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Evaluation of the incidence of bleeding in patients prescribed rivaroxaban for the treatment and prevention of deep vein thrombosis and pulmonary embolism in UK secondary care: an observational cohort study

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ABSTRACT

Objectives To evaluate the short-term (12 weeks) safety and utilisation of rivaroxaban prescribed to new-user adult patients for the treatment of deep vein thrombosis and pulmonary embolism and for the prevention of recurrent deep vein thrombosis and pulmonary embolism in a secondary care setting in England and Wales.

Design An observational cohort study using the technique of Specialist Cohort Event Monitoring.

Setting The Rivaroxaban Observational Safety Evaluation study was conducted across 87 participating National Health Service secondary care trusts in England and Wales.

Participants 1532 patients treated with rivaroxaban for the prevention and treatment of deep vein thrombosis/pulmonary embolism from September 2013 to January 2016.

Interventions Non-interventional postauthorisation safety study of rivaroxaban.

Primary and secondary outcome measures (1) Risk of major bleeding in gastrointestinal, intracranial, and urogenital sites and (2) risk of all major and clinically relevant non-major bleeds.

Results Of a total of 4846 patients enrolled in the study from September 2013 to January 2016, 1532 were treated with rivaroxaban for the prevention and treatment of deep vein thrombosis/pulmonary embolism. The median age of the deep vein thrombosis/pulmonary embolism cohort was 63 years, and 54.6% were men. The risk of major bleeding within the gastrointestinal, urogenital and intracranial primary sites was 0.7% (n=11), 0.3% (n=5) and 0.1% (n=1), respectively. The risk of major bleeding in all sites was 1.5% (n=23) at a rate of 8.3 events per 100 patient-years.

Conclusions In terms of the primary outcome risk of major bleeding in gastrointestinal, intracranial and urogenital sites, the risk estimates in the population using rivaroxaban for deep vein thrombosis/pulmonary embolism were low (<1%) and consistent with the risk estimated from clinical trial data and in routine clinical practice.

Strengths and limitations of this study

- The Specialist Cohort Event Monitoring technique allowed collection of data about the management of patients in secondary care, which are not recorded in primary care data sources.
- Support of the UK Clinical Research Networks to facilitate recruitment and achieve a high response rate.
- Rapid identification of early prescribers and accumulation of an inception cohort.
- Collection of comprehensive and accurate information facilitating the application of clinical trial outcome definitions.
- Potential for under-reporting or selective reporting of outcomes of interest and/or missing data.

Trial registration numbers ClinicalTrials.gov Registry (NCT01871194); ENCePP Registry (EUPAS3979).

INTRODUCTION

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is common and affects 1 in 2000 adults of the general population annually; the incidence of diagnosed PE in the UK has been reported as 7–8 per 10 000 people annually.[1] The risk of VTE is known to increase with age.[1] The treatment of acute VTE has generally required initial parenteral anticoagulation (eg, low-molecular-weight heparin (LMWH)), followed by long-term oral anticoagulation (eg, vitamin K antagonists (VKAs)).[2] However, the more recent introduction of direct oral anticoagulants (DOACs) over the last decade has provided a convenient alternative to these treatments. The DOAC

rivaroxaban was shown to be at least as effective as LMWH/VKA for the acute treatment of DVT and PE in pivotal clinical trials and was approved in 2011 for the treatment of DVT and for the prevention of recurrent DVT and PE.[3–5] The licence was extended to include the treatment of PE in 2012.[5] Rivaroxaban was also licensed for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack).[5]

To increase the knowledge of effectiveness and safety of rivaroxaban in larger groups of patients following the extension of licence for the prevention and treatment of DVT and PE and for the prevention of stroke and systemic embolism in patients with non-valvular AF, additional postmarketing observational studies were included as part of the European Union Risk Management Plan, including two UK-based observational studies conducted in primary and secondary care.[6] We present data from one of these UK-based studies, the Rivaroxaban Observational Safety Evaluation (ROSE) study, a prospective non-interventional cohort study to evaluate the safety and utilisation of patients prescribed rivaroxaban for the prevention of stroke in patients with AF, for the treatment of DVT and PE, and for the prevention of recurrent DVT and PE in a secondary care setting in England and Wales, using the technique of Specialist Cohort Event Monitoring (SCEM).[7] The SCEM registry design has been developed in parallel with the requirement for pharmaceutical companies to undertake a risk management plan as part of postauthorisation safety monitoring. SCEM addresses an existing need for safety surveillance of new medicines initiated in the hospital setting, thereby capturing patients during the acute phase of treatment who may be more complex in terms of underlying disease, comorbidities and concomitant medications than the general disease population treated in primary care.

To compare reasons for choice of anticoagulation type and to explore differences in both the clinical setting of initiation and the baseline risk of bleeding, the ROSE study included a contextual cohort of patients prescribed warfarin. While bleed outcomes were estimated for both the rivaroxaban and warfarin cohorts, due to the different eligibility criteria for the inclusion of patients in the rivaroxaban cohort and for the inclusion of patients in the warfarin cohort (based on differing exposures to previous anticoagulant therapy), the study did not conduct any direct comparisons between the two cohorts, and therefore the warfarin bleed incidence results have not been included. This article reports on the main clinical end point of interest, which was the incidence of major bleeding within the first 3 months among rivaroxaban users treated for DVT and PE, and the prevention of recurrent DVT and PE.

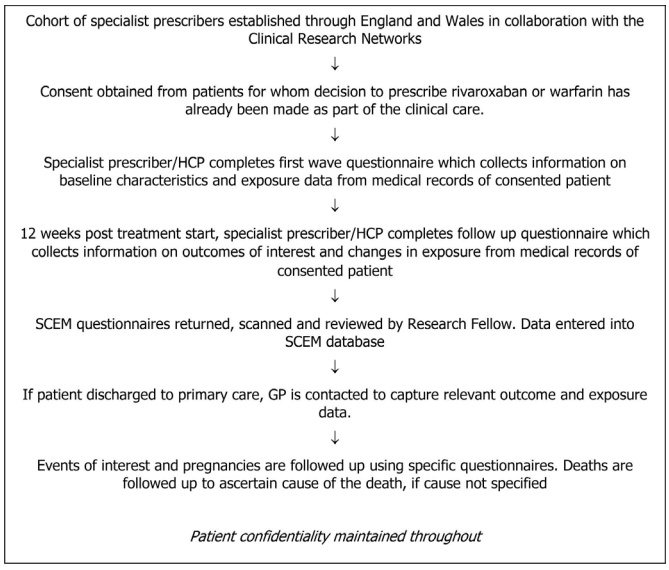

Figure 1 SCEM study process for Rivaroxaban Observational Safety Evaluation. GP, general practitioner; HCP, healthcare professional; SCEM, Specialist Cohort Event Monitoring.

METHODS

Study design and participants

The ROSE study was conducted in secondary care hospitals in England and Wales using the SCEM methodology[7] (figure 1). Patients were identified during the period from September 2013 to January 2016 through clinical specialty groups, supported by Clinical Research Networks. All National Health Service (NHS) trusts in England and Wales were approached to participate.

The study included patients treated for DVT or PE and prevention of recurrent DVT and PE. The diagnosis of VTE was made by the specialist. Patients were eligible for inclusion if they had provided signed informed consent, were at least 18 years old and were rivaroxaban-naïve. Patients were followed up for a period of 12 weeks.

Data sources

Data were collected via secondary use of medical records and relevant data reported by healthcare professionals (HCPs) onto study-specific questionnaires. Only questionnaires with complete analysable clinical data were included. Questionnaires with missing and/or unanalysable data were returned to the HCP to complete and/or provide verification, before inclusion.

Baseline data

Information collected at baseline included demographic characteristics, anticoagulant regimen (total daily dose at treatment initiation), indication for treatment and prior anticoagulation/antiplatelet treatment. In addition, data on bleeding risk (based on HAS-BLED (Hypertension, Abnormal liver/renal function, Stroke history, Bleeding predisposition, Labile international normalised ratios, Elderly, Drug/alcohol usage; HAS-BLED score was abridged for this study as labile international normalised

ratio is only relevant for warfarin patients)) and other baseline clinical characteristics were collected. Although the HAS-BLED score has only been validated in cohorts of patients with AF, there is some evidence to suggest it may have some applicability to patients with VTE[8]; therefore, in this study, the HAS-BLED score was calculated for the DVT/PE indication group.

Study outcomes

The primary outcome was the incidence of major bleeding events according to the International Society on Thrombosis and Haemostasis (ISTH) criteria[9] within gastrointestinal, urogenital and intracranial sites. Secondary objectives included estimating the incidence of all major bleeding (including within other sites) and clinically relevant non-major (CRNM) bleeds.[10] All bleeding events reported by the hospital specialist were classified by a physician at the Drug Safety Research Unit (DSRU) and adjudicated by a second DSRU physician where there was ambiguity. All bleeding events classified as major were confirmed by an external independent medical expert.

Sample size

Based on the 12-week cumulative incidence estimate of 0.4% for the primary outcomes of major bleeding (within gastrointestinal, urogenital and intracranial sites) from clinical trial data, a minimum sample size of 1005 patients was calculated to provide sufficient precision (0.39%) to estimate cumulative incidence for these primary outcomes of interest for patients taking rivaroxaban for the treatment of DVT and PE and for the prevention of recurrent DVT and PE.[3 4 6]

Statistical analysis

The analysable cohort for this article were those patients treated for DVT or PE and prevention of recurrent DVT and PE only. Incident reports were calculated on treatment (+5 drug half-lives (3 days) after stopping to account for drug elimination) during the 12 weeks of observation. Patients were censored according to the first of the following dates: end of the 12-week observation period, loss to follow-up, death, first report of stopping treatment (+5 drug half-lives) or first report of outcome of interest. A Kaplan-Meier curve for the time-to-treatment cessation was produced, including the number of patients at risk. Statistical analyses of baseline data were descriptive, exploratory and largely limited to frequency tables or summary statistics (eg, median+quartiles). Primary and secondary outcome measures are presented as unadjusted cumulative incidence (risk) and incidence rates (per 100 patient-years) with corresponding 95% CIs. Data were analysed using STATA V.15.0 software (StataCorp, College Station, Texas, USA).

The study used the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) cohort reporting guidelines.[11]

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 4846 patients from 83 investigative sites (NHS trusts) provided consent to participate in the study for the period from September 2013 to January 2016. Baseline and 12-week questionnaires were provided for 4625 (95.4%) patients; of these, 4 (0.1%) were ineligible, leaving 4621 evaluable patients. Rivaroxaban was prescribed for 2542 of these evaluable patients (55.0%) and warfarinwas prescribed for 2067 of these evaluable patients(44.7%). In the rivaroxaban cohort, 1532 patients were treated for the prevention and treatment of DVT/PE and most frequently initiated with a total daily dose of 30 mg (76.8%) (table 1). The remaining indications for prescribing rivaroxaban are provided in figure 2.

Baseline characteristics

The baseline demographic and clinical characteristics of the 1532 rivaroxaban patients treated for DVT/PE are summarised in table 1. The median patient age was 63 years; 21.5% were aged >75 years, and 54.6% were men. The median HAS-BLED score was 1. A total of 831 (54.2%) patients were reported to have switched directly from another antithrombotic agent; the majority of these patients switched directly from an LMWH (n=707; 85.1%).

Outcomes

By the end of the 12-week observation period, the number of those at risk (still on treatment with rivaroxaban) had decreased to 1079 patients (figure 3).

The risk of major bleeding within the gastrointestinal, urogenital and intracranial primary sites was 0.7% (95% CI 0.4% to 1.3%), 0.3% (95% CI 0.1% to 0.8%) and 0.1% (95% CI 0.0% to 0.4%), respectively (table 2). The incidence rate for gastrointestinal bleeding was 3.9 events per 100 patient-years (95% CI 2.0 to 7.1). As major bleeding event counts were small (<10) within urogenital and intracranial sites, incidence rates were not calculated. There were no major bleeding events within other critical organ sites (excluding intracranial). For the composite outcome of all major bleeding (ie, at least one major haemorrhagic event, irrespective of the site), the risk was 1.5% (95% CI 1.0% to 2.3%) with a corresponding rate of 8.3 events per 100 patient-years (95% CI 5.3 to 12.5).

CRNM bleeding (irrespective of the site) was more frequently reported than major bleeding in patients taking rivaroxaban for DVT/PE. The risk of CRNM bleeding was 4.9% (95% CI 3.9% to 6.1%) corresponding to an incidence rate of 27.6 (95% CI 21.7 to 34.6). For the composite outcome of all major and CRNM bleeds, the risk was 6.4% (95% CI 5.3% to 7.8%) and the rate was 36.2 events per 100 patient-years (95% CI 29.4 to 44.1).

Table 1 Baseline characteristics and posology of rivaroxaban

	DVT/PE (N=1532)
Baseline characteristics	
Age (years), median (IQR)	63 (48–73)
Gender (male), n (%)	836 (54.6)
BMI, median (IQR)	28.2 (24.8–32.6)*
HAS-BLED, n (%)	
Hypertension†	307 (20.0)
Abnormal renal function	26 (1.7)
Abnormal liver function	33 (2.2)
History of stroke	70 (4.6)
History of bleeding or predisposition	322 (21.0)
Labile INR	NA
Age ≥65 years	701 (45.8)
Drug therapy‡	388 (25.3)
Alcohol (≥8 drinks/week)	89 (5.8)
HAS-BLED score, median (IQR)	1 (0–2)
Score, n (%)	
0	482 (31.5)
1	498 (32.5)
2	314 (20.5)
3	164 (10.7)
4	57 (3.7)
5	12 (0.8)
6	5 (0.3)
7	0 (0.0)
8	0 (0.0)
History of congestive heart failure/ left ventricular dysfunction	51 (3.3)
History of diabetes mellitus	154 (10.1)
History of malignancy (any)	162 (10.6)
Recent malignancy (within 3 months§)	48 (3.1)
Prior use of antithrombotic¶ (within 28 days of start of treatment), n (%)	
Any	1001 (65.3)
Low-molecular-weight heparin**	862 (56.3)
Direct switching from prior antithrombotic,¶ n (%)	831 (54.2)
Low-molecular-weight heparin**	707 (85.1)
Starting total daily dose, n (%)	
10	2 (0.1)
15	154 (10.2)
20	192 (12.8)
25	1 (0.1)
30	1154 (76.8)
Missing	29 (–)

*BMI was missing for 337 patients (22.0%).
†Uncontrolled, >160 mm Hg systolic.
‡Concomitant antiplatelets or non-steroidal anti-inflammatory drugs.
§Within 3 months of start of treatment.
¶Includes oral/parenteral anticoagulants and antiplatelets.
**Includes bemiparin, enoxaparin, tinzaparin and dalteparin.
††Where specified provided, unless otherwise indicated.
BMI, body mass index; DVT, deep vein thrombosis; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding predisposition, Labile international normalised ratios, Elderly, Drug/alcohol usage; INR, international normalised ratio; NA, not applicable; PE, pulmonary embolism.

DISCUSSION

The primary objective of this study was to estimate the incidence (separately) of major bleeding within gastrointestinal, urogenital and intracranial sites during the 12-week observation period. Within this analysis, we examined patients with an indication of DVT or PE only. None of the major bleeds reported in the study resulted in a fatal outcome. The cumulative incidence of major bleeding within the gastrointestinal site was 0.7% (95% CI 0.4% to 1.3%), and the incidence rate was 3.9 per 100 patient-years (95% CI 2.0 to 7.1). This risk in this study is higher than that observed in both the 12-month Xarelto for Long-term and Initial Anticoagulation in venous thromboembolism (XALIA) study (0.1%), a non-interventional study of patients with DVT, which included patients taking rivaroxaban and standard anticoagulation therapy[12] and in rivaroxaban versus standard anticoagulation for symptomatic venous thromboembolism (REMOTEV) (0.4%), a prospective, non-interventional study of patients with acute symptomatic VTE treated with oral rivaroxaban, VKA or parenteral heparin/fondaparinux alone and followed up for 6 months.[13] In the ROSE study, the cumulative incidence of major bleeding within the urogenital site was 0.3% (95% CI 0.1% to 0.8%). Although the EINSTEIN-DVT and EINSTEIN-PE (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism) trials do not specifically report on urogenital bleeds as an outcome, in a post hoc analysis of these trials investigating abnormal uterine bleeding in women aged <60 years, 122 women (13.2%) experienced abnormal uterine bleeding, of which 19 (2.1%) required a transfusion.[14] In the ROSE study, vaginal bleeding was not specifically separated out but was analysed as part of urogenital bleeding. The cumulative incidence of intracranial bleeds in the ROSE study was 0.1% (95% CI 0.0% to 0.4%). In XALIA, major bleeding in the central nervous system (including intracranial, subdural, subarachnoid or cerebral) was 0.2% in the rivaroxaban group.[12]

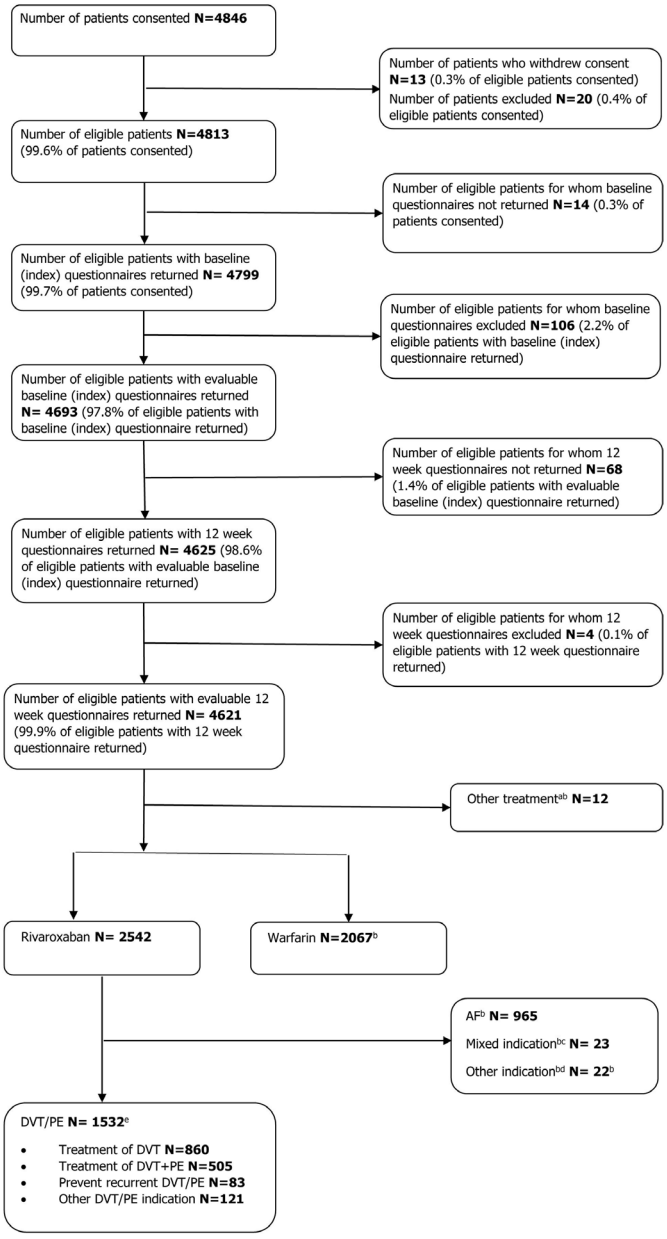

Figure 2 STROBE flowchart of the number of patients recruited over the course of the study. [a]Dalteparin (n=10) and enoxaparin (n=2). [b]Not included in the analysable cohort. [c]Patients reported to have been treated for both atrial fibrillation and DVT/PE. [d]Patients for whom indication was ill-defined and/or off-label (intracardiac thrombus (n=3), thrombophlebitis (n=3), thrombophlebitis superficial (n=3), atrial flutter (n=2), antiphospholipid antibodies (n=1), carotid artery thrombosis (n=1), cerebellar infarction (n=1), cerebrovascular accident (n=1), embolic stroke (n=1), left ventricular dysfunction (n=1), portal vein thrombosis (n=1), subclavian vein thrombosis (n=1), superior sagittal sinus thrombosis (n=1), thrombosis prophylaxis (n=1), not specified (n=1)). [e]Subcategories of all DVT/PE are not mutually exclusive. DVE, deep vein thrombosis; PE, pulmonary embolism; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology.

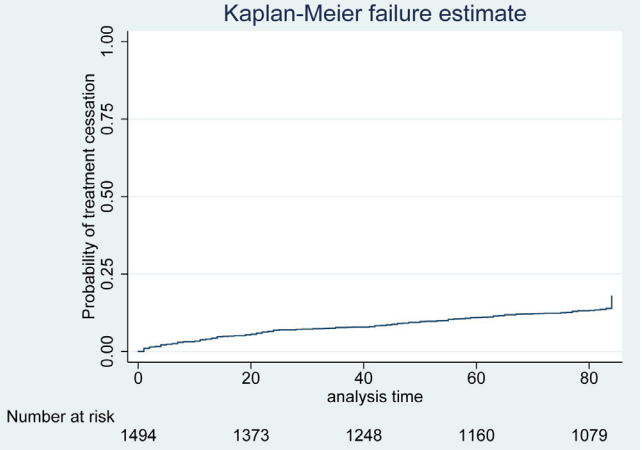

Figure 3 Kaplan-Meier curve for the time-to-treatment cessation, including the number at risk. Thirty-eight patients started and stopped treatment on the same day; hence, the number at risk on the first day is less than the total cohort number.

Secondary outcomes included estimates of major bleeding in other sites and CRNM bleeds. The risk of all major bleeding (at least one major haemorrhagic event, irrespective of the site) was 1.5% (95% CI 1.0% to 2.3%); the corresponding rate was 8.3 events per 100 patient-years (95% CI 5.3 to 12.5). The risk of major bleeding in this study was higher than that observed in the 12-month EINSTEIN-DVT and EINSTEIN-PE trials (0.8% and 1.1%, respectively), which compared rivaroxaban with standard anticoagulation,[3 4] the XALIA study (0.7%)[12] and the REMOTEV study (1.1%).[13] It was also higher than that observed in the SWIss Venous ThromboEmbolism Registry (SWIVTER) (0.5%), a retrospective study comparing rivaroxaban with conventional anticoagulation during a 3-month observation period.[15] However, the risk was lower in this study compared with the Dresden NOAC (non-vitamin K antagonist oral anticoagulant) Registry (1.7% at 90 days), a prospective study of patients with acute VTE followed up for >2 years (mean of 911 days).[16] The risk of CRNM bleeding in the ROSE study was 4.9% (95% CI 3.9% to 6.1%) corresponding to an incidence rate of 27.6 per 100 patient-years (95% CI 21.7 to 34.6). The incidence of CRNM bleeding was similar in the REMOTEV study, 4.3%, and higher in the EINSTEIN-DVT and EINSTEIN-PE trials, 7.3% and 9.5%, respectively.[3 4 13] For the composite outcome of all major and CRNM bleeds, the risk in the ROSE study was 6.4% (95% CI 5.3% to 7.8%) and the rate was 36.2 events per 100 patient-years (95% CI 29.4 to 44.1). In the EINSTEIN-DVT, EINSTEIN-PE and REMOTEV studies, the corresponding risks were 8.1%, 10.3% and 5.4%, respectively.[3 4 13]

In terms of baseline bleeding risk of patients included in the ROSE study, the median HAS-BLED score was 1 (IQR 0–2), reflecting a low bleeding risk in this population. Although this score has only been validated in

Table 2 Cumulative incidence risk and rates of major or CRNM bleeding*

	n=1532		
Bleeding outcome	No. of patients	Risk (%) (95% CI†)	Rate (per 100 patient-years) (95% CI‡)
Major			
Gastrointestinal	11§	0.7 (0.4 to 1.3)	3.9 (2.0 to 7.1)
Urogenital	5¶	0.3 (0.1 to 0.8)	NA**
Intracranial	1	0.1 (0.0 to 0.4)	NA**
Critical organ site††	0	0	NA**
All‡‡	23	1.5 (1.0 to 2.3)	8.3 (5.3 to 12.5)
CRNM§§	75	4.9 (3.9 to 6.1)	27.6 (21.7 to 34.6)
Major bleed (all) and CRNM¶¶	98	6.4 (5.3 to 7.8)	36.2 (29.4 to 44.1)

*Patients may have experienced more than one type of bleeding (eg, major and clinically relevant non-major) within different sites, and so these counts are not mutually exclusive. In cases where multiple bleeding episodes have been reported within the same site, the most serious episode of bleeding was classified, and this bleeding classification with its associated event date was included in the analyses. Where events were reported but with no supporting event date, the patients were excluded.
†95% CI calculated using binomial exact test.
‡95% CI calculated using Poisson exact test.
§Ten patients had a bleed reported with decreased haemoglobin of ≥2 g/dL, and five required a transfusion of ≥2 units of packed red cells or whole blood (a patient could have had more than one ISTH criterion reported).
¶Five patients had a bleed reported with decreased haemoglobin of ≥2 g/dL, and one required a transfusion of ≥2 units of packed red cells or whole blood (a patient could have had more than one ISTH criterion reported).
**Rates were not calculated where event count n ≤10.
††Excluding all intracranial; bleeding events were considered to be critical if they occurred in intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome) or retroperitoneal sites.
‡‡At least one major haemorrhagic event (irrespective of the site).
§§At least one CRNM bleed.
¶¶At least one major haemorrhagic event (irrespective of the site) and/or CRNM bleed.
CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; NA, not applicable.

cohorts of patients with AF, there is some evidence to suggest it may have some applicability to patients with VTE.[8] However HAS-BLED scores were not calculated in the EINSTEIN, XALIA, REMOTEV and SWIVTER studies. Therefore, it is not possible to use the baseline HAS-BLED score to explain the higher incidence of major bleeding observed in the ROSE study compared with these studies. However, individual baseline characteristics, where reported, for patients included in these studies were compared with those observed in ROSE. The majority of patients in the ROSE study were men, which is similar to the EINSTEIN, XALIA and SWIVTER studies. The median age in the ROSE study was comparable with the median age observed in XALIA (63 years vs 59 years, respectively); the mean age reported in the EINSTEIN, SWIVTER and REMOTEV studies ranged from 55.8 years to 62.2 years. In the ROSE study, 3.1% of patients were reported to have had a malignancy within 3 months of starting treatment. This estimate would appear to be at the lower end of the range of baseline malignancies reported in REMOTEV, EINSTEIN, XALIA and SWIVTER studies (2.6%–9.6%). It is acknowledged that these studies differ both in terms of their methodology and study design, in particular with respect to methods of data collection and period of observation; therefore, direct comparisons should be interpreted with caution.

Strengths and limitations

An acknowledged potential weakness of all postauthorisation observational studies, which rely on data collected during routine clinical practice (secondary data usage), is the potential for under-reporting or selective reporting of outcomes of interest and/or missing data. This may result in an underestimation or overestimation of the incidence of bleeding events. However, the misclassification of outcomes is presumed to be non-differential between prescribers. In addition, a limitation of studies relying on medical records is that they do not directly capture patient-reported outcomes. It is therefore possible that minor bleeding events were under-reported to the specialist. However, the aim of the study was to estimate the incidence of major and CRNM bleeds according to the ISTH classification, which are likely to have been reported to the specialist. An added limitation of this method of data capture was that we were unable to present data on the specific anatomical site of bleeding. The SCEM methodology allows the identification of cohorts of patients through prescription data. However, it is not possible to assess the degree to which the patient was compliant with the recommended treatment regimen. Another potential source of bias in this study is non-response bias. It is unknown whether the prescribing patterns and/or patients of specialist HCPs

who returned the questionnaire were different from those of the specialist HCPs who did not return the questionnaire, as is the potential for selection bias in terms of representativeness of patients included in this cohort. However, the response rate was 98.1% in this study (data not shown), and we do not believe that selection bias affects the types or number of bleeding events experienced and reported by a patient after treatment was initiated. Furthermore, widespread recognition of national and local clinical guidelines regarding prescribing of rivaroxaban contributes, to some extent, to reducing the selection bias. For this study, the desire was to obtain a representative sample of patients prescribed rivaroxaban. Certain indicators were compared between hospital trusts that participated in the study and those that did not. While there appeared to be no difference between participating and non-participating trusts for many of these indicators, such as geographical location, some differences were apparent for indicators, including hospital density, population density and the availability of guidelines for use of rivaroxaban. Since the study commenced soon after the market launch of rivaroxaban for the new licensed indications, there is a potential for channelling towards patients with specific risk profiles. This is not unexpected given prescribing guidelines, and given the potential for bias, we have not compared risk of bleeding between those receiving rivaroxaban and those receiving warfarin. We have characterised the rivaroxaban cohort for transparency. Direct comparisons of baseline characteristics, such as renal function, among patients included in the ROSE study against baseline characteristics reported in previous studies were not performed as identical covariates were not collected. In the ROSE study, baseline renal status was ascertained according to chronic kidney disease (CKD) stages 1 and 2, stages 3 and 4, and stage 5, as opposed to creatinine clearance; therefore, direct comparisons were not possible. In addition, due to the low number of bleeding events, stratification by baseline characteristics which may be considered risk factors for bleeding, such as a history of malignancy, was not performed.

In addition to achieving a very high response rate, a key strength of this study and the SCEM design is the ability to identify cohorts of patients treated in secondary care, thereby facilitating the collection of data on a more diverse patient population, including patients with higher levels of comorbidity. For those patients whose treatment was initiated in secondary care, information on the short-term risk of bleeding was collected from the very beginning of treatment, filling an evidence gap not addressed by other studies. The methodology allows the rapid identification of early prescribers and accumulation of an inception cohort. Furthermore, the unique aspect of the study design enabled collection of highly detailed and complete information, allowing the accurate calculation of relevant risk scores and the adoption of clinical trial outcome definitions. As with other observational studies conducted in the real-world setting, a fundamental aspect of the SCEM design is the inclusion of patients likely to have been excluded from clinical trials.

CONCLUSION

In terms of the primary outcome risk of major bleeding in gastrointestinal, intracranial and urogenital sites, the estimates of risk in the DVT/PE rivaroxaban user population were low (<1%), which is consistent with risk estimated from clinical trial data and in routine clinical practice. The SCEM design provides a framework suitable to evaluate the safety of newly marketed medicines in secondary care setting.

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Contributors AE, MD, VO and SS designed the study. VO and DR conducted the statistical analysis, and AE, MD and VO interpreted the data. The manuscript was written primarily by AE. All authors reviewed, contributed to revisions and approved the manuscript and accept full responsibility for its overall content.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by South Central—Hampshire A NHS Research Ethics Committee (part of the European Network of Research Ethics Committees).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are not available in the public domain, but the Drug Safety Research Unit can be contacted if further information about this study is required.

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