PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	An observational cohort study to evaluate the incidence of bleeding in patients prescribed rivaroxaban for the treatment and prevention of deep vein thrombosis and pulmonary embolism in UK secondary care
AUTHORS	Evans, Alison; Davies, Miranda; Osborne, Vicki; Roy, Debabrata; Shakir, Saad

VERSION 1 – REVIEW

REVIEWER	Yasuo Okumura Nihon University School of Medicine, Japan
REVIEW RETURNED	27-Apr-2020

GENERAL COMMENTS	Evans et al. evaluated the short-term (12 weeks) safety and utilisation of rivaroxaban prescribed to newuser adult patients for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent DVT and PE in a secondary care setting in England and Wales. This study has potentially included important information to understand the outcomes in patients with DVT/PE in clinical practice in England and Wales. This reviewer understands this study was a single arm observational study, so most of their results were descriptive. Nonetheless, this reviewer recommends to add several data as described below. In the rivaroxaban cohort, 1532 patients were treated for prevention and treatment of DVT/PE, most frequently with a total daily dose of 30mg (76.8%). → Show a daily dose in the remaining patients. → Show the duration of rivaroxaban 30mg. Did most of all patients have rivaroxaban 30mg for 1 months? Show a total daily dose of rivaroxaban after the initial dose regimen. Kaplan-Meier curve including the number at risk should be shown in the results section. Show the management (discontinuation and resumption of rivaroxaban and requirement of blood transfusion) after gastrointestinal, urogenital, and intracranial major bleeding events, and subsequent major bleeding-related outcomes (recurrent PE/DVT, stroke or death). If major bleeding-related adverse clinical events occurred, when those events had occurred? Despite a small number of patients, show the patient characteristics in those patients. Was a PPI taken in all patients who had experienced gastrointestinal major bleeding? This information would help the readers to understand how to care and manage the patients with major bleeding events. They should

	have had those data because they have addressed the high reliable correction data as one of the strong points of this study. They concluded major bleeding in gastrointestinal, intracranial and urogenital sites, the estimates of risk in the DVT/PE rivaroxaban user population were low (<1%) which is similar to the risk estimated from clinical trial data and in routine clinical practice. However, the follow-up duration of this study was only 12 weeks, so the direct comparisons to other trial or observational studies (in most of studies follow-up period was 1 year) is difficult. Therefore, they used event number per 100 person years. When considering the follow-up period in this study, those major bleeding event rate seems to be higher. Is that right? In addition, secondary outcomes included estimates of major bleeding in other sites and CRNM bleeds also appeared to be higher as compared to the other prior trial or observational studies. Why? The patient was older or at higher risk in this cohort? Discuss this point.

REVIEWER	Ida Ehlers Albertsen Aalborg Thrombosis Research Unit, Aalborg University Hospital, Aalborg, Denmark.
REVIEW RETURNED	13-May-2020

GENERAL COMMENTS	The study by Evans et al investigate risk of major and clinically relevant non-major bleeding in VTE patients treated with rivaroxaban in secondary care. The study has a simple set-up and is well-written. The aim is clear but the novelty of the study can be questioned. Also, simple approaches could strengthen the study that could benefit from more weight. Title Could re-phrase to: "Incidence of major and clinically relevant non-major bleeding in venous thromboembolism patients treated with rivaroxaban in secondary care: results from the....". Abstract - Please limit the use of abbreviations in the abstract. Introduction - Introduction: please refer to rates using only one numerator, i.e. per 1000 person-years - not vary between per 2000 and per 100,000. - Need ref under 'introduction' line 16, the sentence beginning with 'The DOAC, Rivaroxaban,...'. - No comparison to warfarin: 'based on previous anticoagulation', page 4 line 58. What does that mean? Methods -page 5 line 25: specify if incident VTE? - Who were excluded from the study? Were patients with cancer included? This very much need to be addressed. - 'sample size' line 15: 'the clinical trial' should be deliberated -'statistical analyses': not taking the competing risk of death into account when reporting cumulative incidence. This will over-estimate the risk. Death is not mentioned at all in the manuscript. How many died?

	- Please describe how events will be calculated (number of events per 1000 person years?). - Daily dose mentioned on page 7: I assume that the dose was reduced after initial 3 weeks? Should be specified. - page 7, line 38: CRNM more frequent among patients treated for DVT/PE: than who? Please specify reference group/comparator. Limitations - Please specify the consequence of potential under or selective reporting of outcomes that is mentioned. Also, an aim is mentioned about ensuring a representative sample - this aim has not been mentioned previously? - How is the VTE diagnosis validated? What is the positive predictive value of the diagnosis? - Aim: how is the 'utilization' described in the objectives of the study covered? - Please comment on a potential risk of selection bias among excluded/decliners? - Nothing is mentioned on completeness of the questionnaires? - Is it the same physician treating the patient who classified bleeding? This could vary much bias the results and should be mentioned in limitations if so. - Limitations on questionnaires: they were filled out not by the patient themselves. Tables and figures - Figure 2: 'Treatment of DVT/PE' means incident VTE? As opposed to prevent recurrent DVT/PE? What is 'other DVT/PE'? - Table 2: 'incidence risk' rephrase to 'cumulative incidence proportion'. Title: correct 'of' before 'CRNM'. - Table 1: age: mean? Could be relevant to present the baseline information on warfarin patients, although no comparison is done. This will be valuable for the reader to be able to compare the different patient characteristics. How was hypertension defined? Alcohol: did 5.8% drink more than 8 drinks/week? How was malignancy defined? - Table 1: few baseline characteristics. Not a clear picture of the patients treated. - Information on VTE-type: provoked/unprovoked? - this affects the duration of the treatment. - Could have been relevant to describe antithrombotic medicine within previous year, not only 28 days - and perhaps exclude existing users. Discussion - Please write out study names first time when using them, e.g. XALIA General considerations: - Please consider if perhaps prescribers might have selected more healthy individuals right after launch of a new drug indication in 2013. Hence, are we looking at more healthy patients? - Confounding by indication? - Throughout the study is should be specified if the treatment is of incident VTE or treatment of recurrent VTE or both? - is it first time VTE only? - this will largely affect the recurrence risk and hence treatment duration. Furthermore, this information should be included in table 1: how many with incident VTE, how many with treatment for a recurrent VTE?

	- In general, please limit the use of abbreviation, e.g. AF and RPM - Despite the fact that the description of the ROSE study, the SECM, and EU involvement took up a large part of the introduction it is still challenging to decode the link between these things. In line 32 it is written that the study 'report on one of these studies' meaning using data from this study? Major concerns. - The study presents bleeding outcomes within 12 weeks for VTE patients treated with rivaroxaban. This is a very short follow-up period. The majority of patients should/will receive longer treatment. Why is it relevant with a study covering a very short period of time of the total treatment period? The study compares itself with other studies with longer follow-up periods in the discussion. These results are relevant primarily to patients with a major transient risk factor presenting the only group with time-limited treatment. The limitation of a short follow-up period needs to be addressed. - What new information does this study provide? The novelty of this study can be questioned. - The discussion lists results from other studies without giving explanations to differences any thought. Deeper considerations to what the differences are and what this study adds would strengthen the study. - simple studies are good but it seems that this study could benefit from more weight. At least an descriptive comparison with the patients treated with warfarin or more information on the VTE patients. Could also investigate characteristics associated with the bleeding outcome.

REVIEWER	Jeffrey Kline Indiana University School of Medicine Research funding from Janssen and Pfizer
REVIEW RETURNED	01-Jun-2020

GENERAL COMMENTS	This study provided near-real world bleeding outcomes after 12 weeks of rivaroxaban treatment and provides a citeable piece that will be useful in pooled analyses. The main finding was a higher than expected rate of bleeding. My first question is the usual one about what features of a GI bleed crossed the threshold into the ISTH definition, which can be quite vague when applied. Would the authors be willing to provide more detail about the GI bleed criteria. A patient who reports hematemesis with a normal hemoglobin but got an endoscopy with no findings the next day could be positive, as could a patient who exsanguinated and required massive transfusions. Why was the dose 30 mg for 12 weeks. In the US, we prescribe that dose for 21 days. The foreseeable regret and weakness of this study was not collecting data about menorrhagia, which I see as the most frequent problem in younger populations. Can you at least say how many women were at risk of menorrhagia, for example the % <45 or 50 years of age? This absence should be listed as a weakness in the discussion, especially in view of our duty to rectify previous transgressions on considering women's health.

	Something that I do not understand is why report on warfarin at all in the methods? This gave me the impression that you would provide some warfarin data for comparison, (despite your statement in the methods that they "cannot" not be compared.) Maybe it would be better to just label them as excluded because they were "not treated with rivaroxaban". Besides seems to me that other patients would have received other anticoagulants besides warfarin such as apix or dabi. Can you help me know if the HAS-BLED was useful at 0? Did the bleed rate increase with score? I would predict that the HAS-BLED data could generate more reader interest than the primary outcome. We doctors love to use scores.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Please leave your comments for the authors below Evans et al. evaluated the short-term (12 weeks) safety and utilisation of rivaroxaban prescribed to new user adult patients for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent DVT and PE in a secondary care setting in England and Wales. This study has potentially included important information to understand the outcomes in patients with DVT/PE in clinical practice in England and Wales. This reviewer understands this study was a single arm observational study, so most of their results were descriptive. Nonetheless, this reviewer recommends to add several data as described below.
1. In the rivaroxaban cohort, 1532 patients were treated for prevention and treatment of DVT/PE, most frequently with a total daily dose of 30mg (76.8%). Show a daily dose in the remaining patients.
Author response: We thank the reviewer for their review and comments. We have now included the total daily dose for all patients at treatment initiation in Table 1.

2. Show the duration of rivaroxaban 30mg. Did most of all patients have rivaroxaban 30mg for 1 months? Show a total daily dose of rivaroxaban after the initial dose regimen.
Author response: For this manuscript we are only looking at the dose at treatment initiation, as reported by the specialist/healthcare professional. This has now been made clear in the Methods section and in Table 1 i.e. Posology (starting total daily dose):
“Information collected at baseline included demographic characteristics, anticoagulant regimen (total daily dose at treatment initiation), indication for treatment and prior anticoagulation/antiplatelet treatment.”

3. Kaplan-Meier curve including the number at risk should be shown in the results section.
Author response: A Kaplan-Meier curve including the number at risk is now included in the results section. Corresponding additional text has also been added to the Methods section.
4. Show the management (discontinuation and resumption of rivaroxaban and requirement of blood transfusion) after gastrointestinal, urogenital, and intracranial major bleeding events, and subsequent major bleeding-related outcomes (recurrent PE/DVT, stroke or death). If major bleeding-related adverse clinical events occurred, when those events had occurred? Despite a small number of patients, show the patient characteristics in those patients. Was a PPI taken in all patients who had experienced gastrointestinal major bleeding? This information would help the readers to understand how to care and manage the patients with major bleeding events. They should have had those data because they have addressed the high reliable correction data as one of the strong points of this study.
Author response: This is outside the scope of this manuscript which is primarily focussing on the

incidence of major bleeding as opposed to the management of patients who experienced a bleed.
5. They concluded major bleeding in gastrointestinal, intracranial and urogenital sites, the estimates of risk in the DVT/PE rivaroxaban user population were low (<1%) which is similar to the risk estimated from clinical trial data and in routine clinical practice. However, the follow-up duration of this study was only 12 weeks, so the direct comparisons to other trial or observational studies (in most of studies follow-up period was 1 year) is difficult. Therefore, they used event number per 100 person years. When considering the follow-up period in this study, those major bleeding event rate seems to be higher. Is that right?
Author response: We cannot draw conclusions beyond the 12 week time period and therefore any comparisons should be treated with caution. We have included a statement as such in the Discussion: "Since the ROSE study had a different design to these studies, in particular with respect to the observation period, and different objectives, direct comparisons should be interpreted with caution."
6. In addition, secondary outcomes included estimates of major bleeding in other sites and CRNM bleeds also appeared to be higher as compared to the other prior trial or observational studies. Why? The patient was older or at higher risk in this cohort? Discuss this point.
Author response: We have discussed our cohort in terms of baseline bleeding risk of patients (which included age) in the Discussion:
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 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 as compared to these studies.

Reviewer: 2
Please leave your comments for the authors below The study by Evans et al investigate risk of major and clinically relevant non-major bleeding in VTE patients treated with rivaroxaban in secondary care. The study has a simple set-up and is well-written. The aim is clear but the novelty of the study can be questioned. Also, simple approaches could strengthen the study that could benefit from more weight.
1. Title
Could re-phrase to: "Incidence of major and clinically relevant non-major bleeding in venous thromboembolism patients treated with rivaroxaban in secondary care: results from the....".
Author response: We thank the reviewer for their review and comments. We have revised the title as per the Editorial Request to indicate the research question, setting, and study design. This is the preferred format for the journal.:
"An observational Specialist Cohort Event Monitoring study to evaluate the incidence of major and clinically relevant non-major bleeding in patients prescribed rivaroxaban for the treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrent deep vein thrombosis and pulmonary embolism in UK secondary care."
2. Abstract
- Please limit the use of abbreviations in the abstract.
Author response: These have now been removed.
3. Introduction
- Introduction: please refer to rates using only one numerator, i.e. per 1000 person-years - not vary between per 2000 and per 100,000.
Author response: These are reported as per the original reference and have therefore been left as quoted.
4. Need ref under 'introduction' line 16, the sentence beginning with 'The DOAC, Rivaroxaban,...'.
Author response: The references have been added.
5. No comparison to warfarin: 'based on previous anticoagulation', page 4 line 58. What does that mean?
Author response: New users of rivaroxaban comprised of rivaroxaban naïve patients, who may or

may not have been antithrombotic or anticoagulant treatment naive. The contextual cohort comprised of patients for whom no exposure to anticoagulation therapy had occurred within the 12 months prior to initiation. We have amended the sentence slightly to clarify:
“Whilst bleed outcomes were estimated for both the rivaroxaban and warfarin cohorts, due to the different eligibility criteria for inclusion of patients in the rivaroxaban cohort, and 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.”
6. Methods
-page 5 line 25: specify if incident VTE?
Author response: The indication was captured via tickbox questions asking the Specialist healthcare professional to provide the condition requiring treatment initiation. We cannot confirm whether the condition of DVT/PE was an incident event i.e. we cannot confirm whether this was the first-ever event of DVT/PE in each patient.
7. Who were excluded from the study? Were patients with cancer included? This very much need to be addressed.
Author response: Since this was an observational cohort study conducted in a naturalistic setting, open patient entry criteria were applied to maximise external validity. There were no exclusion criteria for the rivaroxaban cohort; the inclusion criteria are already included in the Methods section.
8. 'sample size' line 15: 'the clinical trial' should be deliberated
Author response: We have reworded the sentence to make it clearer:
“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 prevention of recurrent DVT and PE. (3, 4, 6)
9. 'statistical analyses': not taking the competing risk of death into account when reporting cumulative incidence. This will over-estimate the risk. Death is not mentioned at all in the manuscript. How many died?
Author response: We have added the exposure definition, which included censoring at death, to the Methods section:
“Patients were censored according to the first of the following dates: end of 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.”
In addition, none of the major bleeds reported in the study resulted in a fatal outcome. This has been added to the Discussion.
10. Please describe how events will be calculated (number of events per 1000 person years?).
Author response: “per 100 patients years” has now been included in the Methods section:
“Primary and secondary outcome measures are presented as unadjusted cumulative incidence (risk) and incidence rates (per 100 patient years) with corresponding 95% confidence intervals.
11. Daily dose mentioned on page 7: I assume that the dose was reduced after initial 3 weeks? Should be specified.
Author response: For this manuscript we are only looking at the dose at treatment initiation, as reported by the specialist/healthcare professional. This has now been made clear in the Results section and also in the Methods section and in Table 1 where we have now also included the posology (starting total daily dose):
“In the rivaroxaban cohort, 1532 patients were treated for prevention and treatment of DVT/PE, and most frequently initiated with a total daily dose of 30mg (76.8%).”
“Information collected at baseline included demographic characteristics, anticoagulant regimen (total daily dose at treatment initiation), indication for treatment and prior anticoagulation/antiplatelet treatment.”
12. page 7, line 38: CRNM more frequent among patients treated for DVT/PE: than who? Please

specify reference group/comparator.
Author response: We are stating in the sentence that CRNM bleeding is more frequent than major bleeding:
“CRNM bleeding (irrespective of site) was more frequently reported than major bleeding in patients taking rivaroxaban for DVT/PE.”
Limitations
13. Please specify the consequence of potential under or selective reporting of outcomes that is mentioned.
Author response: Under or selective reporting of outcomes of interest and/or missing data may result in an under or over estimation of the incidence of bleeding events. However, the misclassification of outcomes is presumed to be non-differential between prescribers. Additional text has been added to the Strengths and Limitations.
“An acknowledged potential weakness of all post-authorisation observational studies, which rely on data collected during routine clinical practice (secondary data usage), is the potential for under or selective reporting of outcomes of interest and/or missing data. This may result in an under or over estimation of the incidence of bleeding events. However, the misclassification of outcomes is presumed to be non-differential between prescribers.”
14. Also, an aim is mentioned about ensuring a representative sample - this aim has not been mentioned previously?
Author response: This sentence has now been reworded since it was not a specific “aim” as such, more a desire.
“For this study, the desire was to obtain a representative sample of patients prescribed rivaroxaban”
15. How is the VTE diagnosis validated? What is the positive predictive value of the diagnosis?
Author response: The diagnosis is made by the specialist. We do not query or validate clinician diagnoses.
16. Aim: how is the 'utilization' described in the objectives of the study covered?
Author response: The aim of the ROSE study was to include rivaroxaban utilisation, including the degree of compliance with prescribing recommendations, information on use in special populations of patients, and baseline risk of stroke and bleeding. The baseline risk of bleeding (HASBLED) has been included in this paper however a separate paper has been prepared specifically detailing rivaroxaban utilisation.
17. Please comment on a potential risk of selection bias among excluded/decliners?
Author response: Additional text added to the Strengths and Limitations section.
“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 to those of the specialist HCPs who did not return the questionnaire, as is the potential 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.”
18. Nothing is mentioned on completeness of the questionnaires?
Author response: A sentence has been added to the Methods section and further clarification in the Discussion.
“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.”
“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.”
19. Is it the same physician treating the patient who classified bleeding? This could vary much bias the results and should be mentioned in limitations if so.

Author response: The specialist at the hospital treating the patient diagnosed the bleeding events. Bleeding events reported on the questionnaires were then classified according to ISTH criteria by a physician at the Drug Safety Research Unit and adjudicated by a second physician at the Drug Safety Research Unit, where there was ambiguity. All bleeding events classified as major were then confirmed by an external independent medical expert. This has been clarified in the Methods section. "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."

20. Limitations on questionnaires: they were filled out not by the patient themselves.

Author response: The authors agree that a limitation to studies relying on medical records is that there are no direct patient-reported outcomes, therefore there is the potential for missing minor bleeds. However, the aim was to look at major/CRNM bleeding as per ISTH classification which would be reported to the specialists. Additional text has been added to the Strength and Limitations section. "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 ISTH classification, which are likely to have been reported to the specialist."

Tables and figures

21. Figure 2: 'Treatment of DVT/PE' means incident VTE? As opposed to prevent recurrent DVT/PE?

Author response: As per the authors response to point 6 above, the indication was captured via tickbox questions asking the Specialist healthcare professional to provide the condition requiring treatment initiation. The tickboxes separately asked whether the indication was the Treatment of DVT/ PE as opposed to the Prevention of recurrent DVT/PE. However we cannot confirm whether the treatment of DVT/PE was an incident event i.e. we cannot confirm whether this was the first-ever event of DVT/PE in each patient.

22. What is 'other DVT/PE'?

Author response: These included reported DVT/PE events where the HCP ticked an "Other" tickbox and/or included a free text reported event term of DVT or PE.

23. Table 2: 'incidence risk' rephrase to 'cumulative incidence proportion'. Title: correct 'of' before 'CRNM'.

Author response: Title changed to "Cumulative incidence risk and rates of major or CRNM bleeding"

24. Table 1: age: mean?

Author response: We have presented median age to allow for non-normal distribution.

25. Could be relevant to present the baseline information on warfarin patients, although no comparison is done. This will be valuable for the reader to be able to compare the different patient characteristics.

Author response: Background information on the inclusion of the contextual cohort (warfarin) was included to provide an overview of the study design. Since the intention was not to conduct any direct comparisons between the two cohorts in terms of bleed incidence, further characteristics pertaining to the warfarin cohort have not been included here.

26. How was hypertension defined?

Author response: A definition of "Uncontrolled, >160 mmHg systolic" has been added as a footnote to Table 1. Hypertension was diagnosed by the specialist and reported according to the specific tickbox response and included any relevant freetext reports.

27. Alcohol: did 5.8% drink more than 8 drinks/week?

Author response: This is as reported by the HCP and is as per the HASBLED definition, however a clarification that this is 'greater or equal to' has now been added which was initially missing from Table 1.

28. How was malignancy defined?

Author response: Malignancy was diagnosed by the specialist and reported according to the specific tickbox response and included any relevant freetext reports. The authors have also clarified in Table 1

that this is a history of malignancy.
29. Table 1: few baseline characteristics. Not a clear picture of the patients treated.
Author response: The authors have included the baseline characteristics relevant to bleeding risk which are predominantly the factors included in the HASBLED risk score and believe this to be a comprehensive list with respect to the outcome of interest.
30. Information on VTE-type: provoked/unprovoked? - this affects the duration of the treatment.
Author response: Information regarding whether the VTE was provoked or unprovoked is outside the scope of this paper. In addition, the observation period was limited to 12 weeks regardless of the treatment period, therefore the duration of treatment would not have had an impact.
31. Could have been relevant to describe antithrombotic medicine within previous year, not only 28 days - and perhaps exclude existing users.
Author response: As per the study design, the period of interest was within 28 days prior to start of treatment in order to capture information on any recent use or newly prescribed medications that may impact on individual patient baseline risk, in addition to capturing information on switching.
Discussion
32. Please write out study names first time when using them, e.g. XALIA
Author response: Study names for XALIA and REMOTEV have been added in full.
General considerations:
33. Please consider if perhaps prescribers might have selected more healthy individuals right after launch of a new drug indication in 2013. Hence, are we looking at more healthy patients? - Confounding by indication?
Author response: Additional wording has been added to the Strengths and Limitations section.
“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.”
34. Throughout the study is should be specified if the treatment is of incident VTE or treatment of recurrent VTE or both? - is it first time VTE only? - this will largely affect the recurrence risk and hence treatment duration. Furthermore, this information should be included in table 1: how many with incident VTE, how many with treatment for a recurrent VTE?
Author response: As per responses to points 6, 21 and 30 above, the indication was captured via tickbox questions asking the Specialist healthcare professional to provide the condition requiring treatment initiation. We cannot confirm whether the condition of DVT/PE was an incident event i.e. we cannot confirm whether this was the first-ever event of DVT/PE in each patient. In addition, the observation period was limited to 12 weeks regardless of the treatment period, therefore the duration of treatment would not have had an impact.
35. In general, please limit the use of abbreviation, e.g. AF and RPM
Author response: Restricted to commonly used abbreviations.
36. Despite the fact that the description of the ROSE study, the SECM, and EU involvement took up a large part of the introduction it is still challenging to decode the link between these things. In line 32 it is written that the study 'report on one of these studies' meaning using data from this study?
Author response: Reworded for clarification.
We present data from one of these UK-based studies, the Rivaroxaban Observational Safety Evaluation (ROSE) study (EU PAS Register Number EUPAS3979), a prospective non-interventional cohort study to evaluate the safety and utilisation in patients prescribed of rivaroxaban for the prevention of stroke in patients with AF, treatment of DVT and PE, and 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)
Major concerns.
37. The study presents bleeding outcomes within 12 weeks for VTE patients treated with rivaroxaban. This is a very short follow-up period. The majority of patients should/will receive longer treatment.

Why is it relevant with a study covering a very short period of time of the total treatment period? The study compares itself with other studies with longer follow-up periods in the discussion. These results are relevant primarily to patients with a major transient risk factor presenting the only group with time-limited treatment. The limitation of a short follow-up period needs to be addressed.
Author response: The ROSE study was specifically concerned with the short term incidence of bleeding. The complimentary UK study set in Primary care reported on the longer term risk i.e. 12 months. The 12 week observation period was chosen specifically to look at short-term risk of bleeding whilst the patient was still under the care of the specialist, thus filling an evidence gap which many other studies fail to address. This has been added to the Strengths and Limitations section.
"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."
38. What new information does this study provide? The novelty of this study can be questioned.
Author response: This study focusses on the short-term risk of bleeding whilst the patient is still under the care of the specialist, thus filling an evidence gap which many other studies fail to address. This has been added to the Strengths and Limitations section.
39. The discussion lists results from other studies without giving explanations to differences any thought. Deeper considerations to what the differences are and what this study adds would strengthen the study.
Author response: HAS-BLED scores were not calculated in the EINSTEIN, XALIA, REMOTEV and SWIVTER studies, therefore comparison of baseline bleeding risk is not possible between these studies and the ROSE study. In addition, since the ROSE study was different in terms of design and objectives, direct comparisons of the date need to be made with caution. A sentence has been added to the Discussion.
"Since the ROSE study had a different design to these studies, in particular with respect to the observation period, and different objectives, direct comparisons should be interpreted with caution."
40. simple studies are good but it seems that this study could benefit from more weight. At least an descriptive comparison with the patients treated with warfarin or more information on the VTE patients. Could also investigate characteristics associated with the bleeding outcome.
Author response: The focus of this paper is to report on the incidence of major bleeding. Descriptive comparisons with the contextual cohort, characteristics of VTE patients and patients with a bleeding outcome are outside the scope of this manuscript.

Reviewer: 3
Please leave your comments for the authors below This study provided near-real world bleeding outcomes after 12 weeks of rivaroxaban treatment and provides a citeable piece that will be useful in pooled analyses. The main finding was a higher than expected rate of bleeding.

1. My first question is the usual one about what features of a GI bleed crossed the threshold into the ISTH definition, which can be quite vague when applied. Would the authors be willing to provide more detail about the GI bleed criteria. A patient who reports hematemesis with a normal hemoglobin but got an endoscopy with no findings the next day could be positive, as could a patient who exsanguinated and required massive transfusions.
Author response: We thank the reviewer for their review and comments. The focus of this paper is to report on the incidence of major bleeding and therefore descriptive details regarding the bleed criteria are outside the scope of this manuscript and have not been included. However, for your information, 11 patients had a reported GI bleed, 10 were reported with decreased haemoglobin (>2g/dL) and 5 required a transfusion of >2 units of packed red cells or whole blood (a patient could have had more than one criteria reported)
2. Why was the dose 30 mg for 12 weeks. In the US, we prescribe that dose for 21 days.
Author response: UK/EU guidelines also recommend initial treatment of 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent

DVT and PE. However, for this manuscript we are only looking at the dose at treatment initiation, as reported by the specialist/healthcare professional. This has now been made clear in the Methods section and in Table 1 i.e. Posology (starting total daily dose):
"Information collected at baseline included demographic characteristics, anticoagulant regimen (total daily dose at treatment initiation), indication for treatment and prior anticoagulation/antiplatelet treatment."
3. The foreseeable regret and weakness of this study was not collecting data about menorrhagia, which I see as the most frequent problem in younger populations. Can you at least say how many women were at risk of menorrhagia, for example the % <45 or 50 years of age? This absence should be listed as a weakness in the discussion, especially in view of our duty to rectify previous transgressions on considering women's health.
Author response: As the primary objective was to estimate bleeding risk in pre-defined sites (urogenital, intracranial, gastrointestinal), for the primary analysis we were unable to provide further details regarding the specific site of bleeding within these pre-defined overall sites. This has been cited as a limitation of the study.
"An added limitation of this method of data capture was that we were unable to present data on the specific anatomical site of bleeding."

4. Something that I do not understand is why report on warfarin at all in the methods? This gave me the impression that you would provide some warfarin data for comparison, (despite your statement in the methods that they "cannot" not be compared.) Maybe it would be better to just label them as excluded because they were "not treated with rivaroxaban". Besides seems to me that other patients would have received other anticoagulants besides warfarin such as apix or dabi.
Author response: Background information on the inclusion of the contextual cohort (warfarin) was included to provide an overview of the study design. However, since the intention was not to conduct any direct comparisons between the two cohorts in terms of bleed incidence, further characteristics pertaining to the warfarin cohort have not been included here.
5. Can you help me know if the HAS-BLED was useful at 0? Did the bleed rate increase with score? I would predict that the HAS-BLED data could generate more reader interest than the primary outcome. We doctors love to use scores.
Author response: A direct analysis of the risk of bleeding with the HASBLED score was not the intention and is outside the scope of this paper. In addition, the low numbers of bleeding events mean there is insufficient data to comment on any trends.

VERSION 2 – REVIEW

REVIEWER	Yasuo Okumura Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
REVIEW RETURNED	12-Jul-2020

GENERAL COMMENTS	Because of a lack of data, they could not answer some of this reviewer's comments. In particular, their patient background is different, and their study follow-up period is short, so they stated that direct comparisons to other cohorts should be interpreted with caution. This reviewers understand that, but how should the readers understand why secondary outcomes were higher than those seem with other cohorts? They will be able to provide some insights into understanding their patient background by using not only HAS-BLED but also age, body weight, or renal function, and other risk factors. Except that, there were no further comments.

REVIEWER	Ida Ehlers Albertsen Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark.
REVIEW RETURNED	06-Jul-2020

GENERAL COMMENTS	Thank you to the authors for very good responses. The manuscript reads well with a clearly formulated aim. Details to be mentioned: - The authors write that the VTE diagnosis is not validated and rely on the specialist. I do think lack of validation of the diagnoses should be mentioned in the limitations. - Still, nothing is mentioned on patients with cancer? Was this information not part of the questionnaire tickbox or? - I am aware, that the title is changed as per editor request. I would, however, consider leaving out 'and prevention of recurrent deep vein thrombosis and pulmonary embolism'. Thank you.

REVIEWER	jeffrey a kline Indiana University School of Medicine USA similar research interest
REVIEW RETURNED	11-Jul-2020

GENERAL COMMENTS	The authors were not really responsive to making suggested changes and explanations. For example, I do not think that the definition of bleeding criteria for a paper focusing on bleeding is "outside the scope" of the paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Yasuo Okumura

Institution and Country
Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Please state any competing interests or state ‘None declared’:
None

Please leave your comments for the authors below Because of a lack of data, they could not answer some of this reviewer's comments. In particular, their patient background is different, and their study follow-up period is short, so they stated that direct comparisons to other cohorts should be interpreted with caution. This reviewers understand that, but how should the readers understand why secondary outcomes were higher than those seem with other cohorts? They will be able to provide some insights into understanding their patient background by using not only HAS-BLED but also age, body weight, or renal function, and other risk factors. Except that, there were no further comments.

Author response: We thank the reviewer for their review and comments. The characteristics of the cohort have been presented in Table 1. Comparisons of age, sex and history of malignancy across

studies have been added to the discussion, to add context to our findings. Comparisons of other characteristics were not considered possible because we did not collect identical covariates to other studies and comparing these may be considered misleading. This has now been acknowledged in the limitations.

'The majority of patients in the ROSE study were male, which is similar to the EINSTEIN, XALIA, and SWIVTER studies. The median age in the ROSE study was comparable to 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 history of 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%).'
'Direct comparisons of the baseline characteristics, such as renal function, amongst patients included in the ROSE study against baseline characteristics reported in previous studies was not performed as identical covariates were not collected. In the ROSE study, baseline renal status was ascertained according to chronic kidney disease (CKD) stages 1-2, stages 3-4, and CKD stage 5, as opposed to creatinine clearance, therefore direct comparisons were not possible.'

Reviewer: 2
Reviewer Name
Ida Ehlers Albertsen

Institution and Country
Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark.

Please state any competing interests or state 'None declared':
None

Please leave your comments for the authors below Thank you to the authors for very good responses. The manuscript reads well with a clearly formulated aim.

Details to be mentioned:
- The authors write that the VTE diagnosis is not validated and rely on the specialist. I do think lack of validation of the diagnoses should be mentioned in the limitations.
Author response: We thank the reviewer for their review and comments. In common with pharmacoepidemiological observational studies the diagnosis of VTE diagnosis was made by the specialist. We have now added a sentence to the Methods Study design and participants section:
'The diagnosis of VTE was made by the specialist.'

- Still, nothing is mentioned on patients with cancer? Was this information not part of the questionnaire tickbox or?
Author response: The available information on history of malignancy has been presented in Table 1, and we have now also included malignancies reported within 3 months of start of treatment. We have also mentioned this when comparing baseline characteristics of patients included in the ROSE study and other studies. Due to the low number of bleeding events, stratification by history of malignancy was not performed and this has been added to the limitations.
'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%).'
'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.'
- I am aware, that the title is changed as per editor request. I would, however, consider leaving out 'and prevention of recurrent deep vein thrombosis and pulmonary embolism'.

Author response: The title has now been amended as suggested by the Editor as below. We have retained “prevention” since this indication was specifically captured as presented in Figure 2.
‘An observational cohort study to evaluate the incidence of bleeding in patients prescribed rivaroxaban for the treatment and prevention of deep vein thrombosis and pulmonary embolism in UK secondary care’
Thank you.

Reviewer: 3
Reviewer Name
jeffrey a kline

Institution and Country
Indiana University School of Medicine
USA

Please state any competing interests or state ‘None declared’:
similar research interest

Please leave your comments for the authors below The authors were not really responsive to making suggested changes and explanations. For example, I do not think that the definition of bleeding criteria for a paper focusing on bleeding is "outside the scope" of the paper.
Author response: We thank the reviewer for their review and comments. We have now included the criteria for a major bleed for the gastrointestinal and urogenital bleeds as a footnote to Table 2. Intracranial is by definition major according to ISTH definition since it is a critical site.

VERSION 3 – REVIEW

REVIEWER	Yasuo Okumura Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
REVIEW RETURNED	14-Sep-2020

GENERAL COMMENTS	No further comments. Thank you for giving me a chance to review this paper.

REVIEWER	Ida Ehlers Albertsen Aalborg Thrombosis Research Unit, Aalborg, Denmark.
REVIEW RETURNED	17-Sep-2020

GENERAL COMMENTS	The authors have responded sufficiently on the reviewer comments. I still think the relevance of a 3-month bleeding outcome can be discussed. However, the authors state clearly what the purpose of the study is - nothing more nothing less.

REVIEWER	Jeffrey Kline Indiana University School of Medicine USA
REVIEW RETURNED	08-Sep-2020

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.