Systematic Review / Meta-analysis

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Effectiveness of rivaroxaban in preventing cerebral venous thromboembolism: a systematic review and meta-analysis

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Background: Cerebral venous thromboembolism (CVT) poses a significant risk of venous infarction and haemorrhage, which can lead to neurological deficits and, in severe cases, even death. The optimal treatment regimen for patients with CVT remains unclear.

Methods: MEDLINE, Embase, Google Scholar, Web of Science (WoS), and Cochrane Central databases were searched for randomized controlled trials (RCTs) and observational studies assessing the efficacy and safety of rivaroxaban in patients with CVT. All-site venous thromboembolism (VTE), risk of clinically relevant non-major bleeding, incidence of partial recanalization, complete recanalization and major haemorrhage were among outcomes of interest. Mantel–Haenszel weighted random-effects model was used to calculate relative risks (RRs) with 95% CIs.

Results: The analysis included 1 RCT and 3 observational studies containing 211 patients. Compared to vitamin K antagonists (VKAs), rivaroxaban did not significantly decrease the all-site VTE [RR 0.31 (95% CI 0.01, 8.43); $P = 0.49$, $I^2 = 0\%$]. Compared with VKAs, patients on rivaroxaban did not show a significantly reduced risk of recurrent cerebral venous thrombosis. In terms of incidence of partial recanalization, there was no discernible difference between rivaroxaban and VKAs [RR 0.90 (95% CI 0.66, 1.22); $P = 0.49$, $I^2 = 0\%$]. There was no discernible difference in incidence of complete recanalization [RR 0.98 (95% CI 0.32, 3.03); $P = 0.97$, $I^2 = 28\%$] and incidence of major haemorrhage [RR 0.19 (95% CI 0.01, 4.54); $P = 0.30$].

Conclusion: Rivaroxaban was found to have similar efficacy to VKAs. Due to its lower risk of severe bleeding and no need for INR monitoring, rivaroxaban may be a preferable treatment option for CVT.

Keywords: cerebral venous thromboembolism, rivaraxoban, hemorrhage, re-canalization

Introduction

Cerebral venous thromboembolism (CVT) is caused by the partial or complete occlusion of the main cerebral venous sinuses or the smaller feeding cortical veins, which increases the risk of venous infarction and haemorrhage[1]. Young adults (median age of 37 years), children, and women of childbearing age are commonly affected, with an estimated prevalence of 1.3–1.6 cases per 1 000 000 persons, accounting for 0.5% of the causes of stroke[2]. Current recommendations suggest treating acute symptomatic CVT with either low molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for 3–12 months, followed by an oral vitamin K antagonist (VKA)[3]. The national normalised ratio (INR) is targeted to be between 2 and 3 to prevent recurrence. Additionally, the underlying cause must be addressed.

The pathophysiology of CVT involves the formation of blood clots within the cerebral venous system. This condition can be triggered by various factors, including genetic predispositions, coagulopathies, infections, and local factors like head trauma or

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surgery. CVT can result in increased intracranial pressure, venous infarction, and haemorrhagic complications, ultimately leading to a wide range of clinical manifestations. Common symptoms include severe headaches, focal neurological deficits, seizures, and, in severe cases, altered consciousness.

The benefit of direct oral anticoagulants (DOACs) over warfarin as a long-term anticoagulation for CVT has likewise been extensively studied. However, no studies have assessed the risk of rivaroxaban alone in these patients[4]. Multiple new studies that have been published may help make this more likely by giving us a bigger body of evidence to look at. Therefore, in this study, we aimed to assess the efficacy and safety of rivaroxaban as a potential treatment option for CVT patients, providing valuable insights into the management of this condition and the potential role of direct oral anticoagulants.

HIGHLIGHTS

- The benefit of direct oral anticoagulants over warfarin as a long-term anticoagulation for cerebral venous thromboembolism has been extensively studied, yet it has not been approved as first-line therapy in the current practice.
- Multiple new studies that have been published may help make this more likely by giving us a bigger body of evidence to look at.
- In this meta-analysis we aimed to evaluate the effectiveness of rivaroxaban in patients with cerebral venous thromboembolism patients by pooling the evidence from all clinical trials to date.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A350) guidelines and the Risk of Bias in Systematic Reviews and assessment of multiple systematic reviews (AMSTAR) 2 were both followed when doing this meta-analysis[5,6]. The work is reported in line with AMSTAR 2 guidelines, Supplemental Digital Content 2, http://links.lww.com/MS9/A351. The International Prospective Register of Systematic Reviews (PROSPERO), maintained by the National Institute for Health Research (NIHR), contains information about this study. Since the information was accessible to the general public, institutional review board (IRB) approval was not necessary.

Data sources and search strategy

MEDLINE, Embase, Google Scholar, Web of Science (WoS), and Cochrane CENTRAL were comprehensively searched from inception through April 2023 by two independent reviewers. We extracted studies based on abstracts and titles. A full-text appraisal was sought when required. MeSH phrases and keywords were used to find generic and brand names for apixaban, LMWH, and

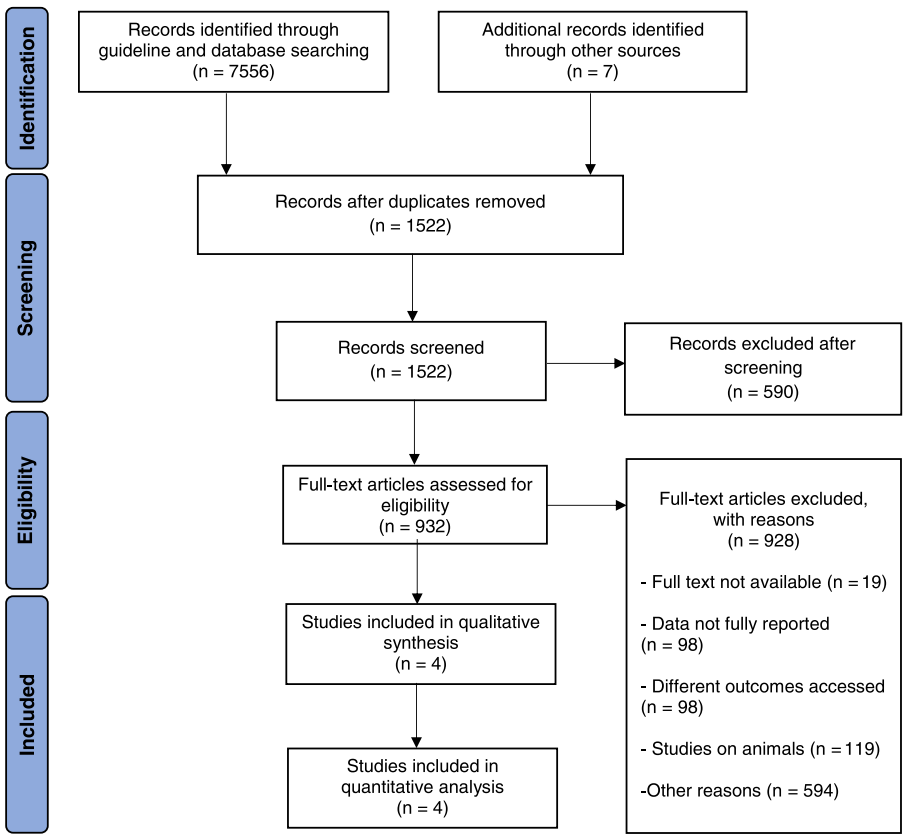

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram of study identification for meta-analysis.

Table 1

Baseline characteristics of included studies.

References	Study design	Study site	Sample size	Mean age of participants	Female, *n* (%)	Acute treatment	DOAC type	Timing of initiation	Control group	Duration of DOAC therapy	Follow-up
Connor *et al.*[9]	RCT	Multicenter	• Rivaroxaban = 73 • Standard anticoagulation = 41	Paediatric population (< 18 years)	• Rivaroxaban = 27 (37) • Standard anticoagulation = 18 (44)	UFH or LMWH or fondaparinux	Rivaroxaban	After 5 to 9 days of anticoagulation with UH or LMWH or fondaparinux	UFH oF LMWH ± warfarin	92 (87–95) days	3 months
Esmaeili *et al.*[7]	Retrospective	Iran	• Warfarin = 13 • Rivaroxaban = 23	• Warfarin = 34 ± 11.22 • Rivaroxaban = 36 ± 11.15	• Warfarin = 12 (92.31) • Rivaroxaban = 17 (73.1)	Heparin or LMWH	Rivaroxaban	NA	Warfarin	12 months	12 months
Maqsood *et al.*[3]	Prospective study	Pakistan	• DOAC = 21 • Warfarin = 24	• DOAC = 26 (15–36) years • Warfarin = 27 (15–45) years	• DOAC = 18 (86) • Warfarin = 19 (79)	UFH or LMWH	Rivaroxaban	After 5 (5–12) days of heparinization	Warfarin	3 (3–12) months	12 months
Geisbüsch *et al.*[8]	Retrospective	Germany	DOAC = 7 Phenprocoumon = 9	DOAC = 31 (18–75) years Phenprocoumon = 43 (17–69) years	DOAC = 7 (100) Phenprocoumon = 6 (66.67)	UFH or LMWH	Rivaroxaban	After 6 (3–9) days of heparinization	Phenprocoumon	8 (6–12) months	8 (5–26) months

DOAC, direct oral anticoagulant; LMWH, low molecular-weight heparin; NA, not applicable; RCT, randomized controlled trial; UFH, unfractionated heparin.

CA- VTE symptoms. Keywords used were 'rivaroxaban', 'cerebral venous thromboembolism', 'CVT', 'Direct Oral Anticoagulants', 'DOAC', 'thrombosis', 'recanalization', and 'haemorrhage'.

Study selection

We included studies if they were: (1) randomized controlled trials (RCTs) or observational studies comparing rivaroxaban and VKAs in different interventional arms, (2) reported any of the following outcomes: all-site venous thromboembolism (VTE), recurrent cerebral thromboembolism, incidence of partial recanalization, complete recanalization and major haemorrhage (3) included patients with risk of CVT. Studies were excluded if they were single arm interventional studies or did not report outcomes of interest. A third investigator was consulted in case of any disagreement regarding study selection. All articles were then uploaded to Endnote Reference Library (Version X7.5; Clarivate Analytics) software to remove any duplicates.

Data extraction and assessment of study quality

Two reviewers independently extracted from the selected studies, including characteristics of the studies, patient demographics, summary events, number of events, sample sizes, and treatment type. Summary events were also extracted for outcomes of interest, and risk ratios (ORs) with 95% CIs were calculated from them. We also extracted the year of publication, follow-up duration, and mean/median ages. There were no conflict of interests encountered during data extraction for this study. The quality of studies across six categories [selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias] was evaluated using the Cochrane Risk of Bias Tool (CRBT).

Statistical analysis

RevMan (version 5.3; Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration) was used for all statistical calculations. We pooled ORs with 95% CI with Mantel–Haenszel (MH) random-effects weighted methods. We assessed heterogeneity across studies by using Higgins I^2. Two outcomes, clinically relevant non-major bleeding, and major bleeding events were stratified into subgroups based on the type of study design to minimise the risk of bias. Egger's regression test was conducted to evaluate the risk of publication bias. Due to the small number of studies, we did not evaluate publication bias using funnel plots. Two-tailed *P* values were used with *P* less than 0.05 considered significant.

Results

Literature search and characteristics of included studies

Of the 2110 articles that were found initially, 1 RCT and 3 observational studies containing 211 patients were finalised for systematic review and meta-analysis[3,7–9]. The mean sample size of studies was 53, with a mean follow-up time of 8 months. PRISMA flow diagrams describe the literature search and research selection procedure (Fig. 1). Table 1 lists the demographic and baseline characteristics of included studies in detail.

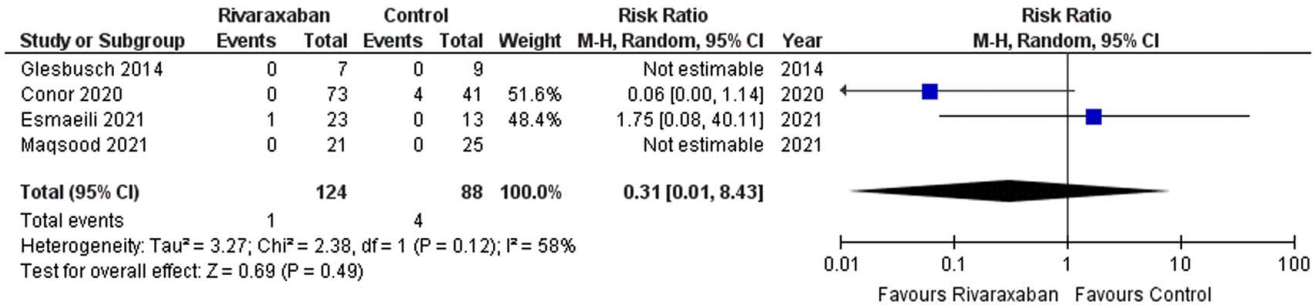

Figure 2. Forest plot showing results of rivaroxaban versus vitamin K antagonist on All-site venous thromboembolism recurrence.

All-Site recurrent venous thromboembolism (VTE)

Two studies (1 RCT, 1 observational studies) reported the outcome of all-site VTE (Fig. 2). Compared to VKAs, rivaroxaban did not significantly decrease the all-site VTE [RR 0.31 (95% CI 0.01, 8.43); $P = 0.49$, $I^2 = 0\%$].

Recurrent cerebral venous thromboembolism

Two studies (1 RCT, 1 observational studies) reported the outcome of recurrent cerebral venous thromboembolism (Fig. 3). Compared to VKAs, rivaroxaban did not significantly decrease the risk of recurrent cerebral venous thromboembolism [RR 0.58 ([95% CI 0.06, 5.44); $P = 0.64$, $I^2 = 0\%$].

Incidence of partial recanalization

Four studies (1 RCT and 3 observational studies) reported events on incidence of partial recanalization. In terms of incidence of partial recanalization, there was no discernible difference between rivaroxaban and VKAs [RR 0.90 (95% CI 0.66, 1.22); $P = 0.49$, $I^2 = 0\%$] (Fig. 4).

Incidence of complete recanalization

Four studies (1 RCT and 3 observational studies) reported incidence of complete recanalization (Fig. 5). No discernible difference was seen between rivaroxaban and VKAs [RR 0.98 (95% CI 0.32, 3.03); $P = 0.97$, $I^2 = 28\%$].

Incidence of major haemorrhage

One RCT provided data on major haemorrhage (Fig. 6). Patients on rivaroxaban had a noticeably reduced risk of major haemorrhage than those on VKAs, according to a meta-analysis, which was however not significant [RR 0.19 (95% CI 0.01, 4.54); $P = 0.30$].

Quality assessment

Observational studies and RCTs were rated as having a moderate risk of bias as per New Castle Ottawa scale and Cochrane risk-of-bias methodology for randomized trials. (Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A352 and Figure 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A352).

Discussion

This meta-analysis updates two previously published meta-analyses by comparing DOACs with VKAs in CVT patients in five new studies[4,10,11]. The efficacy of DOACs in CVT was comparable to that of VKAs in terms of recurrent VTE risk, partial or complete thrombus recanalization, and adequate functional recovery with mRS 2, as well as the safety profile in terms of bleeding events did not differ statistically between the two groups[12]. In a similar meta-analysis, there was no significant difference between DOACs and VKAs in terms of recurrence of VTEs, recanalization rate, functional outcome, overall haemorrhagic events, and overall mortality[13]. In accordance with the existing literature, our meta-analysis found no significant difference in the safety and efficacy profiles of the two treatment groups.

European guidelines currently recommend KAs for long-term anticoagulation for CVT after initial treatment with heparin (LMWH preferred over UFH) for 3–12 months. This is despite

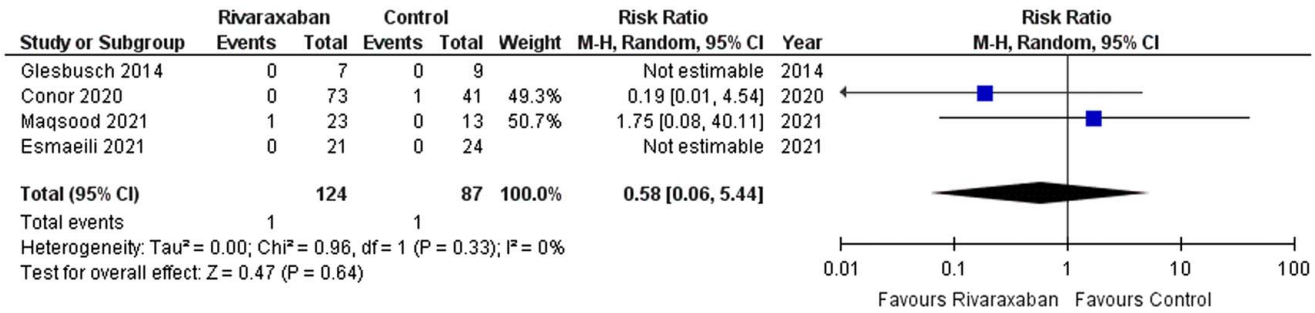

Figure 3. Forest plot showing results of rivaroxaban versus vitamin K antagonist on recurrent cerebral venous thromboembolism.

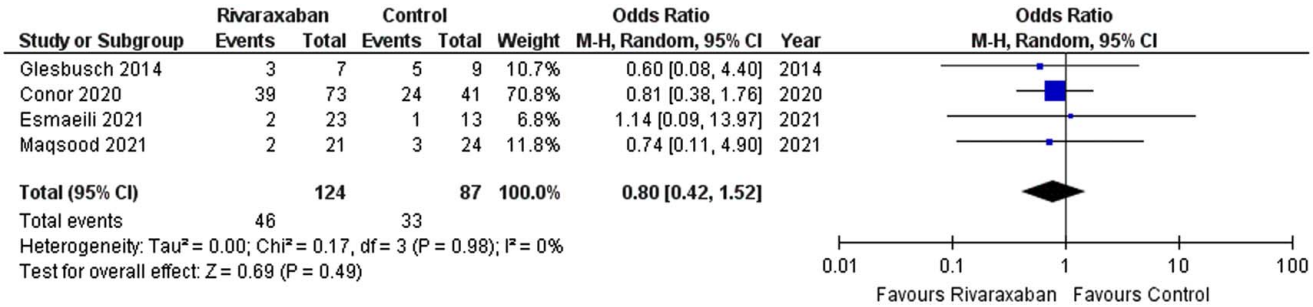

Figure 4. Forest plot showing results of rivaroxaban versus vitamin K antagonist on incidence of partial recanalization.

evidence of the deficiencies of VKAs[14]. Ferro *et al.*[15] published a randomized controlled trial in which greater than 33% of patients treated with warfarin for CVT had INR values outside the therapeutic range. DOACs have a superior safety profile than warfarin due to their predictable pharmacokinetics, lack of INR monitoring requirement, lower intracranial haemorrhage rate, and fewer drug-food interactions[16]. In our study, they were found to be equally effective.

The optimal time to initiate DOACs following the diagnosis of acute CVT is currently unknown. The majority of studies utilised LMWH or UFH prior to initiating DOACs, whereas only a few utilised DOACs explicitly. Evidence suggests the benefits of anticoagulation in preventing further thrombosis and progression outweigh the risk of haemorrhagic conversion and re-bleeding[17]. Since DOACs have a rapid onset and offset, it may be possible to use a single anticoagulation agent for the duration of CVT treatment, which could substantially simplify the treatment plan. Single DOAC agents have demonstrated efficacy in the treatment of VTEs and should be considered for CVT[4]. Patients with a high risk of haemorrhage, such as the elderly, those with a low body weight or renal dysfunction, and those receiving a combination of antiplatelet agents, must be administered DOACs with sufficient caution, as their effects cannot be monitored[18].

The optimal type of DOAC for CVT treatment is an additional research query that must be answered. There are ongoing trials such as rivaroxaban versus warfarin in CVT Treatment (RWCVT) (NCT04569279) and Study of Rivaroxaban for Cerebral Venous Thrombosis (SECRET) (NCT03178864) that, once completed, may establish the safety and efficacy of rivaroxaban in CVT and permit comparisons with other DOACs in CVT treatment[19,20]. Ideally, direct comparative analysis and evaluation should be conducted through head-to-head tests. However, comparative data regarding DOAC may be partially deduced from previous DVT, PE, and AF trials as well as from the known properties of each DOAC[21]. In almost all of the analyses conducted in this investigation, neither publication bias nor heterogeneity were discernible.

Limitations

Limitations in this study must be noted. First, the majority of the studies included were observational, and only two RCTs were included. Similarly, in the included studies, there were inconsistencies in the DOACs used, the duration of anticoagulation, and the follow-up. In addition, a European Union-wide review concluded that the use of direct-acting oral anticoagulants may increase the rate of recurrence of thrombotic events in patients with anti-phospholipid syndrome when compared to treatment with VKAs[22]. However, none of the included studies stratified the results based on the underlying aetiology of CVT. Further investigation into the potential function of rivaroxaban in these are patients. This analysis's accuracy was hindered by a lack of relevant data, and additional RCTs with greater statistical power are required in this particular subgroup to produce a more accurate conclusion. To determine the most effective DOAC for the treatment of CVT, additional research is required. To achieve this objective, high- powered RCTs that could serve as the premise for future guideline revision recommendations are required.

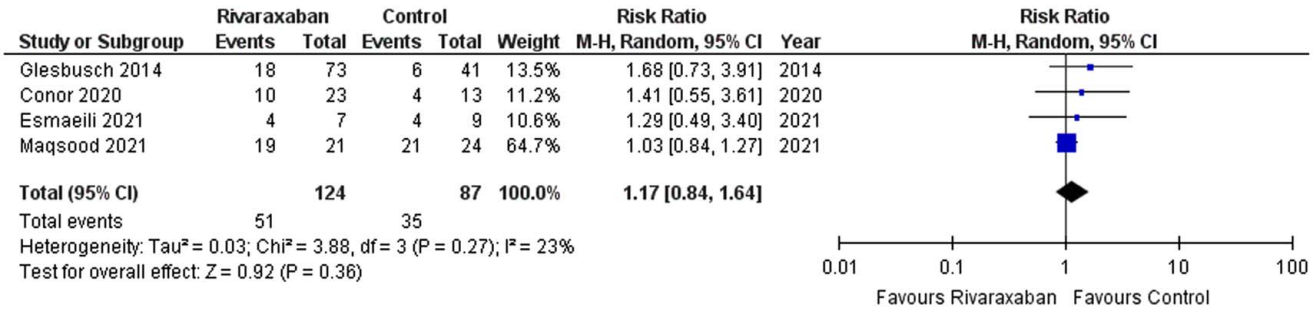

Figure 5. Forest plot showing results of rivaroxaban versus vitamin K antagonist on incidence of complete recanalization.

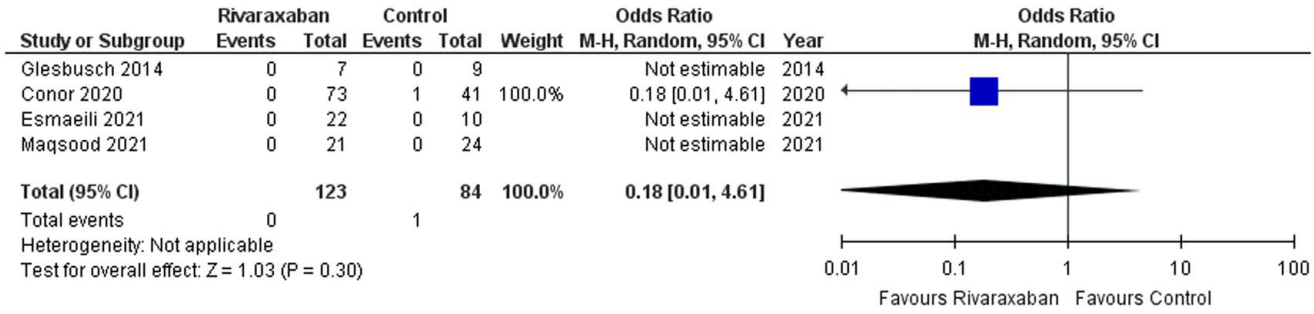

Figure 6. Forest plot showing results of rivaroxaban versus vitamin K antagonist on incidence of major haemorrhage.

Conclusions

In this meta-analysis comparing rivaroxaban and VKAs for treating CVT, rivaroxaban was found to have similar efficacy to VKAs. Due to its lower risk of severe bleeding and no need for INR monitoring, rivaroxaban may be a preferable treatment option for CVT, but additional research is required to validate these conclusions and evaluate its long-term efficacy and safety.

Ethical approval

Since all the data used in this study is publicly available in the trials referenced within the manuscript, ethical approval was not required.

Consent

All the trials included in this study took informed consent from the patients prior to their inclusion. Since all the data used in this study is publicly available in the trials referenced within the manuscript, no patient was directly involved in this study.

Source of funding

Not applicable.

Author contribution

A.N. and S.M. conceived the idea and designed the study. A.A. and A.M. the data and analysed it. A.C. drafted the manuscript. A.M. and U.A. created the illustrations. S.J. critically revised the manuscript.

Conflicts of interest disclosure

There are no conflicts of interest to disclose.

Research registration unique identifying number (UIN)

1. Name of the registry: National Institute for Health Research (NIHR) International prospective register of systematic reviews (PROSPERO).
2. Unique Identifying number or registration ID: CRD420 23434013.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):crd.york.ac.uk/PROSPERO/display_record.php?RecordID = 434013.

Guarantor

Sayed Jawad.

Data availability statement

All the data used in this study are publicly available in the trials, which are referenced in the bibliography.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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