients than for nonelderly patients and for patients with diabetes than for those without.

10.3.1.3.2 VTE-T

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, the incidence rate of urogenital bleeding was 0.66 events per 100 person-years in Germany, 0.33 events per 100 person-years in Sweden, 0.62 events per 100 person-years in the Netherlands and 0.29 events per 100 person-years in the UK. The equivalent incidence rates among SOC users were 0.36, 0.27, 0.71 and 0.29 events per 100 person-years, respectively.

In the Netherlands and the UK, there were too few urogenital bleeding events to identify any trends. In Germany, the incidence rate of urogenital bleeding was higher for female patients than for male patients for both rivaroxaban and SOC users. In Sweden, the incidence rates were similar between male patients and female patients for rivaroxaban users, whereas among SOC users, the incidence rate was higher for male patients than for female patients. There was no apparent trend in incidence rate with advancing age in Germany; however, the incidence rate generally increased with advancing age in Sweden.

Among rivaroxaban users, the incidence rates of urogenital bleeding were higher for patients without diabetes than for those with diabetes in Germany and Sweden. The incidence rate was also higher for patients with normal or near normal renal function than for those with renal impairment in Germany; no patients with renal impairment experienced urogenital bleeding in Sweden. The incidence rate was higher for nonelderly patients than for elderly patients in Germany, whereas the incidence rate was higher for elderly patients than for nonelderly patients in Sweden.

10.3.1.3.3 ACS

Among rivaroxaban users with ACS, there were only six urogenital bleeding events in Germany, one event in the Netherlands, one event in Sweden and none in the UK. Owing to these low numbers of events, meaningful interpretation of stratification by age, sex or subgroup of interest was not possible.

10.3.1.4 Other bleeding

10.3.1.4.1 SPAF

Among rivaroxaban users with SPAF, the incidence rate of other bleeding (defined as hospitalization for bleeding occurring at a site other than the sites included in the primary safety outcomes) was 0.69 events per 100 person-years in Germany, 0.36 events per 100 person-years in the Netherlands, 0.63 events per 100 person-years in Sweden, and 0.14 events per 100 person-years in the UK. The equivalent incidence rates among SOC users were 0.89, 0.69, 0.58 and 0.16 events per 100 person-years, respectively. There were no consistent trends in the incidence rate of other bleeding between male patients and female patients for either study drug. Incidence rates increased with advancing age among both rivaroxaban users and SOC users.

Among rivaroxaban users, the incidence rates of other bleeding were higher for elderly patients than for nonelderly patients. The incidence rates were higher among patients with

renal impairment than among patients with normal or near normal function in Germany and the UK; no patients with renal impairment experienced other bleeding in Sweden and the Netherlands. The incidence rates of urogenital bleeding were higher for patients with diabetes than for those without in Germany and Sweden.

10.3.1.4.2 VTE-T

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, the incidence rate of other bleeding was 0.44 events per 100 person-years in Germany and 0.45 events per 100 person-years in Sweden. Among SOC users, the equivalent incidence rates were 0.73 and 0.50 events per 100 person-years, respectively. In the UK, there were only six other bleeding events among rivaroxaban users and three events among SOC users, corresponding to incidence rates of 0.17 and 0.08 events per 100 person-years, respectively. In the Netherlands, there were also few other bleeding events, including only three in rivaroxaban users (0.62 events per 100 person-years) and nine in SOC users (0.49 events per 100 person-years).

Owing to the low numbers of events in the UK and the Netherlands, trends could only be identified in Germany and Sweden. The incidence rates were higher for female patients than for male patients for both study drugs in Germany, whereas incidence rates were similar between male patients and female patients in Sweden. Incidence rates of other bleeding tended to increase with advancing age for both rivaroxaban users and SOC users. Among rivaroxaban users, the incidence rates of other bleeding were higher for patients with renal impairment than for those with normal or near normal renal function, for elderly patients than for nonelderly patients and for patients with diabetes than for those without.

10.3.1.4.3 ACS

There were only nine other bleeding events among rivaroxaban users with ACS in Germany and one in Sweden. There were no other bleeding events among rivaroxaban users with ACS in the Netherlands or the UK. Owing to the low number of events, no trends in incidence rate could be identified with regard to age, sex or subgroups of interest.

10.3.1.5 Noninfective liver disease

10.3.1.5.1 SPAF

Among rivaroxaban users for SPAF, the incidence rate of noninfective liver disease was 0.19 events per 100 person-years in Germany, 0.24 events per 100 person-years in the UK and 0.34 events per 100 person-years in the Netherlands. In Sweden, the incidence rate was 0.11 events per 100 person-years when the analysis was restricted to principal diagnoses associated with hospitalization and 0.34 events per 100 person-years when secondary diagnoses given in hospital or open care were included.

There were no apparent trends with regard to age or sex; however, the incidence rates were higher among patients with renal impairment than among those with normal or near normal function. Patients with diabetes had higher incidence rates of noninfective liver disease than those without diabetes in Germany and Sweden.

10.3.1.5.2 VTE-T

In the UK, there were only six incidences of noninfective liver disease among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, corresponding to an incidence rate of 0.17 events per 100 person-years. A similar incidence rate of 0.20 events per 100 person-years was observed in Germany and Sweden (including principal and secondary diagnoses in hospital or open care). When restricting to principal diagnoses associated with hospitalization, however, the incidence rate in Sweden was 0.04 events per 100 person-years. In the Netherlands, none of the rivaroxaban users had noninfective liver disease.

There were no observable trends for age or sex. In Germany, the incidence rate of noninfective liver disease was higher among patients with renal impairment than among those with normal renal function. This trend was also observed in the UK and Sweden; however, there were too few events in these countries for meaningful interpretation of subgroups of interest.

10.3.1.5.3 ACS

There were no incidences of noninfective liver disease among rivaroxaban users with ACS in the Netherlands, Germany and the UK. There were two events among rivaroxaban users with ACS in Sweden.

10.3.1.6 DVT/PE

10.3.1.6.1 SPAF

Among rivaroxaban users with SPAF, the incidence rate of hospitalized DVT/PE was 0.15 events per 100 person-years in Germany. The incidence rates were lower in both the UK and the Netherlands (0.08 events per 100 person-years); however, the number of DVT/PE events was low in these cohorts, with only four events per country. In Sweden, the equivalent incidence rate was 0.35 events per 100 person-years.

There were too few events in the UK and the Netherlands for meaningful interpretation of age, sex or subgroups of interest. The incidence rate of DVT/PE was higher among female patients than among male patients in Germany, although this trend was not observed in Sweden. In Sweden, incidence rates of hospitalized DVT/PE were highest at the low age groups (≤ 49 years or 50–59 years) and high age groups (≥ 90 years), whereas incidence rates of hospitalized DVT/PE increased with advancing age in Germany. The incidence rates of DVT/PE were also higher among patients with renal impairment than among those with normal or near normal renal function, among elderly patients than among those aged 75 years or younger and among patients with diabetes than among those without.

10.3.1.6.2 VTE-T

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, the incidence rate of hospitalized DVT/PE was 2.30 events per 100 person-years in Germany, 1.46 events per 100 person-years in the Netherlands and 0.64 events per 100 person-years in the UK. This analysis was not conducted in Sweden because the same codes are used for recurrent DVT/PE events as for follow-up visits after an initial DVT/PE event in the Swedish registers. It might have been possible to identify late recurrences with sufficiently long blanking periods; however, the observation periods on treatment were too short. It was,

therefore, not possible to distinguish early recurrences from initial DVT/PE events in Sweden. This was a known issue for the Swedish registers and, therefore, identification of the DVT/PE outcome was not part of the original protocol for the Swedish study.

There were only seven DVT/PE events in the Netherlands, which precludes meaningful interpretation of subgroups. The incidence rate of DVT/PE was slightly higher among male patients than among female patients in Germany, although incidence rates were similar between the sexes in the UK. In both countries, the incidence rates were highest for those aged 49 years or younger when stratified by age group. There were no observable trends with regard to renal impairment or diabetes; however, the incidence rates of DVT/PE were higher for nonelderly patients than for elderly patients.

10.3.1.6.3 ACS

In Germany, there were only four incidences of hospitalized DVT/PE among rivaroxaban users with ACS, corresponding to an incidence rate of 0.48 events per 100 person-years. In Sweden, there were two events, corresponding to an incidence rate of 1.28 events per 100 person-years. There were no incidences of DVT/PE among rivaroxaban users with ACS in the Netherlands and the UK. There were too few events for meaningful interpretation of trends with regard to age, sex and subgroups of interest.

10.3.1.7 Ischemic stroke

10.3.1.7.1 SPAF

Among rivaroxaban users with SPAF, the incidence rate of ischemic stroke was similar in Germany (1.13 events per 100 person-years) and Sweden (1.52 events per 100 person-years). The incidence rates were lower in the UK and the Netherlands, corresponding to 0.31 and 0.38 events per 100 person-years, respectively.

The incidence rates of ischemic stroke were higher in female patients than in male patients in Germany, Sweden and the UK. In Germany, Sweden and the Netherlands, incidence rates generally increased with advancing age. This trend was also observed in the UK; however, the highest incidence rate in this cohort was observed in patients aged 49 years or younger. The incidence rates were higher for patients with renal impairment than for those with normal or near normal function, for elderly patients than for nonelderly patients and for patients with diabetes than for those without.

10.3.1.7.2 VTE-T

Among rivaroxaban users in the ‘VTE-T without a recent history of cancer’ subcohort, the incidence rate of ischemic stroke was 0.64 events per 100 person-years in Germany and 0.88 per 100 person-years in Sweden. There were only three ischemic strokes in the UK and two ischemic strokes in the Netherlands.

In Germany and Sweden, the incidence rates of ischemic stroke were higher for female patients than for male patients, and they increased with advancing age up to 80–89 years. The incidence rates were higher for patients with renal impairment than for those with normal or near normal function, for elderly patients than for nonelderly patients and for patients with diabetes than for those without.

10.3.1.7.3 ACS

Among rivaroxaban users with ACS, there were five ischemic strokes for Sweden and twelve for Germany. There were no instances of ischemic stroke among rivaroxaban users in the Netherlands and the UK. Owing to the limited number of events included in these analyses, no trends could be identified with regard to age, sex or subgroups of interest.

10.3.1.8 Myocardial infarction

10.3.1.8.1 SPAF

Among rivaroxaban users with SPAF, the incidence rate of myocardial infarction was similar in the Netherlands (0.56 events per 100 person-years) and Germany (0.79 events per 100 person-years). The incidence rate was higher in Sweden at 1.07 events per 100 person-years and lowest in the UK (0.33 events per 100 person-years).

In the Netherlands, Germany and Sweden, the incidence rates were higher for male patients than for female patients; however, in the UK, the incidence rate was higher among female patients than among male patients. The incidence rates of myocardial infarction generally increased with advancing age. This trend was not observed in the Netherlands; however, there were few patients within each age group. Furthermore, no major differences in incidence rates between subgroups of interest were observed in the Netherlands, likely owing to low numbers of events. In the remaining countries, higher incidence rates of ischemic stroke were observed for patients with renal impairment than for those with normal or near normal function, for elderly patients than for nonelderly patients and for patients with diabetes than for those without.

10.3.1.8.2 VTE-T

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, the incidence rate of myocardial infarction was 0.48 events per 100 person-years in Germany and 0.54 events per 100 person-years in Sweden. There were only seven events in the UK and none in the Netherlands. In Sweden, the incidence rate was the same for male patients and for female patients, whereas in Germany the incidence rate was higher among male patients than among female patients. The incidence rates of myocardial infarction tended to increase with advancing age in both countries and were higher among elderly patients than among nonelderly patients. The incidence rates were also higher among patients with renal impairment than among patients with normal or near normal function and among patients with diabetes than among those without.

10.3.1.8.3 ACS

This analysis focused on the incidence rate of hospitalization for new myocardial infarction events occurring after the indication event that necessitated treatment with rivaroxaban; however, owing to the limitations of the data sources, that the exclusion of all indication events cannot be confirmed. Among rivaroxaban users with ACS, the incidence rate of myocardial infarction was 5.28 per 100 person-years in Germany and 8.54 per 100 person-years in Sweden. In the Netherlands and the UK, there were only three myocardial infarction events per country. The incidence rate was higher among male patients than among female patients in Germany, although the opposite was observed in Sweden. There was a trend for higher incidence rates with advancing age in both countries. The incidence rates were higher

for elderly patients than for nonelderly patients and for patients with diabetes than for those without. There were no myocardial infarctions among patients with renal impairment in Sweden; however, in Germany, the incidence rate of myocardial infarction was higher among patients with renal impairment than among patients with normal or near normal function.

10.3.1.9 All-cause mortality

10.3.1.9.1 SPAF

Among rivaroxaban users with SPAF, the incidence rate of all-cause mortality in the Netherlands was 2.56 deaths per 100 person-years. All-cause mortality was higher in the other countries, including 4.50 deaths per 100 person-years in the UK, 5.17 deaths per 100 person-years in Sweden, and 6.08 deaths per 100 person-years in Germany. The incidence rates were higher among female patients than among male patients and, as expected, increased with advancing age. The incidence rates of all-cause mortality were higher for patients with renal impairment than for those with normal or near normal function, for elderly patients than for nonelderly patients and for patients with diabetes than for those without.

10.3.1.9.2 VTE-T

Among rivaroxaban users in the 'VTE-T without a recent history of cancer' subcohort, the incidence rate of all-cause mortality was 3.26 deaths per 100 person-years in Germany, 3.22 deaths per 100 person-years in Sweden and 4.05 deaths per 100 person-years in the UK. There were only nine deaths in the Netherlands, corresponding to an incidence rate of 1.86 deaths per 100 person-years. The incidence rate was similar between male patients and female patients in the UK, whereas in the other countries, the incidence rates were higher for female patients than for male patients. The incidence rates increased with advancing age and were higher among elderly patients than among patients aged 75 years or younger. The incidence rates of all-cause mortality were also higher for patients with renal impairment than for those with normal or near normal function and for patients with diabetes than for those without.

10.3.1.9.3 ACS

Among rivaroxaban users with ACS, the incidence rate of all-cause mortality was 8.99 deaths per 100 person-years in Germany. There were 14 deaths in Sweden, corresponding to an incidence rate of 8.93 deaths per 100 person-years and four deaths in the UK, resulting an incidence rate of 5.36 per 100 person-years. In the Netherlands, none of the rivaroxaban users with ACS died during the first episode of treatment. Owing to the limited number of events, trends in incidence rates regarding age, sex and subgroups of interest could only be identified for Germany. The incidence rate of all-cause mortality was higher among female patients than among male patients, and it increased with advancing age. The incidence rate was higher for patients with renal impairment than for those with normal or near normal function, for elderly patients than for nonelderly patients, and for patients with diabetes than for those without.

10.3.1.10 Summary of cohort analysis results

Table 10–2: Incidence rate of safety outcomes associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – SPAF

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)
Intracranial bleeding												
Rivaroxaban	44	17,576.7	0.25 (0.18–0.34)	17	5064	0.34 (0.19–0.52)	938	175,578.2	0.53 (0.50–0.57)	115	18,328	0.63 (0.61–0.85)
SOC	80	26,251.7	0.30 (0.24–0.38)	45	10,486	0.43 (0.31–0.57)	946	194,598.6	0.49 (0.46–0.52)	1080	135,126	0.80 (0.75–0.85)
Gastrointestinal bleeding												
Rivaroxaban	86	17,535.1	0.49 (0.39–0.61)	51	5017	1.02 (0.75–1.32)	2988	173,832.2	1.72 (1.66–1.78)	237	18,2251	1.30 (1.14–1.47)
SOC	78	26,223.0	0.30 (0.24–0.37)	146	10,308	1.42 (1.19–1.66)	2219	192,655.8	1.15 (1.10–1.20)	1102	134,679	0.82 (0.77-0.87)
Urogenital bleeding												
Rivaroxaban	47	17,544.7	0.27 (0.20–0.36)	17	5047	0.34 (0.19–0.52)	849	175,113.2	0.48 (0.45–0.52)	98	18,305	0.54 (0.44–0.65)
SOC	64	26,189.1	0.24 (0.19–0.31)	44	10,470	0.42 (0.3–0.56)	665	194,178.4	0.34 (0.32–0.37)	556	135,108	0.41 (0.38–0.45)
Other bleeding												
Rivaroxaban	25	17,564.8	0.14 (0.09–0.21)	18	5050	0.36 (0.21–0.54)	1205	174,797.0	0.69 (0.65–0.73)	115	18,310	0.63 (0.52–0.75)
SOC	41	26,226.1	0.16 (0.11–0.21)	72	10,460	0.69 (0.54–0.86)	1719	192,833.7	0.89 (0.85–0.93)	785	134,936	0.58 (0.54–0.62)
Noninfective liver disease												
Rivaroxaban	42	17,547.3	0.24 (0.17–0.32)	17	5050	0.34 (0.19–0.52)	335	175,630.2	0.19 (0.17–0.21)	20	18,356	0.11 (0.07–0.17)

a: Patients were censored at whichever came 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

CI, confidence interval; GP, general practitioner; SOC, standard of care; SPAF, prevention of stroke and systemic embolism in nonvalvular atrial fibrillation

Table 10–3: Incidence rate of effectiveness outcomes associated with first use of rivaroxaban (first episode of treatment [a]) – SPAF

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)
DVT/PE												
Rivaroxaban	14	17,573.6	0.08 (0.04–0.13)	4	5066	0.08 (0.02–0.18)	268	175,660.0	0.15 (0.13–0.17)	65	18,346	0.35 (0.28–0.45)
Ischemic stroke												
Rivaroxaban	55	17,548.6	0.31 (0.24–0.41)	19	5039	0.38 (0.22–0.57)	1978	174,469.8	1.13 (1.08–1.18)	278	18,268	1.52 (1.35–1.71)
Myocardial infarction												
Rivaroxaban	58	17,542.7	0.33 (0.25–0.43)	28	5037	0.56 (0.37–0.79)	1376	175,091.2	0.79 (0.74–0.83)	196	18,268	1.07 (0.93–1.23)
All-cause mortality												
Rivaroxaban	791	17,584.5	4.50 (4.19–4.82)	130	5073	2.56 (2.13–3.03)	10,694	175,865.0	6.08 (5.97–6.20)	950	18,364	5.17 (4.85–5.51)

a: Patients were censored at whichever came 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

CI, confidence interval; DVT, deep vein thrombosis; GP, general practitioner; PE, pulmonary embolism; SOC, standard of care; SPAF, prevention of stroke and systemic embolism in nonvalvular atrial fibrillation

Table 10–4: Incidence rate of safety outcomes associated with first use of rivaroxaban and SOC (first episode of treatment [a]) – 'VTE-T without a recent history of cancer' subcohort

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)
Intracranial bleeding												
Rivaroxaban	6	3435.3	0.17 (0.06–0.38)	2	484	0.41 (0.04–1.2)	67	23,448.5	0.29 (0.22–0.36)	38	9420	0.40 (0.29–0.55)
SOC	6	3765.3	0.16 (0.06–0.35)	3	1844	0.16 (0.03–0.4)	88	28,192.9	0.31 (0.25–0.38)	140	27,739	0.50 (0.43–0.60)
Gastrointestinal bleeding												
Rivaroxaban	20	3429.7	0.58 (0.36–0.90)	3	483	0.62 (0.11–1.55)	264	23,294.5	1.13 (1.00–1.28)	86	9394	0.92 (0.74–1.13)
SOC	14	3761.6	0.37 (0.20–0.62)	9	1842	0.49 (0.22–0.87)	263	28,004.4	0.94 (0.83–1.06)	197	27,665	0.71 (0.62–0.82)
Urogenital bleeding												
Rivaroxaban	10	3427.2	0.29 (0.14–0.54)	3	483	0.62 (0.11–1.55)	155	23,354.1	0.66 (0.56–0.78)	31	9419	0.33 (0.23-0.47)
SOC	11	3758.5	0.29 (0.15–0.52)	13	1838	0.71 (0.37–1.15)	102	28,103.0	0.36 (0.30–0.44)	74	27,766	0.27 (0.21–0.33)
Other bleeding												
Rivaroxaban	6	3433.2	0.17 (0.06–0.38)	3	481	0.62 (0.11–1.55)	103	23,402.7	0.44 (0.36–0.53)	42	9414	0.45 (0.33–0.60)
SOC	3	3764.9	0.08 (0.02–0.23)	9	1842	0.49 (0.22–0.87)	204	28,038.7	0.73 (0.63–0.83)	139	27,698	0.50 (0.42–0.59)
Noninfective liver disease												
Rivaroxaban	6	3433.4	0.17 (0.06–0.38)	-	-	-	46	23,453.4	0.20 (0.14–0.26)	4	9426	0.04 (0.02–0.11)

a: Patients were censored at whichever came 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

CI, confidence interval; GP, general practitioner; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

Table 10–5: Incidence rate of effectiveness outcomes associated with first use of rivaroxaban (first episode of treatment [a]) – 'VTE-T without a recent history of cancer' subcohort

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Events n	**Person-years**	**Incidence rate (95% CI)**	**Events n**	**Person-years**	**Incidence rate (95% CI)**	**Events n**	**Person-years**	**Incidence rate (95% CI)**	**Events n**	**Person-years**	**Incidence rate (95% CI)**
DVT/PE												
Rivaroxaban	22	3424.8	0.64 (0.40–0.97)	7	479	1.46 (0.57—2.77)	529	22,984.7	2.30 (2.11–2.51)	-	-	-
Ischemic stroke												
Rivaroxaban	3	3432.5	0.09 (0.02–0.26)	2	484	0.41 (0.04–1.2)	150	23,383.2	0.64 (0.54–0.75)	83	9399	0.88 (0.71–1.10)
Myocardial infarction												
Rivaroxaban	7	3431.7	0.20 (0.08–0.42)	-	-	-	113	23,416.3	0.48 (0.40–0.58)	51	9405	0.54 (0.41–0.71)
All-cause mortality												
Rivaroxaban	139	3435.5	4.05 (3.40–4.78)	9	485	1.86 (0.82–3.3)	766	23,473.6	3.26 (3.04–3.50)	304	9431	3.22 (2.88–3.61)

a: Patients were censored at whichever came 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

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

Table 10–6: Incidence rate of safety outcomes associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Events n	**Person-years**	**Incidence rate (95% CI)**	**Events n**	**Person-years**	**Incidence rate (95% CI)**	**Events n**	**Person-years**	**Incidence rate (95% CI)**	**Events n**	**Person-years**	**Incidence rate (95% CI)**
Intracranial bleeding												
Rivaroxaban	1	73.6	1.36 (0.03–7.57)	-	-	-	2	833.6	0.24 (0.03–0.87)	1	157	0.64 (0.09–0.45)
Gastrointestinal bleeding												
Rivaroxaban	1	74.6	1.34 (0.03–7.47)	2	29	6.87 (0.59–20.01)	29	816.6	3.55 (2.38– 5.10)	5	156	3.20 (1.33–7.70)
Urogenital bleeding												
Rivaroxaban	-	-	-	1	29	3.44 (0–13.76)	6	826.9	0.73 (0.27–1.58)	1	156	0.64 (0.09–4.54)
Other bleeding												
Rivaroxaban	-	-	-	-	-	-	9	828.6	1.09 (0.50–2.06)	1	157	0.64 (0.09–4.54)
Noninfective liver disease												
Rivaroxaban	-	-	-	-	-	-	0	834.6	0.00 (0.00–0.44)	2	156	1.28 (0.32–5.11)

a: Patients were censored at whichever came 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

ACS, acute coronary syndrome; CI, confidence interval; GP, general practitioner

Table 10–7: Incidence rate of effectiveness outcomes associated with first use of rivaroxaban (first episode of treatment [a]) – ACS

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)	Events n	Person-years	Incidence rate (95% CI)
DVT/PE												
Rivaroxaban	-	-	-	-	-	-	4	828.0	0.48 (0.13–1.24)	2	156	1.28 (0.32–5.13)
Ischemic stroke												
Rivaroxaban	-	-	-	-	-	-	12	825.9	1.45 (0.75–2.54)	5	156	3.20 (1.33–7.69)
Myocardial infarction												
Rivaroxaban	3	71.4	4.20 (0.87–12.29)	3	28	10.72 (1.92–26.68)	42	796.0	5.28 (3.80–7.13)	13	152	8.54 (4.96–14.72)
All-cause mortality												
Rivaroxaban	4	74.6	5.36 (1.46–13.73)	-	-	-	75	834.6	8.99 (7.07–11.26)	14	157	8.93 (5.29–15.09)

a: Patients were censored at whichever came 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

ACS, acute coronary syndrome; CI, confidence interval; DVT, deep vein thrombosis; GP, general practitioner; PE, pulmonary embolism

10.3.2 Nested case-control analysis

A nested case-control analysis was conducted for the four major bleeding outcomes (intracranial bleeding, gastrointestinal bleeding, urogenital bleeding and other bleeding) in the cohorts of patients with SPAF and 'VTE-T without a recent history of cancer'. The number of cases reported for each of the nested case-control analyses are higher than those reported for the cohort analysis because the latter was restricted to cases occurring during the first episode of treatment, with bleeding events occurring after censoring not being included in the cohort analysis. In contrast, the nested case-control analyses included all bleeding events occurring during complete follow-up, with no censoring at the end of the first treatment episode.

For all variables, ORs were adjusted for matching variables. ORs for recency of rivaroxaban and SOC, including analysis of dose and treatment duration, were further adjusted for additional confounding variables.

The results of the nested case-control analysis are described in detail below, with full results available from the individual study reports (Annex 2.1 Individual study reports). A summary of the results for SPAF (Table 10–8) and 'VTE-T without a recent history of cancer' (Table 10–9) are provided in Section 10.3.2.5.

10.3.2.1 Intracranial bleeding

10.3.2.1.1 SPAF

Among patients with SPAF at the start date, there were 3995 cases of intracranial bleeding available for the nested case-control analysis in Germany, 2373 cases in Sweden, 225 cases in the UK and 189 in the Netherlands. In the year prior to the index date, being hospitalized twice or more was associated with a higher risk of intracranial bleeding relative to not being hospitalized; one hospitalization in the year prior to the index date was associated with a higher risk in all countries except Sweden. The risk of intracranial bleeding increased with increasing number of contacts with a GP (UK, Netherlands) or visits to open care (Sweden) in the year prior to the index date. In Sweden and Germany, a higher risk was also observed for patients given a previous alcohol-related diagnosis. Information on polypharmacy was not available for Sweden; however, use of 10 or more medications prior to the index date was associated with a higher risk of intracranial bleeding in Germany and the Netherlands relative to fewer than 5 medications, as well as use of 5–9 medications in Germany.

Of the comorbidities and medical events of interest, only history of ischemic stroke was associated with a higher risk of intracranial bleeding in the UK. History of ischemic stroke was also a risk factor in Sweden and Germany, as well as TIA and several other comorbidities and past medical events. A history of intracranial bleeding was associated with a higher risk of new intracranial bleeding in Germany, Sweden and the Netherlands. In the Netherlands, history of TIA, hypertension and cancer was associated with higher risks of bleeding. The risk of intracranial bleeding increased with worsening modified HAS-BLED score in all countries, and with worsening CHA_2DS_2-VASc score in all countries except the UK.

In the Netherlands, only current use of selective serotonin reuptake inhibitors (SSRIs) was associated with a higher risk of intracranial bleeding. SSRIs were also associated with a higher risk in the UK, as well as current use of antibiotics. Current use of several medications was associated with risk of intracranial bleeding in Sweden, including antiplatelets, parenteral anticoagulants, oral anticoagulants, PPIs, SSRIs, medications that interact with CYP3A4/ P-GP and lipid-lowering medications. Similarly, in Germany, use of antiplatelets, parenteral

anticoagulants, PPIs, SSRIs and antibiotics were associated with higher risks of intracranial bleeding.

The adjusted OR for intracranial bleeding associated with current use of rivaroxaban was 1.32 (95% CI, 1.15–1.51) in Germany, 0.82 (95% CI, 0.64–1.06) in Sweden, 1.52 (95% CI, 0.90–2.58) in the UK and 1.71 (95% CI, 0.98–2.96) in the Netherlands relative to nonuse. For current use of SOC, the ORs for intracranial bleeding were 1.85 (95% CI, 1.61–2.14), 1.30 (95% CI, 1.14–1.49), 1.44 (95% CI, 0.83–2.48) and 5.91 (95% CI, 3.23–10.81), respectively, relative to nonuse. Among current users of SOC in the UK, the highest risk of intracranial bleeding was observed in those with an INR of 4 or greater.

10.3.2.1.2 VTE-T

Among patients in the 'VTE-T without a recent history of cancer' subcohort at the start date, there were 387 cases of intracranial bleeding available for the nested case-control analysis in Sweden, 360 in Germany, 132 in the UK and only 17 in the Netherlands.

No lifestyle factors were associated with a higher risk of intracranial bleeding in the Netherlands. The risk of intracranial bleeding was higher for patients with two or more hospitalizations than for those who had not been hospitalized in the year prior to index in the remaining countries, as well as for patients with one hospitalization in Germany. In Sweden, the risk was almost twice as high for those with 10 or more open care visits during the preceding year than for those who only had 0–4 visits. Socioeconomic factors associated with higher risk of intracranial bleeding in Sweden were the presence of a previous alcohol-related diagnosis, smoking and living alone, while being educated to university level and having a higher than median income were associated with a lower risk. A diagnosis indicating alcohol abuse was also associated with a higher risk of intracranial bleeding in Germany.

In Sweden and Germany, several comorbidities or past medical events were strongly associated with risk of intracranial bleeding, including history of intracranial bleeding and ischemic stroke. No comorbidities or past medical events were associated with a higher risk of intracranial bleeding in the Netherlands or the UK.

In Sweden, current use of parenteral anticoagulants, oral anticoagulants and SSRIs were associated with a higher risk of intracranial bleeding relative to nonuse. In Germany, only current use of parenteral anticoagulants and SSRIs were associated with a higher risk. None of the medications of interest were associated with a higher risk of intracranial bleeding in the Netherlands or the UK.

The adjusted OR associated with current use of rivaroxaban was 1.73 (95% CI, 1.16–2.58) in Germany, 1.56 (95% CI, 0.98–2.50) in Sweden and 2.54 (95% CI, 0.74–8.69) in the UK relative to nonuse. For current use of SOC, the ORs were 2.42 (95% CI, 1.62–3.61), 1.89 (95% CI, 1.32–2.70) and 1.53 (95% CI, 0.42–5.52), respectively, relative to nonuse. The adjusted OR associated with current use of rivaroxaban and current use of SOC were not calculated in the Netherlands, owing to the small number of cases.

10.3.2.2 Gastrointestinal bleeding

10.3.2.2.1 SPAF

Among patients with SPAF at the start date, there were 9769 cases of gastrointestinal bleeding available for the nested case-control analysis in Germany, 3301 cases in Sweden, 292 cases in the UK and 470 cases in the Netherlands.

Several lifestyle factors were associated with a risk of gastrointestinal bleeding in all countries, including two or more hospitalizations in the year prior to index relative to no hospitalizations. One hospitalization in the year prior to index was also associated with a higher risk of bleeding in Germany, the UK and the Netherlands. Risk of gastrointestinal bleeding increased with increasing number of contacts with a GP (UK, Netherlands) or number of open care visits (Sweden) in the year prior to index. Smoking was associated with a higher risk in the UK, the Netherlands and Sweden. In Sweden, other factors associated with higher risk included obesity, a previous alcohol-related diagnosis, living alone and born abroad, while a university-level education was associated with a lower risk of gastrointestinal bleeding. Obesity and a prior diagnosis indicative of alcohol abuse were also associated with a higher risk of gastrointestinal bleeding in Germany. In Germany, the UK and the Netherlands, prescription of 5–9 or 10 or more medications prior to the index date were associated with higher risks relative to fewer than five medications.

In Sweden, almost every comorbidity and past medical event of interest except history of intracranial bleeding was associated with a higher risk of gastrointestinal bleeding. Similarly, in Germany, all comorbidities and medical events demonstrated an association, with the exception of history of TIA. History of gastrointestinal bleeding was strongly associated with higher risk of new gastrointestinal bleeding in all countries. In the Netherlands, other risk factors included history of urogenital bleeding, hypertension, COPD and renal failure. The risk of gastrointestinal bleeding also increased with worsening CHA_2DS_2-VASc and HAS-BLED scores.

In the UK, current use of antiplatelets, PPIs, oral steroids and antibiotics were associated with a higher risk of gastrointestinal bleeding relative to nonuse. In the Netherlands, current use of parenteral anticoagulants was strongly associated with gastrointestinal bleeding, followed by PPIs, antibiotics, SSRIs and oral steroids. With the exception of oral anticoagulants, almost all medications of interest were associated with gastrointestinal bleeding risk in Sweden, of which current use of parenteral anticoagulants had the strongest association. All medications of interest were associated with a higher risk of gastrointestinal bleeding in Germany.

The adjusted OR for risk of gastrointestinal bleeding associated with current use of rivaroxaban was 1.72 (95% CI, 1.57–1.88) in Germany, 1.04 (95% CI, 0.85–1.28) in Sweden, 2.11 (95% CI, 1.31–3.38) in the UK and 1.66 (95% CI, 1.20–2.29) in the Netherlands relative to nonuse. The respective ORs for current use of SOC were 1.43 (95% CI, 1.30–1.57), 1.00 (95% CI, 0.89–1.13), 1.10 (95% CI, 0.66–1.83) and 4.08 (95% CI, 2.85–5.83) relative to nonuse. When stratified by treatment duration, the risk for gastrointestinal bleeding was highest after initiation of rivaroxaban treatment in Sweden and the UK.

10.3.2.2.2 VTE-T

Among patients in the ‘VTE-T without a recent history of cancer’ subcohort at the start date, there were 1080 cases of gastrointestinal bleeding available for the nested case-control analysis in Germany, 634 in Sweden, 81 in the UK and 69 in the Netherlands.

In all countries, the occurrence of two or more hospitalizations in the year prior to the start date was associated with a higher risk of gastrointestinal bleeding relative to no hospitalizations; one hospitalization was also associated with a higher risk in the Netherlands and Germany. In the UK, 20 or more contacts with a GP in the year prior to the index date was associated with a higher risk of gastrointestinal bleeding relative to 0–9 visits. In the Netherlands, the OR increased with the increasing number of contacts with a GP; however, only the occurrence of 10–19 visits was statistically significant relative to 0–4 visits.

Gastrointestinal bleeding risk increased with increasing number of open care visits in Sweden. Other socioeconomic factors associated with higher gastrointestinal bleeding risk in Sweden included obesity, smoking, previous alcohol-related diagnosis and living alone, while a university-level education was associated with a lower risk of bleeding. In Germany, obesity and a prior diagnosis indicative of alcohol abuse were also associated with a higher risk of gastrointestinal bleeding. In Germany, the UK and the Netherlands, use of 5–9 or 10 or more medications prior to the index date was associated with a higher risk of gastrointestinal bleeding relative to use of fewer than five medications.

In Sweden, all comorbidities and medical events of interest with the exception of cancer and history of intracranial bleeding were associated with a higher risk of gastrointestinal bleeding. Likewise, almost all comorbidities and medical events were associated with a higher risk of gastrointestinal bleeding in Germany. The strongest association in all countries was history of gastrointestinal bleeding. In the Netherlands, other associations included CAD, history of myocardial infarction and hyperlipidemia, whereas history of urogenital bleeding, CAD, heart failure and depression were associated with a higher risk of gastrointestinal bleeding in the UK.

In Germany, all medications of interest were associated with a higher risk of gastrointestinal bleeding. In Sweden, all medications of interest were associated with a higher risk of gastrointestinal bleeding except current use of medications interacting with CYP3A4/P-GP, which is a category unique to the Swedish study. In the UK, current use of PPIs, SSRIs, antibiotics and lipid-lowering medications were associated with a higher risk of gastrointestinal bleeding. Current use of PPIs and antibiotics were also associated with a higher risk in the Netherlands, as well as use of parenteral anticoagulants and oral steroids.

The adjusted OR for risk of gastrointestinal bleeding associated with current use of rivaroxaban was 2.24 (95% CI, 1.79–2.82) in Germany, 3.20 (95% CI, 2.18–4.68) in Sweden, 4.10 (95% CI, 1.90–8.87) in the UK and 2.39 (95% CI, 0.52–11.02) in the Netherlands relative to nonuse; the respective ORs associated with current use of SOC were 2.24 (95% CI, 1.76–2.84), 2.29 (95% CI, 1.70–3.09), 2.40 (95% CI, 0.99–5.84) and 6.76 (95% CI, 2.20–20.80). In Sweden and the UK, the risk of gastrointestinal bleeding decreased with increasing rivaroxaban treatment duration.

10.3.2.3 Urogenital bleeding

10.3.2.3.1 SPAF

Among patients with SPAF at the start date, there were 2774 urogenital bleeding cases available for the nested case-control analysis in Germany, 1935 cases in Sweden, 172 cases in the UK and 166 cases in the Netherlands.

In the year prior to the index date, the occurrence of two or more hospitalizations was associated with a higher risk of urogenital bleeding in all countries. Additionally, one hospitalization was associated with a higher risk in Germany, the UK and the Netherlands. In the UK, 20 or more contacts with a GP in the year prior to index was associated with a higher risk of urogenital bleeding relative to 0–19 contacts, whereas 10–19 contacts was associated with increased risk relative to 0–4 contacts in the Netherlands. In Sweden, the risk of urogenital bleeding increased with increasing number of open care visits. In Germany, obesity was associated with a higher risk of urogenital bleeding. Lifestyle factors associated with a higher risk of urogenital bleeding in Sweden included obesity and living alone, while a university education was associated with a lower risk. In Germany, the UK and the Netherlands, use of 10 or more medications prior to the index date was associated with a

higher risk of urogenital bleeding, as well as use of 5–9 medications in the Netherlands and Germany, relative to fewer than five medications.

History of urogenital bleeding was strongly associated with a higher risk of new urogenital bleeding in all countries. In Germany, almost all comorbidities and medical events of interest were associated with urogenital bleeding. Several comorbidities, including renal failure, depression, hypertension, hyperlipidemia, heart failure, asthma and cancer, were associated with a higher risk of urogenital bleeding in the Netherlands. Similarly, in Sweden, heart failure, chronic kidney disease, depression, hypertension, hyperlipidemia, diabetes, COPD and asthma were associated with a higher risk of urogenital bleeding, as well history of myocardial infarction and DVT/PE. History of gastrointestinal bleeding, diabetes and cancer were associated with a higher risk in the UK. The risk of urogenital bleeding increased with worsening CHA_2DS_2-VASc and HAS-BLED scores.

Almost all medications of interest were associated with a higher risk of urogenital bleeding in Germany, including strong associations for parenteral anticoagulants and antibiotics. Current use of antibiotics, oral steroids and PPIs was associated with a higher risk of urogenital bleeding relative to nonuse in the Netherlands. Current use of antibiotics, as well as SSRIs, was also associated with a higher risk of urogenital bleeding in the UK. In Sweden, the strongest association was current use of parenteral anticoagulants, followed by medications interacting with CYP3A4/PG-P, SSRIs, oral corticosteroids, antiplatelets and PPIs.

The adjusted OR associated with current use of rivaroxaban was 1.69 (95% CI, 1.43–2.00) in Germany, 1.29 (95% CI, 0.97–1.71) in Sweden, 1.79 (95% CI, 0.99–3.25) in the UK and 1.55 (0.89–2.68) in the Netherlands relative to nonuse; the respective ORs associated with current use of SOC were 1.45 (95% CI, 1.21–1.73), 0.99 (95% CI, 0.84–1.16), 1.05 (95% CI, 0.55–1.98) and 7.73 (95% CI, 3.78–15.80). In Sweden and the UK, the risk of urogenital bleeding decreased with increasing treatment duration for both current users of rivaroxaban and current users of SOC.

10.3.2.3.2 VTE-T

Among patients in the ‘VTE-T without a recent history of cancer’ subcohort at the start date, there were 465 urogenital bleeding cases available for the nested case-control analysis in Germany, 319 cases in Sweden, 42 cases in the Netherlands and 40 cases in the UK.

Two or more hospitalizations in the year prior to the index date were associated with a higher risk of urogenital bleeding in all countries; one hospitalization was also associated with higher bleeding risk in Germany, the UK and the Netherlands. In the UK, 20 or more contacts with the GP in the year prior to the index date was also associated with higher risk of urogenital bleeding relative to 0–19 contacts. In Sweden, the risk of urogenital bleeding increased with increasing number of open care visits. Previous alcohol-related diagnosis was associated with a higher risk of urogenital bleeding in Sweden. In Germany, obesity was associated with higher risk of urogenital bleeding. Use of 10 or more medications prior to the index date was associated with a higher risk of urogenital bleeding in Germany, the UK and the Netherlands, as well as 5–9 medications in the UK and Germany, relative to fewer than five medications.

A history of urogenital bleeding was strongly associated with a higher risk of new urogenital bleeding in Germany, the UK and Sweden; patient numbers were too low to calculate the OR in the Netherlands. In Sweden, heart failure, chronic kidney disease, depression, hypertension, hyperlipidemia, diabetes, COPD and history of gastrointestinal bleeding were also associated with a higher risk of urogenital bleeding. Similarly, in Germany, several medical events and comorbidities were associated with higher risks of urogenital bleeding. History of urogenital

bleeding and CAD were associated with a higher risk of urogenital bleeding in the Netherlands.

In the UK, current use of antibiotics and PPIs was associated with higher risk of urogenital bleeding relative to nonuse. In the Netherlands, current use of parenteral anticoagulants was most strongly associated with urogenital bleeding, followed by current use of PPIs, antiplatelets and antibiotics. In Sweden, current use of several medications of interest, including antiplatelets, parenteral anticoagulants, oral anticoagulants, PPIs, SSRIs and lipid-lowering medications, was associated with a higher risk of urogenital bleeding. Use of parenteral anticoagulants was strongly associated with higher risk of urogenital bleeding in Germany, followed by antibiotics and PPIs.

The adjusted OR associated with current use of rivaroxaban was 3.02 (95% CI, 2.07–4.41) in Germany, 2.75 (95% CI, 1.57–4.82) in Sweden, 2.29 (95% CI, 0.61–8.62) in the UK and 8.77 (95% CI, 0.49–155.9) in the Netherlands relative to nonuse; the respective adjusted ORs associated with current use of SOC were 1.79 (95% CI, 1.20–2.68), 2.64 (95% CI, 1.67–4.19), 0.47 (95% CI, 0.10–2.10) and 21.06 (95% CI, 3.71–119.5). In Sweden and the UK, the risk of urogenital bleeding decreased with increasing duration of rivaroxaban treatment. This trend was also observed for treatment with SOC in Sweden and Germany.

10.3.2.4 Other bleeding

10.3.2.4.1 SPAF

Among patients with SPAF at the start date, there were 7178 cases of other bleeding available for the nested case-control analysis in Sweden, 4924 cases in Germany, 117 cases in the UK and 247 cases in the Netherlands.

The occurrence of two or more hospitalizations in the year prior to the index date was associated with a higher risk of other bleeding in all countries; one hospitalization was also associated with increased bleeding risk in Germany, the UK and the Netherlands. The risk of other bleeding increased with number of contacts with a GP in the Netherlands and the UK. In Sweden, obesity, smoking, a previous alcohol-related diagnosis, and living alone were associated with a higher risk of other bleeding, while a university-level education and higher than median income were associated with lower risks. In Germany, obesity and a diagnosis indicating alcohol abuse were both associated with a higher risk of other bleeding. Use of 10 or more medications prior to the index date was associated with a higher risk of other bleeding relative to fewer than five medications in Germany, the UK and the Netherlands, as well as 5–9 medications in the Netherlands and Germany.

A history of gastrointestinal bleeding was associated with a higher risk of other bleeding in all countries, as well as a history of urogenital bleeding in Germany, the Netherlands and Sweden. All comorbidities and medical events of interest were associated with a higher risk of other bleeding in Sweden and almost all in Germany. The strongest associations in Sweden included chronic kidney disease and a history of gastrointestinal bleeding, whereas in Germany, hypertension demonstrated the largest OR. In the UK and the Netherlands, several comorbidities including CAD, renal failure, asthma and COPD were associated with higher risks of other bleeding, as well as a history of myocardial infarction, among others. The risk of other bleeding increased with worsening CHA_2DS_2-VASc and HAS-BLED scores.

In Germany, parenteral anticoagulants were most strongly associated with other bleeding, followed by antibiotics, antiplatelets, PPIs, oral steroids, NSAIDs and lipid-lowering medications. Current use of parenteral anticoagulants, PPIs and oral steroids/corticosteroids

were associated with a higher risk of other bleeding in the Netherlands and Sweden. Antibiotics were also associated with a higher risk of other bleeding in the Netherlands, whereas NSAIDs, SSRIs, medications interacting with CYP3A4/P-GPs and lipid-lowering medications were associated with higher risks of other bleeding in Sweden. None of the medications of interest were associated with risk of other bleeding in the UK.

The adjusted OR associated with current use of rivaroxaban was 1.92 (95% CI, 1.66–2.22) in Germany, 0.98 (95% CI, 0.86–1.12) in Sweden, 2.51 (95% CI, 1.10–5.71) in the UK and 1.01 (95% CI, 0.61–1.65) in the Netherlands relative to nonuse; the respective adjusted ORs associated with current use of SOC were 2.84 (95% CI, 2.46–3.28), 1.01 (95% CI, 0.93–1.09), 2.59 (95% CI, 1.09–6.20) and 7.16 (95% CI, 4.10–12.51).

10.3.2.4.2 VTE-T

Among patients in the 'VTE-T without a recent history of cancer' subcohort at the start date, there were 1462 cases of other bleeding available for the nested case-control analysis in Sweden, 520 cases in Germany, 26 cases in the UK and 32 cases in the Netherlands.

The occurrence of two or more hospitalizations in the year prior to the index date was associated with a higher risk of other bleeding in Germany, the Netherlands and Sweden. The risk of other bleeding increased with the number of open care visits in Sweden. In Sweden and Germany, obesity and a previous alcohol-related diagnosis were associated with higher risks of other bleeding. Additionally, in Sweden, smoking and living alone were associated with higher risks, while a university-level education and a higher than median income were associated with lower risks. In the Netherlands and Germany, use of 5–9 medications or 10 or more medications prior to the index date was associated with a higher risk of other bleeding compared with fewer than five medications, as well as 10 or more medications in Germany.

No comorbidities or medical events of interest were associated with a higher risk of other bleeding in the Netherlands or the UK. In Sweden and Germany, almost all comorbidities and medical events of interest were associated with a higher risk of other bleeding.

None of the medications of interest were associated with risk of other bleeding in the UK, and only current use of oral steroids was associated with a higher risk of other bleeding in the Netherlands. In Sweden, all medications of interest were associated with a higher risk of other bleeding. In Germany, higher risks of other bleeding were determined for current use of parenteral anticoagulants, antibiotics, oral steroids and antiplatelets, as well as PPIs and NSAIDs.

The adjusted OR associated with current use of rivaroxaban was 3.02 (95% CI, 2.03–4.48) in Germany, 2.57 (95% CI, 2.04–3.25) in Sweden, 2.41 (95% CI, 0.50–11.68) in the UK and 0.60 (95% CI, 0.01–26.74) in the Netherlands relative to nonuse; the respective adjusted ORs associated with current use of SOC were 5.85 (95% CI, 3.95–8.65), 2.45 (95% CI, 2.03–2.96), 0.19 (95% CI, 0.04–1.02) and 1.37 (95% CI, 0.21–9.05).

10.3.2.5 Summary of nested case-control analysis results

Table 10–8: Relative risk of bleeding in users of rivaroxaban or SOC associated with recency of use – SPAF cohort at the start date

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [a]	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [b]	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [c]	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [d]
Intracranial bleeding												
Total	900	225	-	621	189	-	39,881	3995	-	9492	2373	-
Rivaroxaban												
Nonuse	594 (66.0)	140 (62.2)	1	560 (90.2)	167 (87.3)	1	4487 (11.3)	325 (8.1)	1	1776 (18.7)	401 (16.9)	1
Current use	270 (30.0)	73 (32.4)	1.52 (0.90–2.58)	56 (9.0)	24 (12.7)	1.71 (0.98–2.96)	16,217 (40.7)	1452 (36.3)	1.32 (1.15–1.51)	1420 (15.0)	309 (13.0)	0.82 (0.64–1.06)
SOC												
Nonuse	314 (34.9)	82 (36.4)	1	251 (40.4)	35 (18.50)	1	4487 (11.3)	325 (8.1)	1	1776 (18.7)	401 (16.9)	1
Current use	496 (55.1)	123 (54.7)	1.44 (0.83–2.48)	348 (56.0)	144 (76.2)	5.91 (3.23–10.81)	10,771 (27.0)	1235 (30.9)	1.85 (1.61–2.14)	5318 (56.0)	1459 (61.5)	1.30 (1.14–1.49)
Gastrointestinal bleeding												
Total	1168	292	-	1492	470	-	97,347	9769	-	13,204	3301	-
Rivaroxaban												
Nonuse	772 (66.1)	146 (50.0)	1	1316 (88.2)	387 (82.3)	1	9350 (9.6)	739 (7.6)	1	2219 (16.8)	575 (17.4)	1
Current use	352 (30.1)	136 (46.6)	2.11 (1.31–3.38)	158 (10.6)	75 (16.0)	1.66 (1.20–2.29)	40,734 (41.8)	4508 (46.1)	1.72 (1.57–1.88)	2336 (17.7)	594 (18.0)	1.04 (0.85–1.28)
SOC												
Nonuse	426 (36.5)	131 (44.9)	1	674 (45.2)	117 (24.9)	1	9350 (9.6)	739 (7.6)	1	2219 (16.8)	575 (17.4)	1
Current use	656 (56.2)	120 (41.1)	1.10 (0.66–1.83)	734 (49.2)	325 (69.1)	4.08 (2.85–5.83)	27,757 (28.5)	2500 (25.6)	1.43 (1.30–1.57)	7300 (55.3)	1791 (54.3)	1.00 (0.89–1.13)
Urogenital bleeding												
Total	688	172	-	483	166	-	27,604	2774	-	7740	1935	-
Rivaroxaban												
Nonuse	462 (67.2)	96 (55.8)	1	428 (88.6)	135 (81.3)	1	3044 (11.0)	223 (8.0)	1	1318 (17.0)	342 (17.7)	1
Current use	201 (29.2)	70 (40.7)	1.79 (0.99–3.25)	48 (9.9)	28 (16.9)	1.55 (0.89–2.68)	11,340 (41.1)	1280 (46.1)	1.69 (1.43–2.00)	1385 (16.6)	350 (18.1)	1.29 (0.97–1.71)
SOC												
Nonuse	226 (32.8)	72 (41.9)	1	220 (45.5)	38 (22.9)	1	3044 (11.0)	223 (8.0)	1	1318 (17.0)	342 (17.7)	1
Current use	404 (58.7)	87 (50.6)	1.05 (0.55–1.98)	238 (49.3)	113 (68.1)	7.73 (3.78–15.80)	7819 (28.3)	714 (25.7)	1.45 (1.21–1.73)	4345 (56.1)	1059 (54.7)	0.99 (0.84–1.16)

Other bleeding												
Total	468	117	-	807	247	-	49,129	4924	-	28,712	7178	-
Rivaroxaban												
Nonuse	302 (64.5)	68 (58.1)	1	708	217	1	4689 (9.5)	250 (5.1)	1	4917 (17.1)	1329 (18.5)	1
Current use	148 (31.6)	47 (40.2)	2.51 (1.10–5.71)	90	26	1.01 (0.61–1.65)	20,172 (41.1)	1782 (36.2)	1.92 (1.66–2.22)	5346 (18.6)	1265 (17.6)	0.98 (0.86–1.12)
SOC												
Nonuse	173 (37.0)	42 (35.9)	1	373	41	1	4689 (9.5)	250 (5.1)	1	4917 (17.1)	1329 (18.5)	1
Current use	253 (54.1)	62 (53.0)	2.59 (1.09–6.20)	401	192	7.16 (4.10–12.51)	14,479 (29.5)	1,867 (37.9)	2.84 (2.46–3.28)	15,307 (53.3)	3901 (54.3)	1.01 (0.93–1.09)

a: OR adjusted by matching variables, current use of rivaroxaban, current use of warfarin, hospitalization in prior year, polypharmacy, and modified HAS-BLED and CHA_2DS_2-VASc scores

b: OR adjusted for age, use of rivaroxaban (for SOC related outcomes), hospitalization in prior year, polypharmacy, and HAS-BLED and CHA_2DS_2-VASc scores

c: Potential confounders included in the models were lifestyle factors, medical history, risk scores, and current use of medication of interest

d: OR with adjustment for age, education, income, living alone, born abroad, alcohol, previous intracranial, gastrointestinal or urogenital bleeding, myocardial infarction, ischemic stroke, venous thromboembolism, chronic kidney disease, hypertension, hyperlipidemia, diabetes and cancer

CI, confidence interval; GP, general practitioner; OR, odds ratio; SOC, standard of care; SPAF, prevention of stroke and systemic embolism in nonvalvular atrial fibrillation

Table 10–9: Relative risk of bleeding in users of rivaroxaban or SOC associated with recency of use – 'VTE-T without a recent history of cancer' subcohort at the start date

	UK			Netherlands (GP subcohort)			Germany			Sweden		
	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [a]	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [b]	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [c]	Controls n (%)	Cases n (%)	Adjusted OR (95% CI) [d]
Intracranial bleeding												
Total	132	30	-	23	17	-	3481	360	-	1606	387	-
Rivaroxaban												
Nonuse	95 (72.0)	18 (60.0)	1	23 (100.0)	14 (82.4)	-	891 (25.6)	62 (17.2)	1	715 (44.5)	132 (34.1)	1
Current use	24 (18.2)	9 (30.0)	2.54 (0.74–8.69)	0 (0.0)	3 (17.6)	-	965 (27.7)	111 (30.8)	1.73 (1.16–2.58)	305 (19.0)	70 (18.1)	1.56 (0.98–2.50)
SOC												
Nonuse	70 (53.0)	16 (53.3)	1	13 (56.5)	6 (35.3)	1	891 (25.6)	62 (17.2)	1	715 (44.5)	132 (34.1)	1
Current use	43 (32.6)	12 (40.0)	1.53 (0.42–5.52)	7 (30.4)	9 (52.9)	n/a	740 (21.3)	109 (30.3)	2.42 (1.62–3.61)	497 (31.5)	164 (42.9)	1.89 (1.32–2.70)
Gastrointestinal bleeding												
Total	337	81	-	72	69	-	10,484	1080	-	2723	634	-
Rivaroxaban												
Nonuse	222 (65.9)	34 (42.0)	1	65 (90.3)	57 (82.6)	1	2575 (24.6)	176 (16.3)	1	1196 (43.9)	185 (29.2)	1
Current use	73 (21.7)	39 (48.1)	4.10 (1.90–8.87)	4 (5.6)	10 (14.5)	2.39 (0.52–11.02)	3152 (30.1)	395 (36.6)	2.24 (1.79–2.82)	574 (21.1)	168 (26.5)	3.20 (2.18–4.68)
SOC												
Nonuse	210 (62.3)	52 (64.2)	1	56 (77.8)	23 (33.3)	1	2575 (24.6)	176 (16.3)	1	1196 (43.9)	185 (29.2)	1
Current use	84 (24.9)	21 (25.9)	2.40 (0.99–5.84)	12 (16.7)	32 (46.4)	6.76 (2.20–20.80)	2565 (24.5)	296 (27.4)	2.24 (1.76–2.84)	824 (30.3)	249 (39.3)	2.29 (1.70–3.09)
Urogenital bleeding												
Total	173	40	-	48	42	-	4571	465	-	1417	319	-
Rivaroxaban												
Nonuse	137 (79.2)	23 (57.5)	1	47 (97.9)	36 (85.7)	1	1046 (22.9)	70 (15.1)	1	632 (44.6)	90 (28.2)	1
Current use	22 (12.7)	12 (30.0)	2.29 (0.61–8.62)	1 (2.1)	5 (11.9)	8.77 (0.49–155.9)	1415 (31.0)	210 (45.2)	3.02 (2.07–4.41)	277 (19.5)	85 (26.6)	2.75 (1.57–4.82)
SOC												
Nonuse	81 (46.8)	23 (57.5)	1	36 (75.0)	11 (26.2)	1	1046 (22.9)	70 (15.1)	1	632 (44.6)	90 (28.2)	1
Current use	65 (37.6)	11 (27.5)	0.47 (0.10–2.10)	9 (18.8)	25 (59.5)	21.06 (3.71–119.5)	1085 (23.7)	108 (23.2)	1.79 (1.20–2.68)	432 (30.5)	127 (39.8)	2.64 (1.67–4.19)

Other bleeding												
Total	112	26	-	28	32	-	5065	520	-	6657	1462	-
Rivaroxaban												
Nonuse	77 (68.8)	15 (57.7)	1	27 (96.4)	29 (90.6)	1	1033 (20.4)	46 (8.8)	1	3113 (46.8)	443 (30.3)	1
Current use	15 (13.4)	8 (30.8)	2.41 (0.50–11.68)	1 (3.6)	3 (9.4)	0.60 (0.01–26.74)	1610 (31.8)	150 (28.8)	3.02 (2.03–4.48)	1314 (19.7)	349 (23.9)	2.57 (2.04–3.25)
SOC												
Nonuse	65 (58.0)	18 (69.2)	1	17 (60.7)	10 (31.3)	1	1033 (20.4)	46 (8.8)	1	3113 (46.8)	443 (30.3)	1
Current use	30 (26.8)	5 (19.2)	0.19 (0.04–1.02)	5 (17.9)	16 (50.0)	1.37 (0.21–9.05)	1419 (28.0)	227 (43.7)	5.85 (3.95–8.65)	1908 (28.7)	584 (39.9)	2.45 (2.03–2.96)

a: OR adjusted by matching variables, current use of rivaroxaban, current use of warfarin, hospitalization in prior year, polypharmacy, and modified HAS-BLED and CHA_2DS_2-VASc scores

b: OR adjusted for age, use of rivaroxaban (for SOC related outcomes), hospitalization in prior year, polypharmacy, and HAS-BLED and CHA_2DS_2-VASc scores

c: Potential confounders included in the models were lifestyle factors, medical history, risk scores, and current use of medication of interest

d: OR with adjustment for age, education, income, living alone, born abroad, alcohol, previous intracranial, gastrointestinal or urogenital bleeding, myocardial infarction, ischemic stroke, venous thromboembolism, chronic kidney disease, hypertension, hyperlipidemia, diabetes and cancer

CI, confidence interval; GP, general practitioner; n/a, not applicable; OR, odds ratio; SOC, standard of care; VTE-T, treatment and secondary prevention of venous thromboembolism

10.4 Main results

See Sections 10.2 and 10.3.

10.5 Other analyses

None.

10.6 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

This is the final report of four post-authorization studies, collectively entitled "Pharmacoepidemiological Study of Rivaroxaban Use and Potential Adverse Outcomes in Routine Clinical Practice in the UK, Germany, the Netherlands and Sweden". These studies form part of a comprehensive European epidemiological PASS program designed to monitor patterns of rivaroxaban use over time, starting from its launch in Europe, and to characterize the benefit–risk profile of rivaroxaban when used in routine clinical practice.

In this report, we present the combined results from four studies that were conducted in parallel by independent research teams using healthcare data sources from the UK, the Netherlands, Germany and Sweden. These studies were designed and initiated several years ago, before the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) and other large-scale approaches to the harmonization and analysis of data from disparate healthcare data sources were widely used. The approach of using multiple databases for epidemiological research has been previously used by other studies, however, including Crestor (59) and the IMI-PROTECT project (60), which reported valid comparisons and risk estimations for safety outcomes.

The studies shared common objectives but followed separate protocols developed following ENCePP methodological standards, including the ENCePP checklist. All the studies used data from existing healthcare databases, including retrospective data as well as prospective data collected routinely over the course of the study. Operational definitions of exposures and outcomes were harmonized as much as possible between the studies. The creation of a data strategy document (DSD) that detailed the agreed definitions for each database was of immense help to minimize differences between the studies. The DSD also included a statistical analysis plan and templates for output tables to be followed by all researchers, which ensured the analyses were conducted in a similar manner and facilitated comparisons between the studies. Additionally, the codes used to ascertain all outcomes and variables were reviewed and adjusted to drive greater harmonization between the studies. Some differences remain, however, because not all variables were available from each of the data sources, and additional variables could be included in the analyses based on their availability in the individual data sources.

Owing to the different coding systems and the different availability of information in each of the data sources, it was challenging to devise an algorithm to assign patients to an indication, as well as to determine study drug exposure using a similar method, across all four studies. Although we successfully reached an agreement, there is still potential for improvement, and some misclassification most likely remains with a varying magnitude between the databases.

While harmonizing the approach to data analysis, frequent communication between investigators was necessary. The frequency and methods of communication between research team members worked well; regular teleconferences and annual face-to-face meetings were crucial to keep the teams engaged and reach a consensus on important issues. In between meetings, responses to email communications about specific queries were timely and helpful. When discrepancies arose in the results, these were discussed and the research teams concluded that those differences were most likely related to the heterogeneity in the sources of information and methods used to capture the data (e.g. different codes used in selection criteria; differences in healthcare systems underlying specifics of entering the codes by physicians, age effect). The final outcome of this collaboration between the research teams has been very positive; it has allowed us to use the granularity of information available in each individual data source while maintaining sufficient correlation between the studies to meet common objectives and to interpret the results of the four studies in a combined format.

Overall, the rivaroxaban PASS program provided an excellent opportunity to compare information from multiple healthcare data sources, while acknowledging that there is heterogeneity between the data sources in terms of the structure, terminology and methods of data capture, as well as differences in the underlying healthcare systems in each of the countries. Indeed, the results of each individual study should be interpreted in this context. The impact and value of this PASS program have been demonstrated through the ongoing scientific output, with several abstracts presented at International Society for Pharmacoepidemiology, European Society of Cardiology and American Heart Association congresses. A manuscript describing our collaborative approach to conducting an epidemiological PASS program has been published (61), as well as several manuscripts depicting the results of validation studies that arose from the program, which we believe will be of use for future studies and beneficial to the wider scientific community (13, 16–18).

These studies present data on the patterns of rivaroxaban use and the efficacy and safety of rivaroxaban in routine clinical practice, complementing the results of randomized controlled trials (RCTs) and other post-authorization initiatives that use primary data collection, such as international observational field cohort studies, national observational field studies in specific populations that are conducted under some controlled conditions, and routine pharmacovigilance activities. Although it is of interest to interpret the results of the present observational studies in the context of the results obtained from the pivotal RCTs, neither the background information nor the outcome events are captured in the same manner by these two distinct study types. As such, the magnitude and direction of effects obtained across these four studies should provide the basis for benefit–risk assessments, rather than the specific point estimates.

11.1 Key results

Patterns of rivaroxaban prescription and unadjusted incidence rates of safety and effectiveness outcomes were assessed in first-time users of rivaroxaban and first-time users of SOC who were assigned to one of the mutually exclusive indication cohorts. Many patients had several concomitant potential indications for treatment, and the decision to prioritize the SPAF cohort above the other indications in some studies will likely have contributed to making the SPAF cohort the largest one. Because the ACS indication was approved in 2013, the enrollment period for ACS was shorter than for the other indications. Furthermore, uptake of rivaroxaban for ACS remained very low throughout the enrollment period across all study sites, which limited the analyses that could be conducted for this cohort. Overall, use of rivaroxaban increased during the study period in all four countries, reflecting the uptake of the drug in Europe. The key results for each indication are presented in the following sections.

11.1.1 SPAF

The characteristics of first prescription of rivaroxaban were in line with dose recommendations for the SPAF indication. Patients receiving rivaroxaban or SOC for SPAF were more often male than female and were aged in their seventies, on average. This is consistent with the ROCKET AF trial population, in which the median age was PPD and 60.3% of patients were male (62).

Uptake of rivaroxaban increased for this indication over the enrollment period up to 2015/2016. SOC was more commonly prescribed to patients who were naive to oral

anticoagulation than rivaroxaban, though this difference tended to disappear at the end of the enrollment period.

Hypertension was prevalent among SPAF patients in all countries. Generally, greater proportions of comorbidities and past medical events were observed in rivaroxaban users and SOC users in Germany than in the other countries. Furthermore, the median CHA_2DS_2-VASc score of 5 in Germany was higher than the median score of 3 in the other countries. These apparent differences could be in part due to the nature of administrative clinical data used in Germany and differences between the studies in how the CHA_2DS_2-VASc score was calculated. There were some differences in comorbidities and past medical events between the users of study drugs; most notably, patients with a history of bleeding were more often prescribed rivaroxaban than SOC. Although patient numbers were low, patients with advanced renal impairment were prescribed SOC slightly more often than rivaroxaban.

As expected, the mean age of rivaroxaban users was slightly higher in most of the studies than in the ROCKET AF trial. The prevalence of some comorbidities, such as heart failure and diabetes, was higher in the ROCKET AF rivaroxaban cohort than in the present studies (62). This could be due to different definitions and ascertainment of these conditions from healthcare databases compared with RCTs or could reflect differences between populations in routine clinical practice and clinical trials. Patients who initiated rivaroxaban treatment for SPAF often received several cardiovascular medications before and on the start date; this has also been reported in other studies, including ROCKET AF (62), and may reflect the high cardiovascular risk profile of these patients.

The incidence rates of intracranial and gastrointestinal bleeding among rivaroxaban users were similar to the rates reported in patients randomized to rivaroxaban in ROCKET AF (Table 11–1). Generally, incidence rates of intracranial and other bleeding were lower for rivaroxaban users than for SOC users, whereas incidence rates of gastrointestinal bleeding and urogenital bleeding were higher. This trend is consistent with ROCKET AF, which observed lower incidence rates of intracranial hemorrhage and higher incidence rates of gastrointestinal bleeding for rivaroxaban compared with warfarin (62, 63). There were some minor deviations from this trend, however, in the individual countries. Caution is needed when comparing differences between crude bleeding incidence rates for rivaroxaban and SOC within the present studies, because median time at risk during the first episode of treatment was shorter for rivaroxaban users than for SOC users in the UK, Sweden and Germany. Because bleeding risk is highest soon after initiation of anticoagulation, this likely constitutes a bias in favor of SOC. Furthermore, because 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 formal comparative statistical analyses were conducted between the study drugs.

Among rivaroxaban users, all-cause mortality during the first episode of treatment was higher in the present studies than reported for patients randomized to rivaroxaban in ROCKET AF (safety population, 1.87 events per 100 person-years) while on treatment (i.e. up to the last dose plus 2 days) (62). In registry and database studies, however, it is not possible to determine exactly when a patient stops treatment because information is only available about when and, in some cases, for how long a drug was prescribed or dispensed. As such, the all-cause mortality observed in the present studies is likely to include deaths occurring while receiving rivaroxaban, as well as some events after treatment has been terminated. In contrast, it is standard practice in RCTs to record the date at which a patient stops taking a drug. Unnecessary medication is often terminated in patients at imminent risk of death; events occurring during this period will be included in the analyses in the present studies but are likely to be excluded from the on-treatment analysis in RCTs. We, therefore, consider rates from the intent-to-treat (ITT) population, which use a longer data scope, to be closer

methodologically to our estimates. Indeed, in the rivaroxaban ITT population, the all-cause mortality was 4.58 events per 100 person-years (62), which is similar to the results observed in the present studies, with all-cause mortality of 4.50 (UK), 2.56 (Netherlands), 6.08 (Germany) and 5.17 (Sweden) events per 100 person-years (Table 11–1). In the rivaroxaban ITT population in ROCKET AF, incidence rates of primary ischemic stroke and myocardial infarction population were 1.69 events per 100 person-years and 0.98 events per 100 person-years, respectively (62). The incidences of these cardiovascular outcomes among rivaroxaban users in the present studies were either similar to or lower than these rates (Table 11–1).

Table 11–1: Summary of incidence rates of safety and effectiveness outcomes among rivaroxaban users during the first treatment episode in the present studies and ROCKET AF

	Incidence rate per 100 person-years (95% CI)				
	UK	**Netherlands**	**Germany**	**Sweden**	**ROCKET AF**
Intracranial bleeding	0.25 (0.18–0.34)	0.34 (0.19–0.52)	0.53 (0.50–0.57)	0.63 (0.61–0.85)	0.49 [a]
GI bleeding	0.49 (0.39–0.61)	1.02 (0.75–1.32)	1.72 (1.66–1.78)	1.30 (1.14–1.47)	2.00 [a]
Ischemic stroke	0.31 (0.24–0.41)	0.38 (0.22–0.57)	1.13 (1.08–1.18)	1.52 (1.35–1.71)	1.69 [b]
Myocardial infarction	0.33 (0.25–0.43)	0.56 (0.37–0.79)	0.79 (0.74–0.83)	1.07 (0.93–1.23)	0.98 [b]
All-cause mortality	4.50 (4.19–4.82)	2.56 (2.13–3.03)	6.08 (5.97–6.20)	5.17 (4.85–5.51)	4.58 [b]

a: Safety population, on treatment (62, 63)
b: Intent-to-treat population, regardless of treatment exposure (62)
CI, confidence interval; GI, gastrointestinal

Risk factors were similar for the four bleeding outcomes; as expected, prior history of bleeding was often associated with a strong risk of new bleeding events. The occurrence of one or more hospitalizations in the year prior to the index date was also a common risk factor. In the nested case-control analysis, current use of rivaroxaban was associated with a higher risk of intracranial bleeding and urogenital bleeding relative to nonuse in Germany, but not in the UK, the Netherlands or Sweden. Current use of rivaroxaban was associated with a higher risk of gastrointestinal bleeding relative to nonuse in all countries except Sweden. Current use of rivaroxaban was associated with a higher risk of other bleeding relative to nonuse in Germany and the UK, but not in the Netherlands or Sweden. Some of the differences in results between the countries could be due to Sweden and Germany using different operational definitions of nonuse than the UK and the Netherlands.

11.1.2 VTE-T

The patients treated for the VTE-T indication were further stratified into subcohorts with and without a recent history of cancer, owing to a number of differences between these groups. First, VKAs are the SOC for non-cancer-associated thrombosis in routine clinical practice, whereas low molecular weight heparin or VKAs are commonly used to treat cancer-associated thrombosis. Second, patients with cancer-associated thrombosis have significantly higher rates of recurrent VTE and bleeding than patients without cancer, as well as high mortality, which could confound the results if analyzed as a single cohort (9). Last, patients

with cancer are highly heterogeneous owing to differences in type of cancer, stage and treatments, making it challenging to estimate the true frequency of occurrence of safety and effectiveness outcomes in a meaningful way. Owing to the long lookback period of 3 years, we cannot state that patients in the subcohort 'with a recent history of cancer' have active cancer; however, this lookback period was applied to maximize the number of patients without cancer-associated thrombosis in the other subcohort (i.e. VTE-T without a recent history of cancer), who were included in the outcomes analysis. This discussion focuses on the 'VTE-T without a recent history of cancer' subcohort.

For VTE-T, the recommended dose is 15 mg bid for 3 weeks followed by 20 mg od for six months. The characteristics of the first prescription were mostly in line with dose recommendations. As expected, 15 mg was the most commonly recorded tablet strength at the start date in the Netherlands, Germany and Sweden; however, in the UK, the 20 mg tablet was more common. A potential explanation for this discrepancy in the UK is that, in these patients, the first pack of rivaroxaban treatment (15 mg bid for three weeks) may have been initiated in hospital in a number of patients and, therefore, was not captured by the IMRD-UK database.

Among patients in the 'VTE-T without a recent history of cancer' subcohort, the male-to-female ratio differed between countries, with an approximately equal ratio in the UK and Sweden, but a slightly higher proportion of female patients in the Netherlands and Germany. On average, rivaroxaban and SOC users were aged in their early sixties, which is younger than observed for the SPAF cohorts but older than patients included in the EINSTIN DVT and EINSTEIN PE studies (pooled mean, 57 years) (8). Uptake of rivaroxaban for this indication generally increased over the enrollment period. SOC was more commonly prescribed to patients who were naive to oral anticoagulation than rivaroxaban. In most countries, rivaroxaban was more often prescribed than SOC to patients with a history of VTE any time prior to the event necessitating treatment; this could partly reflect the greater number of non-naive users in the rivaroxaban cohort. Although absolute numbers of patients with advanced renal impairment were low, these patients were prescribed SOC slightly more often than rivaroxaban, a trend that was also observed for SPAF.

Incidence rates of safety and effectiveness outcomes among rivaroxaban users for VTE-T were generally in line with the cumulative incidences reported for the EINSTEIN DVT and PE clinical trials (64, 65) (Table 11–2). In a pooled analysis of the EINSTEIN DVT/PE studies, the incidence rate of major bleeding among patients without active cancer was lower for those randomized to rivaroxaban than for those randomized to enoxaparin/VKA (8). In Sweden and Germany, incidence rates of intracranial and other bleeding were generally lower among rivaroxaban users than SOC users, but rates of urogenital bleeding were higher. This trend was not observed in the UK and the Netherlands; however, numbers of events were low. Incidence rates of gastrointestinal bleeding were higher among rivaroxaban users than SOC users in all countries. As mentioned previously, comparisons of crude incidence rates should be interpreted with caution because no comparative statistical analyses were conducted between rivaroxaban and SOC. As observed for SPAF, median time at risk during the first episode of treatment was shorter for rivaroxaban users than SOC users for VTE-T in Germany, the UK and Sweden and, therefore, comparisons are likely biased in favor of SOC.

Table 11–2: Summary of incidence rates of effectiveness outcomes and mortality among rivaroxaban users in the present studies and EINSTEIN DVT/PE

	Incidence rate per 100 person-years (95% CI)				n (%)	
	UK	Netherlands	Germany	Sweden	EINSTEIN DVT [a, b]	EINSTEIN PE [a, b]
DVT and PE [c]	0.64 (0.40–0.97)	1.46 (0.57–2.77)	2.30 (2.11–2.51)	-	1 (< 0.1)	0 (0.0)
Recurrent PE only [c]					18 (1.1)	22 (1.0)
Recurrent DVT only [c]					12 (0.7)	18 (0.8)
Ischemic stroke	0.09 (0.02–0.26)	0.41 (0.04–1.2)	0.64 (0.54–0.75)	0.88 (0.71–1.10)	1 (< 0.1)	9 (0.4)
STEMI	0.20 (0.08–0.42)	-	0.48 (0.40–0.58)	0.54 (0.41–0.71)	1 (< 0.1)	5 (0.2)
NSTEMI					3 (0.2)	2 (< 0.1)
Death (PE)	4.05 (3.40–4.78)	1.86 (0.82–3.3)	3.26 (3.04–3.50)	3.22 (2.88–3.61)	1 (< 0.1)	3 (0.1)
Death (PE not excluded)					2 (0.1)	7 (0.3)
Death (cardiovascular)					0 (0.0)	10 (0.4)
Death (bleeding)					0 (0.0)	4 (0.2)
Death (other)					13 (0.8)	18 (0.8)

a: Patients without active cancer (64, 65)
b: Intent-to-treat population, until the end of the intended treatment duration (median treatment duration, 182 days in EINSTEIN DVT, 183 days in EINSTEIN PE) (64, 65)
c: Symptomatic
CI, confidence interval; DVT, deep vein thrombosis; NSTEMI, non-ST-elevation myocardial infarction; PE, pulmonary embolism; STEMI, ST-elevation myocardial infarction

Factors associated with an increased risk of bleeding in the VTE-T cohorts were similar to those for the SPAF cohort, with prior history of bleeding identified as a strong risk factor for new bleeding. In the UK and the Netherlands specifically, few bleeding risk factors were identified, likely owing to the low number of events included in these analyses. In the nested case-control analysis, current use of rivaroxaban was not associated with a higher risk of intracranial bleeding relative to nonuse in Sweden or the UK, but a higher risk was associated with current use of rivaroxaban in Germany. Current use of rivaroxaban was associated with a higher risk of gastrointestinal bleeding relative to nonuse in all countries except the Netherlands. Current use of rivaroxaban was associated with higher risk of urogenital and other bleeding relative to nonuse in Germany and Sweden, but not in the UK or the Netherlands.

11.1.3 ACS

Despite the large cohorts of rivaroxaban users ascertained in each country, very few were assigned to the ACS indication and even fewer were prescribed the recommended dose of 2.5 mg bid. Within the ACS cohorts, the 2.5 mg tablet strength was prescribed to only one patient in Sweden, two patients in the Netherlands, 13 patients in the UK and 24 patients in Germany. Instead, most patients assigned to the ACS indication received the 15 mg or 20 mg tablet, suggesting that there may be some misclassification of indication. It is unlikely that a substantial number of patients with ACS have been misclassified within another indication, because only a minute proportion of patients were prescribed the 2.5 mg tablet within the SPAF, VTE-T or TKR/THR cohorts. Some ACS patients may have more than one indication for rivaroxaban (e.g. comorbid ACS and AF) and, therefore, have been prescribed a higher

dose of rivaroxaban based on the dose recommendations for the other indication. However, all patients assigned to the ACS cohort in the UK study were validated by manual review to ensure that they did not have another potential indication for treatment and greater priority was given to the SPAF, VTE-T and TKR/THR indications over the ACS indication in the other studies. Overall, these results indicate that uptake of rivaroxaban for the ACS indication was extremely low in Europe at the time of study enrollment.

Patients who received rivaroxaban for ACS were predominantly male and aged in their early seventies. Patients prescribed low-dose rivaroxaban (i.e. the 2.5 mg tablet strength or a daily dose < 10 mg) were younger on average than those who were prescribed a higher dose (i.e. 15 mg or 20 mg) and had lower healthcare resource utilization and polypharmacy. Patterns of antiplatelet use prior to and after prescription of rivaroxaban differed between the countries, as well as the specific combinations of antiplatelet agents used.

The incidence rates of cardiovascular outcomes and all-cause mortality in the present studies were higher than those of the ATLAS ACS 2–TIMI 51 trial population (66) (Table 11–3). Owing to the low patient numbers and heterogeneity of the cohorts, limited conclusions can be made regarding the safety and effectiveness of rivaroxaban for prevention of atherothrombotic events after an ACS; however, no new safety concerns were identified within the small ACS cohorts.

Table 11–3: Summary of incidence rates of cardiovascular outcomes and all-cause mortality among rivaroxaban users in the present studies and ATLAS ACS 51–TIMI 2

	Incidence rate per 100 person-years (95% CI)				
	UK	**Netherlands**	**Germany**	**Sweden**	**ATLAS ACS–51 TIMI 2 [a]**
Ischemic stroke	-	-	1.45 (0.75–2.54)	3.20 (1.33–7.69)	0.93 [b]
Myocardial infarction	4.20 (0.87–12.29)	10.72 (1.92–26.68)	5.28 (3.80–7.13)	8.54 (4.96–14.72)	3.66
All-cause mortality	5.36 (1.46–13.73)	-	8.99 (7.07–11.26)	8.93 (5.29–15.09)	2.28

a: Modified intent-to-treat population, events occurring at or after randomization and the earliest date of the global treatment end date, 30 days after study drug was prematurely discontinued and 30 days after randomization for those subjects who were randomized but not treated (66)
b: Any stroke type
CI, confidence interval

11.1.4 TKR/THR

In all studies, most rivaroxaban users undergoing TKR/THR were prescribed 10 mg od for a short duration, which is consistent with dose recommendations for this indication. Patient characteristics were similar between the countries, with a greater proportion of female patients than male patients and a median age ranging from PPD Uptake of rivaroxaban for TKR/THR was generally consistent across the study enrollment period.

11.1.5 Strengths

- The four studies shared common objectives and were conducted in a harmonized manner so that the results could be contrasted between countries, despite differences in

prescribing environments, national healthcare systems, the availability of information and diagnostic coding systems.

- These studies further increase our understanding of the prescribing practices, and safety and efficacy of rivaroxaban in routine clinical practice, including patients who are commonly excluded from RCTs, such as elderly or frail individuals, patients with renal impairment, and those with multiple comorbidities.
- The inclusion of patients prescribed VKAs, which were the SOC for SPAF and VTE-T at the time of rivaroxaban launch, allows the findings to be viewed in the context of traditionally prescribed drugs.
- The data sources used are well-validated resources for pharmacoepidemiology research and are representative of the respective European populations.
- This program uses observational data from patients treated in routine clinical practice with no selection and no possibility of influencing prescribing behavior, limiting the potential for enrollment or physician bias.
- In the UK study, anonymized profiles of patients with each outcome event, including any free-text comments related to the event, were manually reviewed.
- A separate validation study conducted in IMRD-UK determined that gastrointestinal and urogenital bleeding rates identified using Read codes are overestimated in the absence of manual profile review (16).
- A separate validation study conducted in IMRD-UK showed a three-fold overestimation of the incidence rate of VTE based on coded diagnoses only compared with the corresponding incidence rate after manual review (17).
- A separate validation study conducted using the Swedish registers has demonstrated high sensitivity (85.5%) and specificity (95.9%) for the detection of major bleeding events associated with hospitalization (18).
- A separate validation study was conducted to determine the optimal method to ascertain renal function from the Swedish registers when there is no information on laboratory test results (13).

11.2 Limitations

- Incidence rates were not standardized for age or sex.
- Subgroup analyses should be interpreted with caution when the sample sizes are very small.
- It is possible for unmeasured confounders to affect the data. Rivaroxaban and SOC are likely to be prescribed to groups of patients with different characteristics that cannot be fully adjusted for in the analyses. Because residual confounding was likely to have affected any direct comparison of rivaroxaban and SOC, the nested case-control analysis focused instead on recency of use (i.e. current use versus nonuse).
- Severity of disease is typically poorly captured; data recorded in the data sources are mostly binary, whereas the natural history of disease is a continuum. For example, a diagnosis of hypertension will cover both patients with borderline hypertension and malignant hypertension, although the impact on the prognosis is very different. If doctors let severity of disease affect choice of treatment, this may constitute a selection bias.

- There is potential for misclassification of exposure to SOC owing to complex dosing with multiple strengths of tablet.
- Misclassification of indication may have occurred for patients with more than one potential indication. It is unlikely that this should have biased the overall results substantially.
- There is incomplete information regarding medication compliance.
- The mean duration of the first treatment episode among rivaroxaban users was shorter than for SOC users in the UK, Sweden and Germany. This is likely due to the skewed uptake for rivaroxaban use toward the end of the study period, resulting in a lower likelihood of long treatment episodes for rivaroxaban users than SOC users.
- The greatest period of hazard for events such as bleeding or mortality is observed at the initiation of anticoagulation therapy. Because a higher proportion of time at risk among rivaroxaban users accumulated in the early high-risk period than among SOC users, comparisons of crude incidence rates between the drugs are likely biased in favor of SOC.
- AF is a chronic condition; therefore, it is important to highlight that in the SPAF cohort, 'nonusers' at some point in time still have AF and may not being treated for several possible reasons (e.g. discontinued for medical reasons, old age, terminal diagnosis).
- A substantial number of incident episodes of DVT do not necessitate hospitalization, so analyses that are restricted to hospitalized events likely underestimate the number of DVT events occurring in the population. Conversely, analyses including all outpatient events are likely to overestimate the number of DVT events because the same codes are used both for an incident DVT event and a routine follow-up visit.
- Bleeding outcomes were restricted to events leading to hospital admission. This restriction was necessary to minimize differential misclassification caused by variability in patients' behavior in seeking care for less severe bleeds. Similarly, physicians' attitudes toward recording these events may differ for a new drug compared with SOC. The consequence of this restriction is that bleeding events leading to death before hospital admission were missed, but it was assumed that the number of bleeding events missed due to this operational definition was small. An additional analysis conducted in Sweden to identify patients who died outside of hospital from bleeding supported this assumption.
- There are potential gaps in availability of prescription/dispensation information for some databases (e.g. medications received in a hospital setting).

11.3 Interpretation

These observational studies use data from routine clinical practice in four European countries to monitor drug utilization and describe patient characteristics, as well as to assess the safety and efficacy of rivaroxaban starting shortly after its introduction in the market. The data sources are representative of the respective populations in each country in terms of sex and age distribution; therefore, the results can be extrapolated to the general population. The population-based data sources used have no selection bias, but there is potential for misclassification of outcomes. The results showed that usage of rivaroxaban increased over time and patterns of use for each indication were generally in line with label recommendations for SPAF, VTE-T and TKR/THR. Owing to differences in the data sources

and healthcare systems in the respective countries, no pooled analyses of the studies were performed. The objectives and methodologies of the studies were, however, sufficiently harmonized that the results can be compared. Indeed, although point estimates vary between the individual studies, the direction of trends and magnitudes of effect are broadly similar. Overall, the safety and effectiveness profile of rivaroxaban for SPAF and VTE-T in these studies is consistent with its expected profile in real-world populations, based on knowledge from RCTs and other studies. 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.

11.4 Generalizability

The data are representative in terms of sex and age distribution for the respective populations of each country. Indeed, the Swedish study is based on the entire population including all filled prescriptions; thus, generalizability is not an issue. The nature of the data sources makes selection bias unlikely and, overall, the results of this study are likely to reflect routine clinical practice in the UK, Germany, the Netherlands and Sweden.

12. Other information

Not applicable.

13. Conclusion

Uptake of rivaroxaban increased during the study in all countries. In general, characteristics of the first prescription or dispensation for rivaroxaban corresponded well with label recommendations for SPAF, VTE-T and TKR/THR. Limited conclusions can be made regarding the ACS indication, owing to very low uptake of rivaroxaban for this indication. Analysis of the safety and effectiveness outcomes has not raised any new safety concerns.

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Appendices

Annex 1 List of stand-alone documents

None.

Annex 2 Additional information

Annex 2.1 Individual study reports

Annex 2.1.1 The UK

Annex 2.1.2 Germany

Annex 2.1.3 Netherlands

Annex 2.1.4 Sweden

Annex 2.2 Data strategy document

Annex 3 Signature Pages

Signature Page – OS Conduct Responsible

Title	Final study report comprising the pharmacoepidemiological study program of rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK, Germany, the Netherlands and Sweden
Report version and date	V1.0, 26 NOV 2020
IMPACT study number	UK: 16647 Germany: 16159 The Netherlands: 16646 Sweden: 17543
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	UK: EUPAS11299 Germany: EUPAS11145 The Netherlands: EUPAS11141 Sweden: EUPAS9895
Medicinal product	Xarelto®
Reference therapy	UK: warfarin Germany: phenprocoumon The Netherlands: acenocoumarol or phenprocoumon Sweden: warfarin
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: PPD

Date, Signature: _____, _____

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Name: PPD

Role: OS Safety Lead / PV Country Head
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Role: OS Medical Expert
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Role: OS Statistician
Name: PPD

Role: OS Epidemiologist
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