Health Science Reports _Open Access_ **WILEY**

Direct oral anticoagulants compared to warfarin in long-term management of cerebral venous thrombosis: A comprehensive meta-analysis

Redoy Ranjan[1,2] 🅐 | Gie Ken-Dror[2] | Pankaj Sharma[2,3]

[1]Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[2]Institute of Cardiovascular Research, Royal Holloway University of London (ICR2UL), Greater London, UK

[3]Department of Clinical Neurology, Imperial College London Healthcare NHS Trust, London, UK

Correspondence
Pankaj Sharma, Institute of Cardiovascular Research, Royal Holloway University of London (ICR2UL), Egham, Greater London TW20 0EX, UK.
Email: pankaj.sharma@rhul.ac.uk

Abstract

Objectives: We compared the safety and efficacy of direct oral anticoagulants (DOACs) with those of warfarin in the long-term (≥6 months) treatment of cerebral venous thrombosis (CVT).

Methods: We searched electronic databases up to November 2023 to compare the use of DOACs and warfarin in CVT management. Modified Rankin scores (mRS), new intracranial hemorrhage, all-cause mortality, recurrence and nonrecanalisation events were used to assess outcome. RevMan v5.4 software and the Cochran-Mantel-Haenszel method were utilized to analyse data.

Results: A total of 25 studies involving 2301 patients were identified as having treated CVT with either DOACs or warfarin. Good long-term mRS scores 0–2 (risk ratio [RR] = 1.01, 95% CI = 0.98–1.03; $p = 0.61$), new intracranial hemorrhage (RR = 1.00, 95% CI = 0.48–2.08; $p = 0.99$), all-cause mortality (RR = 1.00, 95% CI = 0.50–1.98; $p = 0.99$), nonrecanalisation (RR = 0.95, 95% CI = 0.77–1.18; $p = 0.65$) and recurrence venous thrombosis events (RR = 0.63, 95% CI = 0.33–1.22; $p = 0.17$) were similar between the two treatment arms. Subgroup analysis found recurrence of venous thrombosis was lower in the rivaroxaban group compared to warfarin (2.2% vs. 8.5%, RR = 0.33, 95% CI = 0.11–0.98; $p = 0.05$).

Conclusion: DOACs and warfarin provide comparable long-term safety and efficacy profiles. DOACs may be preferred over warfarin due to their ease of clinical management.

KEYWORDS
apixaban, cerebral venous thrombosis, dabigatran, direct oral anticoagulants, edoxaban, efficacy, rivaroxaban, safety, warfarin

1 | INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare form of stroke, accounting for approximately 0.5% of all strokes and is caused by a thrombus in the dural venous sinuses or cerebral veins.[1] CVT requires rapid treatment to prevent significant neurological disability and death due to hemorrhagic complications and venous infarction.[1,2] All-cause mortality in CVT is found to diminish to 5%–15% with early diagnosis and prompt management, but morbidity rates remain high at 20%–30%.[2,3]

Current guidelines suggest using systemic anticoagulant therapy with unfractionated or low molecular weight heparin followed by long-term warfarin to improve recanalisation and prevent a recurrence.[3–5] Small numbers of randomized controlled trials and observational studies have suggested that direct oral anticoagulants (DOACs) are potentially a better alternative to warfarin, but most of these studies have been underpowered.[6–30] However, DOACs have several benefits, including improved patient compliance, ease of clinical management, lower risk of bleeding and fewer interactions.[2–5] Nevertheless, considering the rare occurrence of CVT, undertaking large-scale RCTs comparing the safety and efficacy of DOACs and warfarin is challenging. Meta-analysis potentially offers a method to overcome these challenges by increasing the sample size in a timely manner and reducing the effects of bias.

This comprehensive meta-analysis evaluated the safety and efficacy of DOACs compared to warfarin for long-term (≥6 months) anticoagulation management of CVT patients.

2 | METHODS

The study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines (PRISMA checklist supplied as a supplementary file).[31] The primary study objective was to explore the efficacy of the DOACs compared to warfarin measured with good clinical outcomes based on the modified Rankin scale (mRS) score. Further, the secondary objectives were to compare the all-cause mortality, new onset of intracranial hemorrhage (ICH), nonrecanalisation, and recurrence of thrombosis events between the DOACs and warfarin arms.

3 | SEARCH STRATEGY

We searched all published original research articles in English for the safety and efficacy of DOACs versus warfarin in long-term anticoagulation for cerebral venous thrombosis in MEDLINE, EMBASE, CINAHL via EBSCO host, and the Web of Science Collection up to November 2023. Boolean search operators "AND" and "OR" were used to link search terms. Search terms for the disease were "cerebral venous thrombosis" OR "Cerebro-venous thrombosis" OR "cerebral venous sinus thrombosis" OR "venous sinus thrombosis" OR "cortical vein thrombosis" OR "dural venous sinus thrombosis" OR "deep cerebral vein thrombosis" OR "intracranial venous sinus thrombosis" OR "CVT" OR "CVST" AND

treatment "direct oral anticoagulant" OR "direct oral anticoagulation" OR "novel oral anticoagulant" OR "novel oral anticoagulation" OR "new oral anticoagulant" OR "DOACs" OR "NOAC" OR "rivaroxaban" OR "dabigatran" OR "apixaban" OR "edoxaban" OR "warfarin" OR "vitamin K antagonists" OR "factor Xa inhibitor" OR "direct thrombin inhibitor". For an advanced literature search, MeSH (medical subject headings) and Emtree terms were also utilized to find the preceding search terms in PubMed and Embase databases. The literature search was expanded to cover additional references from thesis or dissertation repositories, preprint servers, and manual searching of reference lists from identified articles.

4 | STUDY SELECTION CRITERIA

We included randomized and observational prospective and retrospective cohort studies of CVT patients in all age groups that compared the long-term anticoagulation effects of DOACs and warfarin.[6–30] We excluded case reports, case series, review papers, and studies based on phenprocoumon anticoagulant.[32,33] The intervention was defined as direct oral anticoagulants (apixaban, rivaroxaban, edoxaban, or dabigatran), while the control group was warfarin treatment. We excluded phenprocoumon, another vitamin K antagonist, as its pharmacodynamics is distinct from warfarin and could be a potential source of outcome bias.

5 | DATA VARIABLES

Detailed demographic information on studies was documented, including study type and population, treatment duration of DOACs and warfarin, age, gender, and prior medical history related to CVT. The safety outcomes were measured by all-cause mortality and new onset of intracranial hemorrhage (ICH) events between the DOACs and warfarin arms. In contrast, the efficacy of the DOACs and warfarin was observed using a good modified Rankin scale (mRS) score defined as 0–2, nonrecanalisation, and recurrence of thrombosis events.[34–40] Nonrecanalisation events were defined as any case that failed to completely or partially resolve its thrombus following further imaging. Recurrence of venous thrombosis was defined as the occurrence of second events of CVT or any DVT despite long-term anticoagulation therapy. Although included studies evaluated anticoagulation exposure for 3 to ≥12 months, for our meta-analysis, we defined ≥6 months of anticoagulation with either warfarin or DOACs as a long-term treatment. Results reporting outcomes at fewer months were extrapolated to 6 months. Studies with no events in either DOACs or warfarin treatment arms were excluded from the individual analysis.

6 | RISK OF BIAS ANALYSIS

Two independent investigators evaluated each study for risk of bias using the Cochrane Risk of Bias tool 2.0 (ROB 2) for randomized trials[41] and the Risk of Bias in Nonrandomised Studies (ROBINS-I)

tool for observational cohorts.[42] Publication bias across individual studies was graphically assessed using the ROBINS-I tool for the appropriate outcomes. The ROB 2 and ROBINS-I tools assess bias in seven domains covering the randomization process, selection of participants and intervention, deviation from the intended intervention, lack of outcome data, outcome measures and selection of reported outcomes.

7 | STATISTICAL ANALYSIS

This meta-analysis was performed using RevMan v5.4 software and the Cochran-Mantel-Haenszel statistical method with a random effects model. Pooled risk ratios (RRs) with 95% confidence intervals (CI) and

heterogeneity, were calculated for each study. We explored all forms of clinical, methodological, and statistical heterogeneity when considering pooled results. We calculated the inter-study heterogeneity I^2 index, and the statistical significance threshold was set at $p \leq 0.05$.

8 | RESULTS

8.1 | Summary of search and screening

We identified a total of 2274 published articles, of which 25 studies (5 RCTs and 20 observational studies) involving 2301 CVT patients met our study inclusion criteria, illustrated in the PRISMA flow diagram (Figure 1). RCTs evaluated 370 patients (DOACs $n = 200$: warfarin $n = 170$)[6–10]

Identification of studies via databases and registers

Identification

2274 papers identified through database search → Records removed before screening:
1. Duplicate records removed (n = 115)

Screening

Records screened (n = 2159) → Records excluded (n = 2108)
1. Non-relevant articles (n=1967)
2. Review articles (n=141)

Reports sought for retrieval (n = 51) → Reports not retrieved (n = 2)

Reports assessed for eligibility (n = 49) → Reports excluded (n=26)
1. Studies on Phenprocoumon (2)
2. Case series (n=11)
3. Case reports (n=13)

Included

Studies included in Meta-analysis (n= 25)

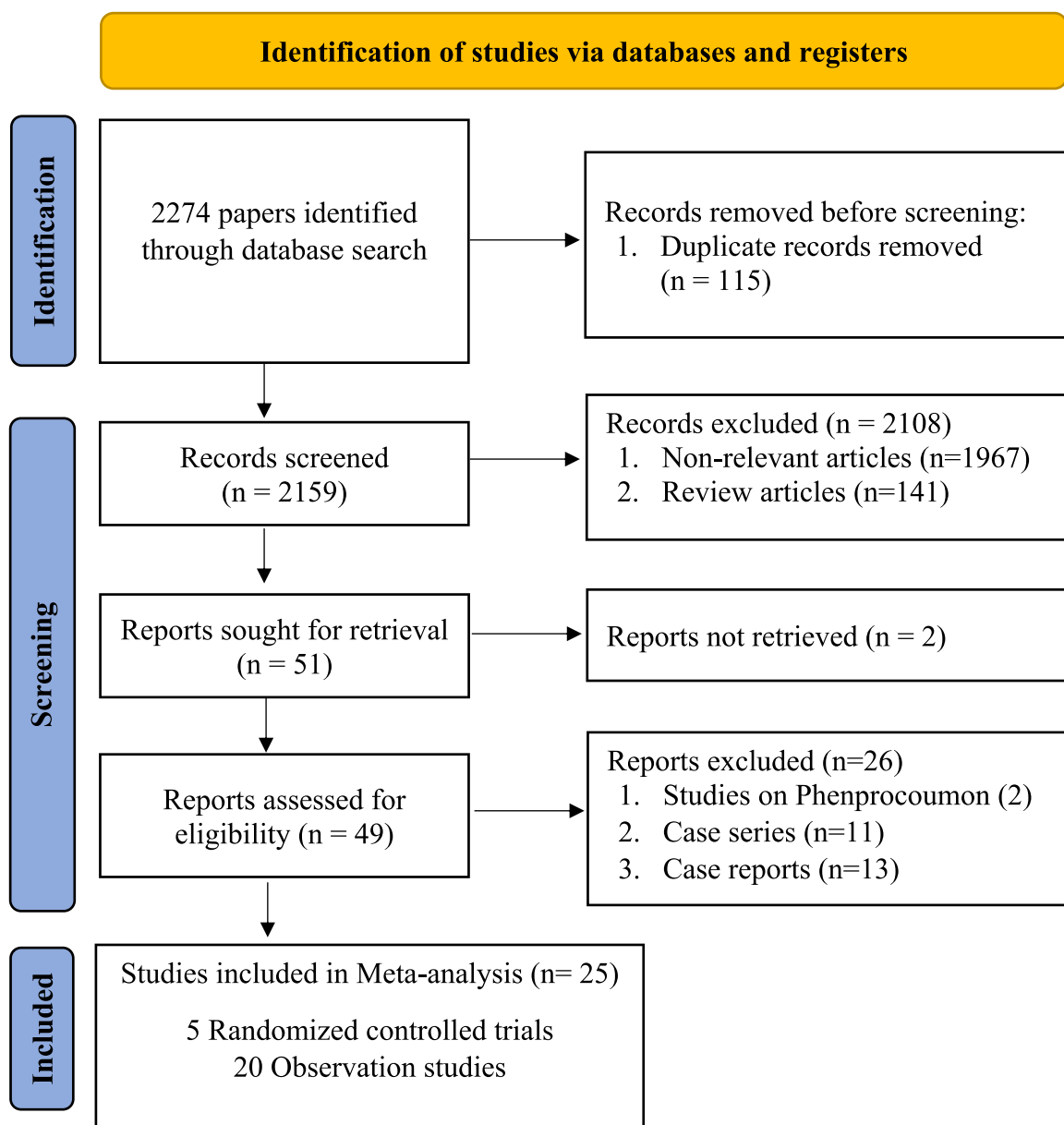5 Randomized controlled trials
20 Observation studies

FIGURE 1 PRISMA flow diagram according to PRISMA 2020 guidelines[31] illustrates difference phases of systemic review.

while observational cohort studies comprised 1931 patients (DOACs; n = 699: warfarin n = 1232).[11–30] Most common reasons for the exclusion of articles were duplication (n = 115), studies not compatible with inclusion criteria (n = 1967), and review articles (n = 141). The clinical characteristics and outcomes of the patients from each study are shown in Supplementary Table 1. However, RCTs and observational cohorts with no events in either the DOACs or warfarin treatment arms were excluded from the forest plots.

8.2 | Disability and functional recovery

Approximately 90.6% of the 797 CVT patients from RCT and observational studies had a good clinical outcome.[6–8,11,15–17,19,21–24,26,28] Analysis based on the eventful RCTs and observational cohorts found comparable functional recovery events between the DOACs and warfarin arms in observational and randomized control studies

(93.8% vs 89.6%, I² = 0%, p = 0.61; RR = 1.01, 95% CI = 0.98–1.03) (Figure 2).[6–8,11,15–17,19,21–24,26,28] There was no evidence of interstudy heterogeneity (I² = 0%, p = 0.76) or publication bias.

8.3 | New onset intracranial hemorrhage

A total of 920 CVT patients (RCT and observational) were assessed for new ICH events. Only 2.8% of patients experienced new ICH events.[6,8–11,13–27,29,30] However, new ICH events were similar across the DOACs and warfarin arms (2.6% vs. 2.9%, p = 0.99; RR = 1.00, 95% CI = 0.48–2.08, I² = 0%) (Figure 3).[6,8,10,13,14,16,18,22,24,25,29,30] Further analysis excluding pediatric CVT study[10] also found similar outcomes between DOACs and warfarin arms (RR = 1.10, 95% CI = 0.52–2.33, p = 0.81, I² = 0%).[6,8,13,14,16,18,22,24,25,29,30] The symmetrical funnel plot suggests no publication bias. There was no evidence of heterogeneity (I² = 0%, p = 0.80).
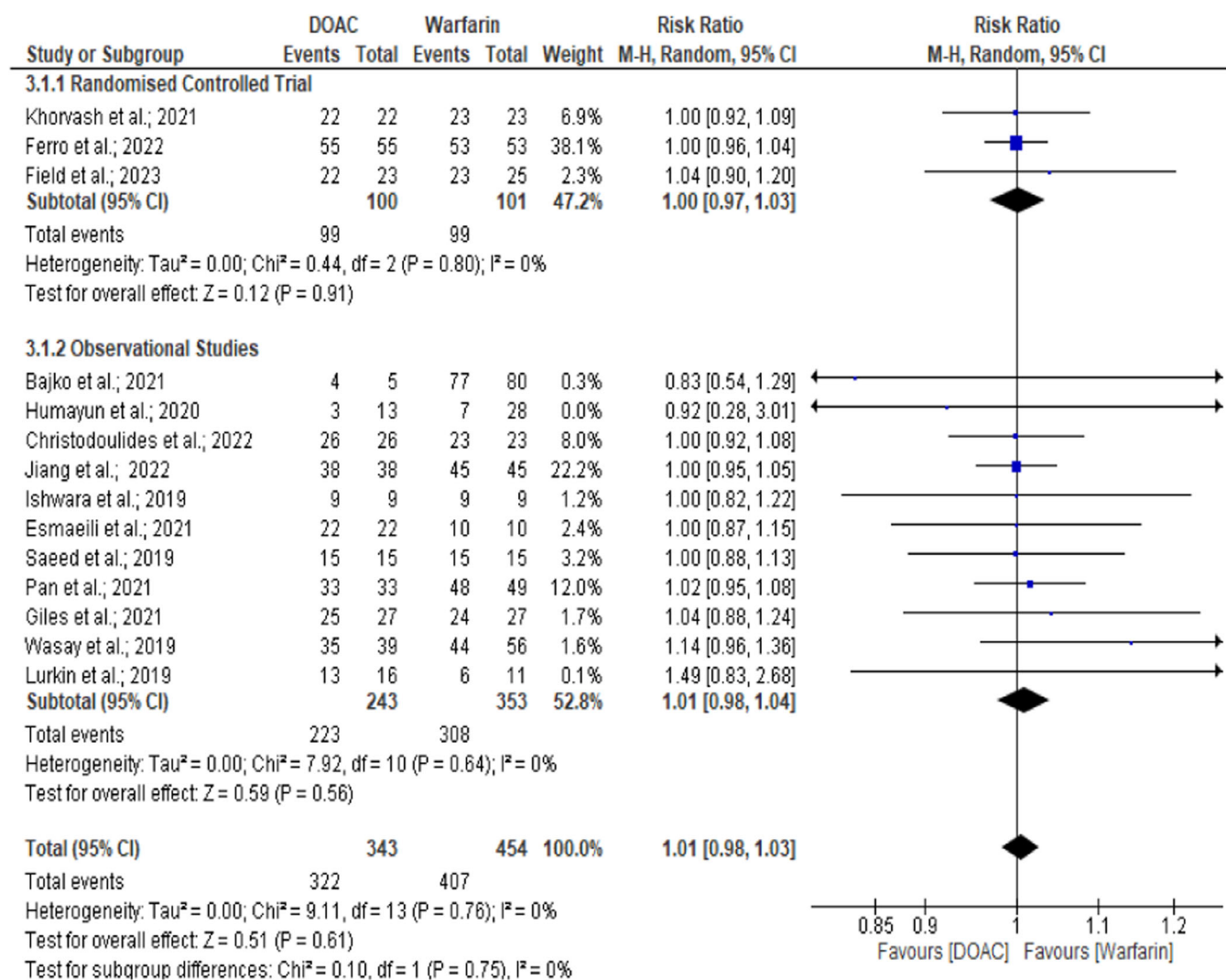
FIGURE 2 Good clinical outcome based on mRS 0–2 score between DOACs and warfarin therapy arms.
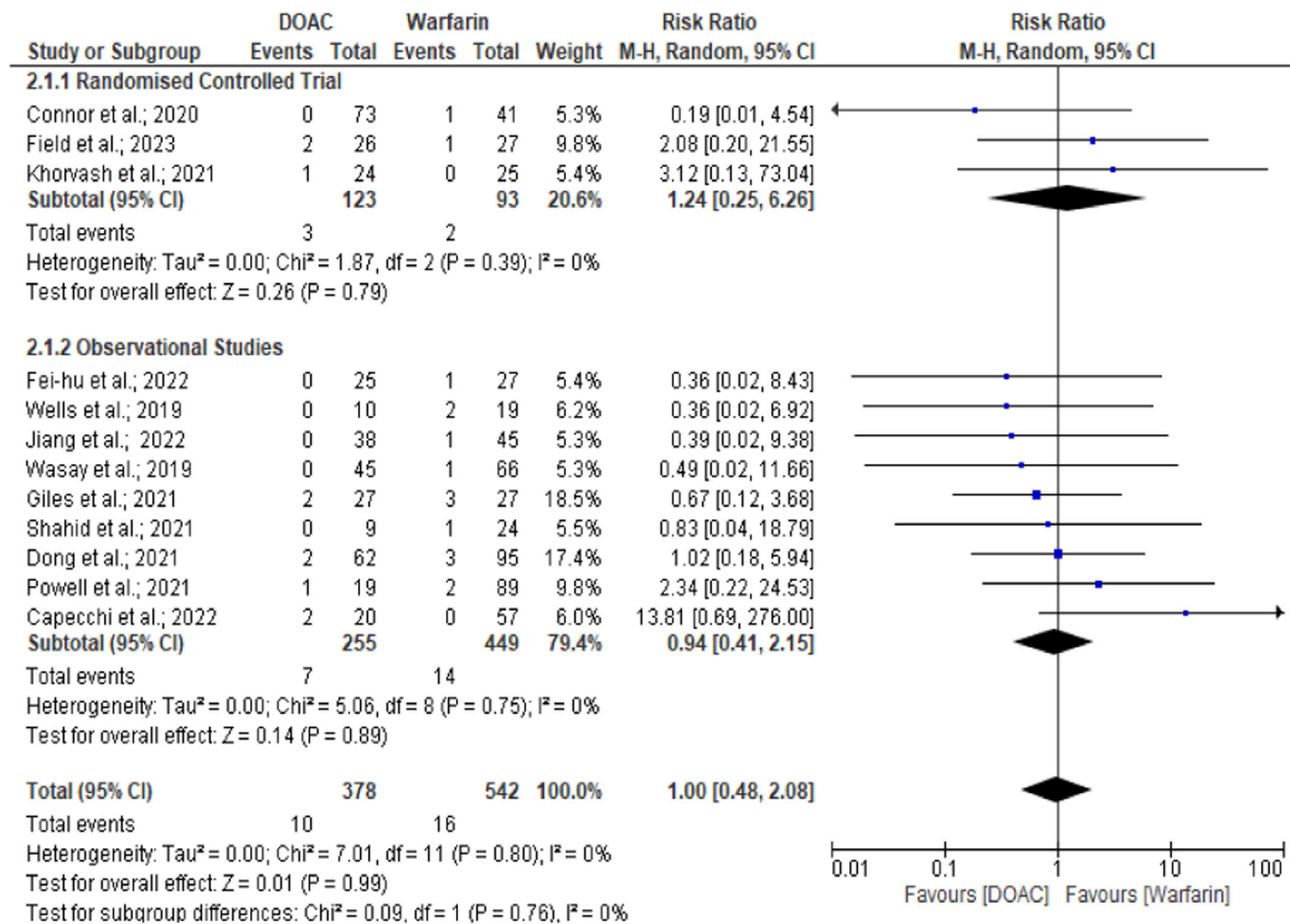
FIGURE 3 The occurrence of new intracranial hemorrhage (ICH) between DOACs and warfarin therapy arms.

8.4 | All-cause mortality

A total of 2142 CVT patients were evaluated for all-cause mortality. Overall mortality was 2.6%, with observational cohorts all-cause mortality being comparable (2.4% vs 2.7%, $I^2 = 0\%$, p = 0.99; RR = 1.00, 95% CI = 0.50–1.98) among the DOACs and warfarin group patients (Figure S1).[12,13,16–18,20,22,24] The funnel plot showed no evidence of publication bias. There was no evidence of heterogeneity ($I^2 = 0\%$, p = 0.60).

8.5 | Nonrecanalisation events

The overall occurrence of nonrecanalisation events was 19.6% of 1371 CVT patients. The analysis yielded similar events between the DOACs and warfarin groups (19.4% vs. 19.7%, $I^2 = 0\%$, p = 0.65; RR = 0.95, 95% CI = 0.77–1.18) (Figure S2).[7,10–12,14–16,18,19,21,23–25,28,29] Additionally, analysing only studies of adult CVT also observed identical findings between DOACs and warfarin groups (RR = 0.97, 95% CI = 0.77–1.21, p = 0.78, I^2 =0%).[7,11,12,14–16,18,19,21,23–25,28,29] The funnel plot was symmetrical suggesting no evidence of publication bias. There was no evidence of interstudy heterogeneity ($I^2 = 0\%$, p = 0.88).

8.6 | Recurrence of venous thrombosis

There was no consistent time frame for defining recurrence, with each study describing the event during its own follow-up period (Supplementary Table 1). However, insofar as can be analysed, the overall mean recurrence of venous thrombosis, either CVT or DVT events, was 2.9% among all 1436 patients (1.8% vs. 3.7% between the DOACs and warfarin arms, respectively) from both RCTs and observational cohorts.[6,7,9–11,13–17,19–24,26–30] Analysis of eventful RCTs and cohort studies found similar outcomes between the two treatment arms (3.5% vs. 7.5%, $I^2 = 0\%$, p = 0.17; RR = 0.63, 95% CI = 0.33–1.22) (Figure S3).[6,10,11,14–16,23,24,27–30] Further analysis excluding Connor et al.[10] also found similar events between DOACs and warfarin arms (RR = 0.69, 95% CI = 0.35–1.35, p = 0.28, $I^2 = 0\%$). There was no interstudy heterogeneity ($I^2 = 0\%$, p = 0.83) or publication bias.

8.7 | Subgroup analysis: Safety and efficacy of rivaroxaban versus warfarin

A subgroup analysis observes that recurrence of venous thrombosis, either CVT or DVT, was higher in the warfarin group than in rivaroxaban

(8.5% vs. 2.2%, RR = 0.33, 95% CI = 0.11–0.98; I² = 0%, p = 0.05) (Figure 4).[6,10,15,24,30] However, disability and functional recovery (RR = 1.00, 95% CI = 0.97–1.04; I² = 0%, p = 0.77), (Figure S4)[6,8,15,17,19,21,24] new intracranial hemorrhage (RR = 0.82, 95% CI = 0.22–3.06; I² = 0%, p = 0.77), (Figure S5)[6,8,10,24,30] all-cause mortality (RR = 0.74, 95% CI = 0.15–3.59; I² = 0%, p = 0.71), (Figure S6)[6,17,24] and nonrecanalisation rate (RR = 0.91, 95% CI = 0.61–1.34; I² = 0%, p = 0.63), (Figure S7)[10,15,19,21,24] were comparable among rivaroxaban and warfarin arms. Further analysis excluding pediatric CVT study[10] also observed similar recurrence (RR = 0.38, 95% CI = 0.12–1.24, p = 0.11, I² = 0%),[6,15,24,30] new intracranial hemorrhage (RR = 1.11, 95% CI = 0.26–4.70, p = 0.88, I² = 0%),[6,8,24,30] and nonrecanalisation (RR = 0.96, 95% CI = 0.59–1.56, p = 0.87, I² = 0%)[15,19,21,24] events between rivaroxaban and warfarin arms. There was no evidence of interstudy heterogeneity or publication bias for the recurrence of venous thrombosis (I² = 0%, p = 0.83),[6,10,15,24,30] good functional recovery (I² = 0%, p = 0.98),[6,8,15,17,19,21,24] new intracranial hemorrhage (I² = 0%, p = 0.63),[6,8,10,24,30] all-cause mortality (I² = 0%, p = 0.70),[6,17,24] and non-recanalisation rate (I² = 0%, p = 0.89)[10,15,19,21,24] events between rivaroxaban and warfarin treatment arms.

8.8 | Quality and bias assessment

The risk of bias analysis for RCT[6–10] and observational cohort studies[11–30] is illustrated in Figure 5. One of the 5 RCTs had methodological concerns relating to randomization and allocation concealment,[9] and four other studies[6–8,10] were judged to be at high risk of bias mostly due to randomization processes, deviations from intended interventions, and bias in the measurement of the outcome (Figure 5A). We judged 20 observational cohorts to have at least moderate risk bias; 8 papers[14,17,19,20,22,27,29,30] had serious, and four studies[18,21,26,28] had a critical risk of bias (Figure 5B). To ensure the robustness of our results in light of these identified biases, all analyses were repeated excluding studies[14,17–22,26–30] with serious and critical risk of bias, but the overall results remained unchanged. Furthermore, to ensure the reliability of our findings, we also repeated all analyses, excluding the pediatric CVT study,[10] but the outcome remained the same. Despite no significant heterogeneity documented, we utilized the random effects model in our study.

9 | DISCUSSION

We have shown that the use of either DOACs or warfarin in treating CVT achieves comparable clinical outcomes in terms of efficacy, safety, all-cause mortality and recurrence of venous thrombosis. A subgroup analysis between rivaroxaban and warfarin found a lower recurrence of venous thrombosis in the rivaroxaban group than in warfarin, with similar other safety and efficacy profiles.
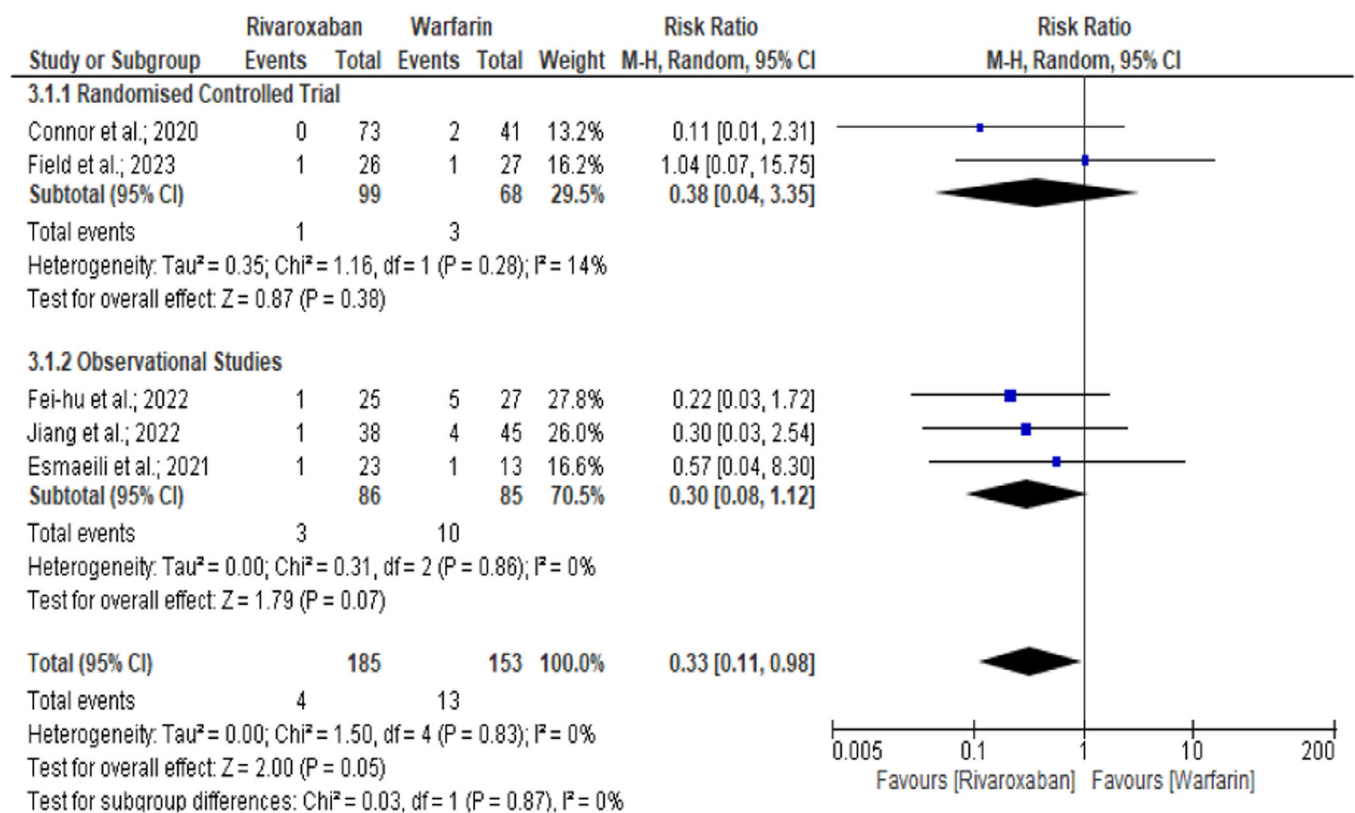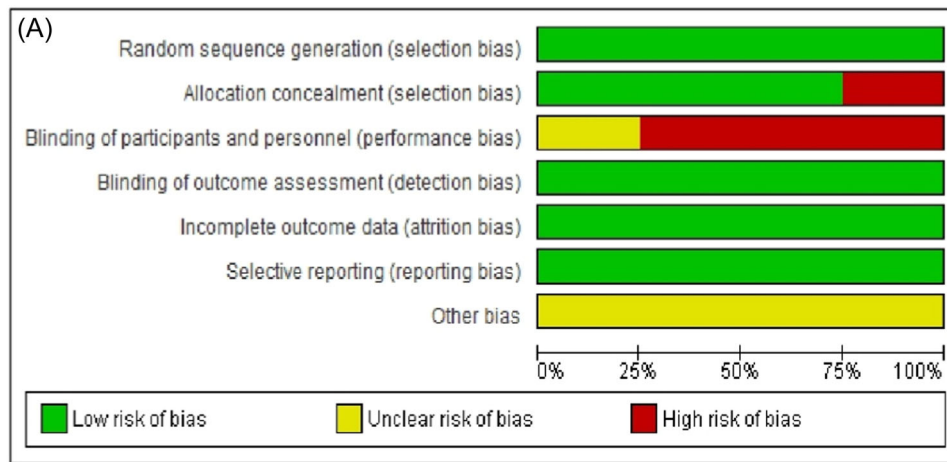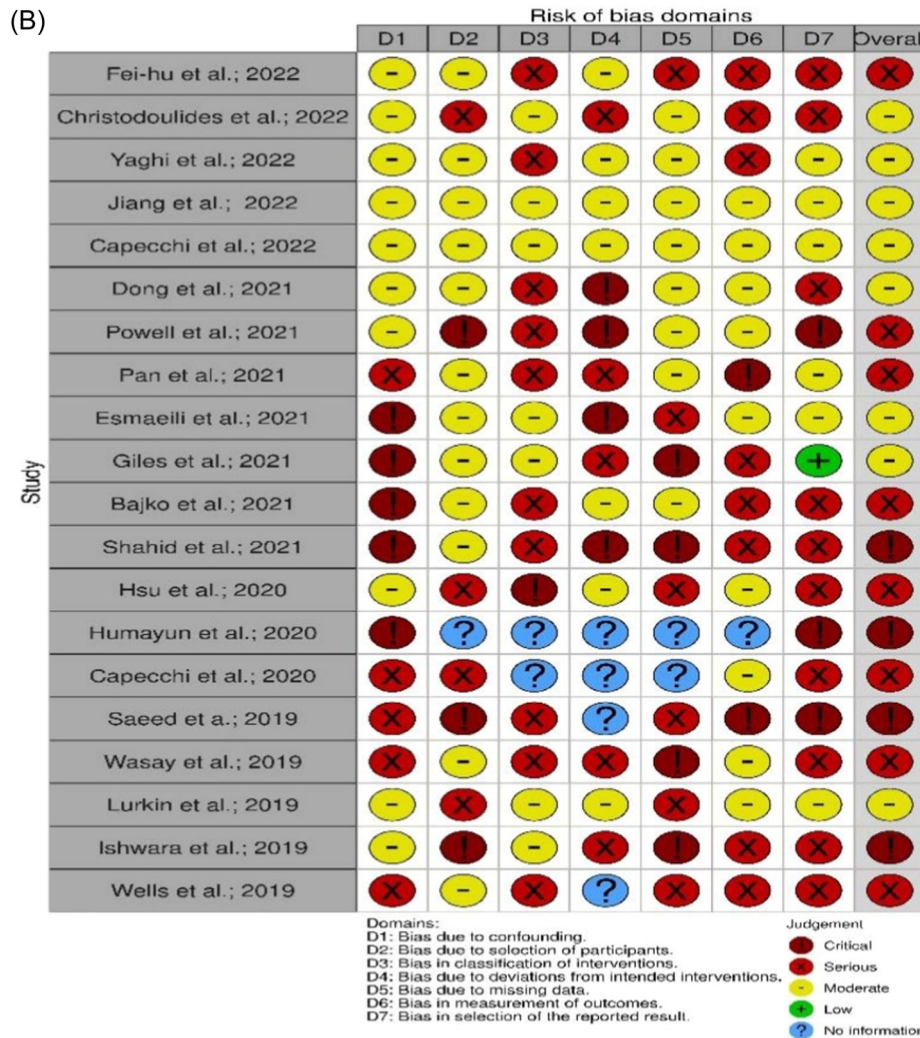

FIGURE 4 The recurrence of venous thrombosis between rivaroxaban and warfarin arms.

FIGURE 5   Risk of bias graph for RCTs (A) and observational cohort studies (B).

To ensure a comprehensive analysis, we exclude phenprocoumon-based observational studies[32,33] as their pharmacodynamics is distinct from warfarin, which would otherwise have lead to a potential risk of bias compared to previous meta-analyses.[35–40] In addition, we present a detailed risk of bias assessment for included studies, which needed to be demonstrated in the previous papers[35,37,39] and focus on warfarin anticoagulant specifically as that is the world's most commonly used anticoagulant.

Long-term oral anticoagulation in CVT aims to prevent thrombus propagation, reduce recurrence, and enhance endogenous fibrinolysis to expedite thrombus resolution and recanalisation.[30,43-46] Current European and American guidelines recommend using warfarin following bridging with heparin as a long-standing anticoagulant in CVT treatment.[3,4] However, concerns about the use of warfarin relate to the need for regular follow-up with international normalized ratio (INR), dose adjustment, interactions with food and drugs and risk of bleeding.[47] Conversely, the advantage of DOACs includes the rapid onset of action and not requiring regular blood testing or dose adjustments, added to few food and drug interactions.[48-51] A recent RCT, RE-SPECT CVT[7] and a multicentre observational cohort study[12] also observed similar results to our findings between DOACs and warfarin regarding all-cause mortality, thrombus recanalisation, and recurrence events.

10 | STRENGTHS AND LIMITATIONS

This is the first comprehensive meta-analysis involving a large CVT cohort of pediatric and adult subjects, yielding comparable safety and efficiency between DOACs and warfarin in long-term CVT management. Additionally, we find a lower recurrence of venous thromboembolism in rivaroxaban-treated arms than in warfarin with similar safety and efficacy profiles. However, as with any study, several limitations need to be noted. Our meta-analysis was based on English-language papers, and not all clinical outcomes were well-defined in every study, potentially limiting our overall findings.[52] Nevertheless, considering the rarity of CVT occurrence and the absence of large and powered RCTs, our current comprehensive meta-analysis is, to the best of our knowledge, the largest conducted to-date. Although most studies[6-8,11,12,14,15,17-23,25,27-29] use anticoagulation therapy for at least 6 months, the diversity in the duration of anticoagulation use in some studies[9,10,13,16,24,26,30] could lead to heterogeneity and bias. However, the absence of significant heterogeneity in our study results demonstrates that the risk of outcome bias is minimal. The length of treatment for anticoagulation varies from 3 to 12 months, but the most common treatment time is 6 months, hence our choice in deciding the timescale for analysis,[53] consistent with ESO guidelines.[3] For studies[9,10,13,16,24,26,30] with shorter outcome timescales, we have extrapolated to 6 months, but we accept that we make this an assumption. The small sample size in RCTs, the lack of events in some studies, and the use of different DOACs may limit interpretation of our results. Although the etiology of childhood and adult CVT may be different, when we did the analysis for the two groups separately no significant difference to our overall conclusion was found.

11 | CONCLUSION

Compared to warfarin, long-term (≥6 months) use of DOACs in managing CVT provides similar clinical outcomes regarding functional recovery, new ICH, all-cause mortality, recurrence and recanalisation events. However, DOACs may be preferred over warfarin in long-term CVT management because of ease of clinical management.

AUTHOR CONTRIBUTIONS

Redoy Ranjan: Conceptualization; data curation; formal analysis; methodology; resources; validation; visualization; writing—original draft; writing—review and editing. **Gie Ken-Dror**: Conceptualization; methodology; supervision; validation; writing—review and editing. **Pankaj Sharma**: Conceptualization; data curation; formal analysis; investigation; methodology; resources; supervision; validation; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

Redoy Ranjan is an Editorial Board member of Health Science Reports but was excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article and its supplementary materials.

ETHICS STATEMENT

The authors have nothing to report.

TRANSPARENCY STATEMENT

The lead author Pankaj Sharma affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Redoy Ranjan http://orcid.org/0000-0003-1927-5023

REFERENCES

1. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: a cross-sectional study. *Stroke*. 2012;43:3375-3377.
2. Sheng S, Nalleballe K, Pothineni NV, et al. Use of direct oral anticoagulants in cerebral venous thrombosis: a systematic review. *Blood Coagul Fibrinolysis*. 2020;31(8):501-505.
3. Ferro JM, Bousser MG, Canhão P, et al. European Stroke Organization. European stroke organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. *Eur J Neurol*. 2017;24: 1203-1213.
4. Kernan WN, Ovbiagele B, Black HR, et al. American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients

with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160-2236.

5. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363: 2499-2510.

6. Field TS, Dizonno V, Almekhlafi MA, et al. Study of rivaroxaban for cerebral venous thrombosis: a randomized controlled feasibility trial comparing anticoagulation with rivaroxaban to Standard-of-Care in symptomatic cerebral venous thrombosis. *Stroke*. 2023;54(11): 2724-2736.

7. Ferro JM, Bendszus M, Jansen O, et al. Recanalization after cerebral venous thrombosis. A randomized controlled trial of the safety and efficacy of dabigatran etexilate versus dose-adjusted warfarin in patients with cerebral venous and dural sinus thrombosis. *Int J Stroke*. 2022;17(2):189-197.

8. Khorvash F, Farajpour-Khanaposhtani MJ, Hemasian H, Saadatnia SM. Evaluation of rivaroxaban versus warfarin for the treatment of cerebral vein thrombosis: a case-control blinded study. *Curr J Neurol*. 2021;20(3):125-130.

9. Maqsood M, Imran Hasan Khan M, Yameen M, Aziz Ahmed K, Hussain N, Hussain S. Use of oral rivaroxaban in cerebral venous thrombosis. *J Drug Assess*. 2020;10(1):1-6.

10. Connor P, Sánchez van Kammen M, Lensing AWA, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). *Blood Adv*. 2020;4(24):6250-6258.

11. Christodoulides A, Bohnstedt BN. Warfarin versus factor Xa inhibitors in the long-term treatment of cerebral venous sinus thrombosis a single-center retrospective analysis. *eNeurologicalSci*. 2022;28:100412.

12. Yaghi S, Shu L, Bakradze E, et al. Direct oral anticoagulants versus warfarin in the treatment of cerebral venous thrombosis (ACTION-CVT): a multicenter international study. *Stroke*. 2022;53(3):728-738.

13. Dong X, Liu X, Liu Y, Jiang L, Zhang H, Liu B. Clinical efficacy of conventional heparin anticoagulation combined with apixaban in the treatment of patients with cerebral venous thrombosis and its effect on serum D-Dimer and FIB expression. *Comput Math Methods Med*. 2021;2021:4979210.

14. Powell M, Tremolet de Villers K, Schwarz K, Case D, Trujillo T. A single-center retrospective evaluation of the use of oral factor Xa inhibitors in patients with cerebral venous thrombosis. *Annals of Pharmacotherapy*. 2021;55(3):286-293.

15. Esmaeili S, Abolmaali M, Aarabi S, et al. Rivaroxaban for the treatment of cerebral venous thrombosis. *BMC Neurol*. 2021; 21(1):73.

16. Giles JA, Balasetti VKS, Zazulia AR. Non-vitamin K antagonist oral anticoagulants for the treatment of cerebral venous sinus thrombosis: a retrospective, matched cohort analysis. *Neurocrit Care*. 2021;35:783-788.

17. Bajko Z, Maier S, Motataianu A, et al. Rivaroxaban for the treatment of cerebral venous thrombosis: a single-center experience. *Acta Neurol Belg*. 2022;122(1):105-111.

18. Shahid R, Zafar A, Nazish S, et al. An observational study comparing the safety and efficacy of conventional anticoagulation versus new oral anticoagulants in the management of cerebral venous sinus thrombosis. *Prim Care Companion CNS Disord*. 2021;23(6):21m02927.

19. Pan L, Wang M, Zhou D, Ding Y, Ji X, Meng R. Efficacy and safety of rivaroxaban in cerebral venous thrombosis: insights from a prospective cohort study. *J Thromb Thrombolysis*. 2022;53(3):594-600.

20. Hsu A, Mistry H, Lala N, Reagan JL. Preliminary findings regarding the use of direct oral anticoagulants in cerebral venous thrombosis. *Clin Neurol Neurosurg*. 2020;198:106204.

21. Saeed FA, Ahmad ZN. Comparison of warfarin and rivaroxaban in treatment of cerebral venous sinus thrombosis. *Indo Am J Pharm Sci*. 2019;6:8487-8492.

22. Wasay M, Khan M, Rajput HM, et al. New oral anticoagulants versus warfarin for cerebral venous thrombosis: a multi-center, observational study. *J Stroke*. 2019;21(2):220-223.

23. Lurkin A, Derex L, Fambrini A, et al. Direct oral anticoagulants for the treatment of cerebral venous thrombosis. *Cerebrovasc Dis*. 2019; 48(1-2):32-37.

24. Jiang Y, Chen L, Wu X, et al. Efficacy and safety assessment of rivaroxaban for the treatment of cerebral venous sinus thrombosis in a Chinese population. *Clin Appl Thromb Hemost*. 2022; 28:10760296221144038.

25. Capecchi M, Abbattista M, De Simone P, et al. Direct oral anticoagulants for the treatment of cerebral vein thrombosis. *Thromb Res*. 2022;220:153-155.

26. Ishwara PRP, Raghavendra BS. Oral anticoagulation in cerebral venous sinus thrombosis-experience from a tertiary care hospital in karnataka, south India. IP Indian. *J Neurosci*. 2019;5(3):113-116.

27. Capecchi M, Abbattista M, Gianniello F, et al. Direct oral anticoagulants and vitamin K antagonists for treatment of cerebral vein thrombosis. res pract. *Thromb Haemost*. 2020;4(S1):PB2414.

28. Humayun M, Schmitt B, Humayun M, et al. Prescription of direct oral anticoagulants following cerebral venous sinus thrombosis (1974). *Neurology*. 2020;94:1974.

29. Wells J, Ehrlich M, Johansen M, et al. Novel oral anticoagulants (NOACs) vs. warfarin in the treatment of cerebral venous sinus thrombosis (CVST): a retrospective study of functional and radiographic outcomes among patients enrolled in BEAST (biorepository to establish the Aetiology of Sinovenous thrombosis) at UVA. *Neurology*. 2019;92:P5.3-012.

30. Fei-hu L, Xue Y. Clinical observation of rivaroxaban and warfarin in the treatment of cerebral venous sinus thrombosis. *Acta Neuropharmacol*. 2022;12(3):5-10.

31. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.

32. Geisbüsch C, Richter D, Herweh C, Ringleb PA, Nagel S. Novel factor xa inhibitor for the treatment of cerebral venous and sinus thrombosis: first experience in 7 patients. *Stroke*. 2014;45(8): 2469-2471.

33. Herweh C, Griebe M, Geisbüsch C, et al. Frequency and temporal profile of recanalization after cerebral vein and sinus thrombosis. *Eur J Neurol*. 2016;23(4):681-687.

34. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607.

35. Nepal G, Kharel S, Bhagat R, et al. Safety and efficacy of direct oral anticoagulants in cerebral venous thrombosis: a meta-analysis. *Acta Neurol Scand*. 2022;145(1):10-23.

36. Yaghi S, Saldanha IJ, Misquith C, et al. Direct oral anticoagulants versus vitamin K antagonists in cerebral venous thrombosis: a systematic review and meta-analysis. *Stroke*. 2022;53(10): 3014-3024.

37. Lee GKH, Chen VH, Tan CH, et al. Comparing the efficacy and safety of direct oral anticoagulants with vitamin K antagonist in cerebral venous thrombosis. *J Thromb Thrombolysis*. 2020;50:724-731.

38. Li H, Yao M, Liao S, Chen J, Yu J. Comparison of novel oral anticoagulants and vitamin k antagonists in patients with cerebral venous sinus thrombosis on efficacy and safety: a systematic review. *Front Neurol*. 2020;11:597623.

39. Bose G, Graveline J, Yogendrakumar V, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: a systematic review. *BMJ Open*. 2021;11(2):e040212.

40. Riva N, Galea F, Buhagiar I, Gatt A, Calleja-Agius J. Efficacy and safety of the direct oral anti-coagulants in patients with cerebral vein thrombosis: a systematic review and meta-analysis. *Br J Haematol*. 2022;198:165-182.

41. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.

42. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.

43. Mekaj A, Mekaj Y, Duci S, Miftari E. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther Clin Risk Manag*. 2015;11:967-977.

44. Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. *Cochrane Database Syst Rev*. 2011;2011(8):CD002005.

45. Miranda B, Aaron S, Arauz A, et al. The benefit of EXtending oral antiCOAgulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. *Int J Stroke*. 2018;13(7):771-774.

46. Dentali F, Poli D, Scoditti U, et al. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. *J Thromb Haemostasis*. 2012;10(7):1297-1302.

47. Crader MF, Johns T, Arnold JK. Warfarin drug interactions. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2022.

48. Ferro JM, Coutinho JM, Dentali F, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. *JAMA Neurol*. 2019;76(12):1457-1465.

49. Rusin G, Wypasek E, Papuga-Szela E, Żuk J, Undas A. Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience. *Neurol Neurochir Pol*. 2019;53(5):384-387.

50. Mendonça MD, Barbosa R, Cruz-e-Silva V, Calado S, Viana-Baptista M. Oral direct thrombin inhibitor as an alternative in the management of cerebral venous thrombosis: a series of 15 patients. *Int J Stroke*. 2015;10(7):1115-1118.

51. Nguyen TH, Ngo TM, Phan BV, et al. The novel oral anticoagulants (NOACs) for the treatment of cerebral venous thrombosis: a case study of 32 Vietnamese patients. *J Stroke Med*. 2021;4(2):105-110.

52. Thornton A. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol*. 2000;53(2):207-216.

53. Saposnik G, Barinagarrementeria F, Brown Jr. RD, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(4):1158-1192.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.