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Direct oral anticoagulants in treatment of cerebral venous thrombosis: a systematic review

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ABSTRACT

Objectives Current guidelines do not recommend direct oral anticoagulants (DOACs) to treat cerebral venous thrombosis (CVT) despite their benefits over standard therapy. We performed a systematic review to summarise the published experience of DOAC therapy in CVT.

Data sources MEDLINE, Embase and COCHRANE databases up to 18 November 2020.

Eligibility criteria All published articles of patients with CVT treated with DOAC were included. Studies without follow-up information were excluded.

Data extraction and synthesis Two independent reviewers screened articles and extracted data. A risk of bias analysis was performed.

Primary and secondary outcome measures Safety data included mortality, intracranial haemorrhage (ICH) or other adverse events. Efficacy data included recurrent CVT, recanalisation rates and disability by modified Rankin Scales (mRS).

Results 33 studies met inclusion criteria. One randomised controlled trial, 5 observational cohorts and 27 case series or studies reported 279 patients treated with DOAC for CVT: 41% dabigatran, 47% rivaroxaban, 10% apixaban and 2% edoxaban, in addition to 315 patients treated with standard therapy. The observational cohorts showed a similar risk of death in DOAC and standard therapy arms (RR 2.12, 95% CI 0.29 to 15.59). New ICH was reported in 2 (0.7%) DOAC-treated patients and recurrent CVT occurred in 4 (1.5%). A favourable mRS between 0 and 2 was reported in 94% of DOAC-treated patients, more likely than standard therapy in observational cohorts (RR 1.13, 95% CI 1.02 to 1.25).

Conclusion The evidence for DOAC use in CVT is limited although suggests sufficient safety and efficacy despite variability in timing and dose of treatment. This systematic review highlights that further rigorous trials are needed to validate these findings and to determine optimal treatment regimens.

Strengths and limitations of this study

- We performed an all-encompassing review of patients treated with direct oral anticoagulant (DOAC) for cerebral venous thrombosis (CVT).
- Given the heterogeneity of the literature, a risk of bias analysis was performed.
- We compared DOAC and standard therapy in one randomised controlled trial and five observational cohorts.
- Meta-analysis comparing different DOACs was not possible and is a limitation of this study.

INTRODUCTION

Cerebral venous thrombosis (CVT) requires rapid treatment to prevent neurological disability or death due to venous infarct and haemorrhage. The estimated incidence is 1 per 100 000 per year with a mean age of onset 39 years.[1] Although the mortality rate has reduced to 5%–15% due to advances in detection and treatment, morbidity rates can reach as high as 20%–30%.[2] A Cochrane review in 2011 showed anticoagulation to be safe in CVT and was associated with a reduction in death prompting international guidelines to recommend acute treatment of CVT with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH).[3–6] Longer term anticoagulation is required since recurrent venous thromboembolism (VTE) is highest within the first year of CVT.[7] Thus, at least 3 months of ongoing anticoagulation in low-risk patients and indefinitely for unprovoked, high-risk patients, or those with malignancy, is recommended.[6 8] The transition from acute treatment of CVT with LMWH or UFH to an oral anticoagulant, such as warfarin, is standard practice despite no randomised controlled trial (RCT) comparing warfarin with UFH or LMWH.

Direct oral anticoagulants (DOACs) were introduced to treat symptomatic VTE over the past 10 years and have advantages over warfarin: more predictable pharmacokinetics, no international normalised ratio (INR) monitoring requirement or daily dose adjustments, while demonstrating similar

efficacy in treatment of acute VTE with lower rates of intracranial haemorrhage (ICH).[9] Guideline recommendations, however, do not support DOAC treatment for CVT given the paucity of evidence.[6] Recent larger studies on DOAC therapy for VTE in atypical locations included CVT, thus assessment of the appropriateness of these anticoagulants for the treatment of CVT is warranted.[10–12]

The objective of this study was to review all available evidence to assess data on safety and efficacy of DOACs in the treatment of CVT.

METHODS

Search strategy and selection criteria

The protocol for this systematic review was registered (PROSPERO ID: CRD42017078398)[13] and published.[14] We followed Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols,[15] Preferred Reporting Items for Systematic Reviews and Meta-Analyses[16] and Synthesis without meta-analysis (SWiM)[17] guidelines where applicable. The search strategy was iteratively developed with assistance of a research librarian (RS) and is available in the supplement (online supplemental appendix 1. We searched Ovid MEDLINE, Embase and the Cochrane Central Register of Controlled Trials for original reports of patients with a diagnosis of CVT treated with a DOAC up to 18 November 2020. We included all available peer-reviewed studies including RCTs, prospective or retrospective observational cohorts, case series and case studies. Studies without follow-up data were excluded. Two authors (GB and JG) independently reviewed titles and abstracts for inclusion.

Data items

Study type and number of patients were collected. Patient data included age, sex and medical history; CVT information included location of venous thrombosis and ICH; and DOAC data included type, dosage, timing of initiation after immediate therapy and duration of treatment. Safety outcomes included mortality, occurrence of intracranial and extracranial bleeding as defined by authors and any other reported adverse events. Efficacy outcomes included recurrent CVT, recanalisation rates and disability measured by the modified Rankin Scale (mRS). The mRS is a six-point scale ranging from 0 (no symptoms) to 6 (death), with a score of 2 indicating slight disability but able to look after own affairs without assistance.[18] When applicable, authors were contacted for further data.

Risk of bias analysis

We used the Cochrane Risk of Bias Tool for randomised trials;[19] the Newcastle Ottawa Scale for observational cohorts;[20] and Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case studies and case series.[21] The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was used to assess the certainty of absolute treatment effects.[22]

Statistical analysis

Data were reported as counts and proportions for dichotomous data, medians and ranges for non-normally distributed continuous data, or means with SD for normally distributed continuous data. We reported risk ratios (RRs) with 95% CIs and study heterogeneity (I^2) wherever possible. Case series and case report outcomes are presented as pooled descriptive statistics for each DOAC. Statistics were performed using STATA/IC V.15.1 and RevMan V.5.4.1.

Patient and public involvement

This systematic review had no individual patient involvement.

RESULTS

Search results

Of 1843 titles, 33 studies met inclusion criteria (figure 1), representing 279 patients with CVT treated with a DOAC listed in table 1. We identified one RCT consisting of 60 patients treated with dabigatran and 60 patients treated with warfarin;[23] five observational cohorts of 101 patients treated with rivaroxaban (n=80), dabigatran (n=11) and apixaban (n=10) compared with warfarin (n=301) or LMWH (n=14);[24–28] six case series of patients treated with rivaroxaban (n=44), dabigatran (n=36) and apixaban (n=13);[29–34] and 21 case studies of rivaroxaban (n=8), dabigatran (n=8), apixaban (n=4) and edoxaban (n=5).[35–55] The clinical characteristics and outcomes of the patients are listed in table 2.

Dabigatran

A total of 115 patients (41.2%) were treated with dabigatran. In a multicentre, open-label, blinded end-point RCT by Ferro *et al*, 'A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis' (RE-SPECT CVT, NCT02913326)[23] patients were initially treated with LMWH or UFH for 5–15 days, followed by dabigatran 150 mg twice daily for 24 weeks. No patient died in the study. No new ICH occurred in the dabigatran group, while two occurred in the warfarin group. There were seven patients (11.7%) who discontinued dabigatran due to adverse events: one for worsening CVT-related baseline ICH, one intestinal haematoma and five non-bleeding adverse events. None of the four (6.7%) patients who discontinued warfarin did so due to adverse events. Follow-up data on 55 dabigatran-treated patients showed no radiographic CVT improvement in 40%, compared with 33% treated with warfarin (RR 1.22, 95% CI 0.74 to 2.03, p=0.44). At 24 weeks, a favourable mRS of 0–2 was reported in 58 of 59 (98.3%) in the dabigatran group and 56 of 58 (96.6%) in the warfarin group (p=0.62).

Descriptive studies of dabigatran reported an additional 44 patients. A case series by Mendonça *et al*[33] provided patient-level data on request for 18 patients treated initially with UFH for a median 13 days followed

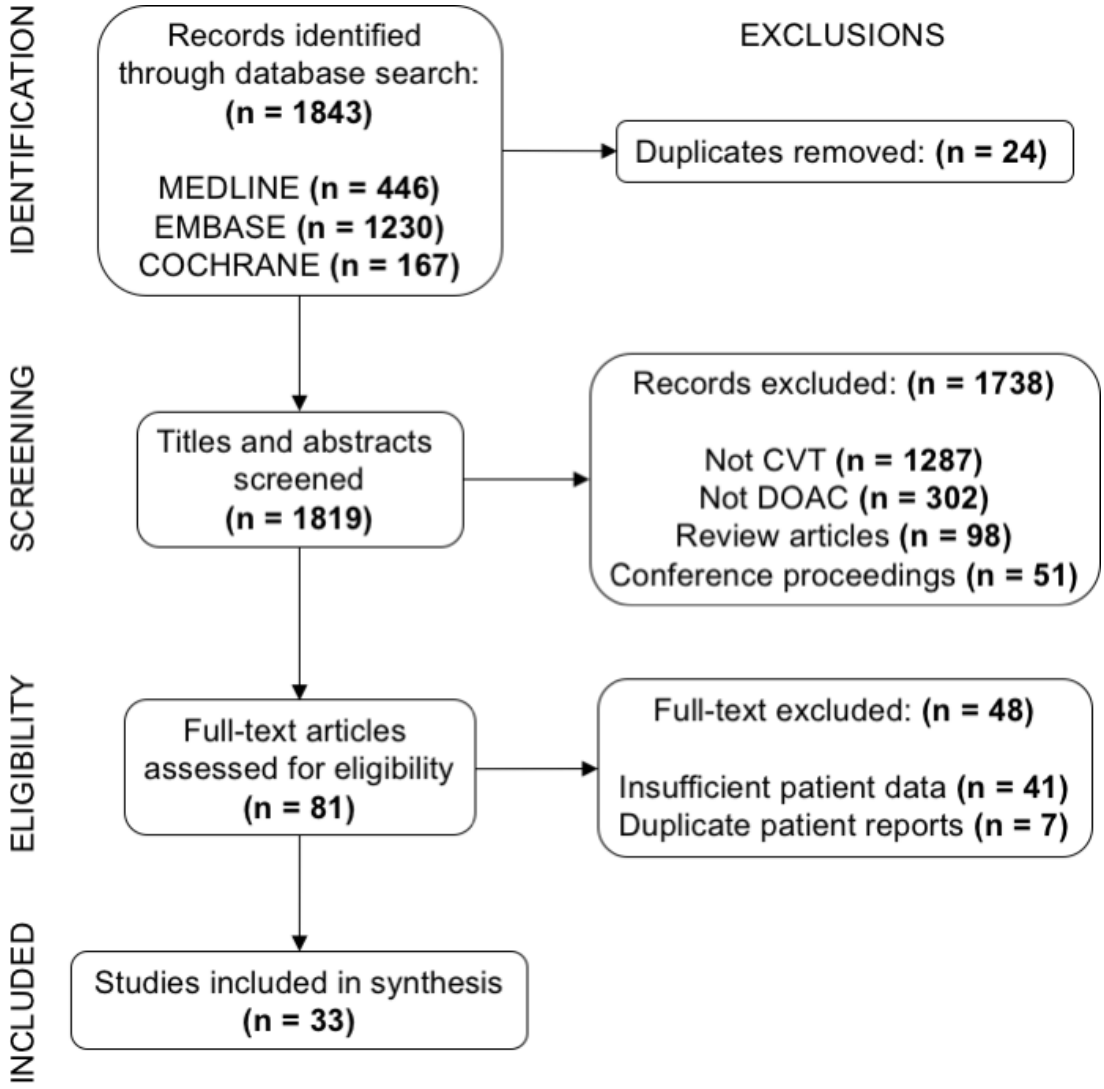

Figure 1 PRISMA flow diagram of studies included in systematic review. CVT, cerebral venous thrombosis; DOAC, direct oral anticoagulant; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

by dabigatran for a median 6 months, 150 mg twice daily in 16 patients (89%) and 110 mg twice daily in two patients (11%). No deaths or ICH were reported, though one patient (6%) had a major intestinal bleed and one (6%) had minor intestinal bleed. At 6 months, mRS of 0 or 1 was reported in 15 patients (83%) and one (6%) had mRS of 3 (moderate disability, dependent on others but can walk). Rusin *et al*[31] reported pooled data on 18 patients with dabigatran, 150 mg twice daily in 16 and 110 mg twice daily in 2, as well as rivaroxaban 20 mg daily in 10 and apixaban 5 mg twice daily in eight patients treated for a median of 8.5 months. During the 30-month follow-up, no death or ICH was reported, but three (8.3%) had major bleeding. Recurrent CVT occurred in two (5.6%) at 5 and 20 months after DOAC completion. Complete recanalisation occurred in 10 on dabigatran (55.6%), 6 on rivaroxaban (60.0%) and 6 on apixaban (50.0%). At 6–12 months after CVT, an excellent mRS of 0 or 1 was reported in 24 patients (66.7%), independent mRS of 2 in 10 (27.8%) and two (5.6%) had significant disability. Case studies of dabigatran reported one new ICH due to development of a dural arteriovenous fistula (DAVF) despite a reportedly complete recanalisation of their CVT[37] and one myocardial infarction in the context of double thrombophilia from both plasminogen activator inhibitor-1 (PAI-1) 4G/4G homozygous genotype and protein C and S deficiency and required transition to warfarin.[39] Otherwise, no patient had reported mortality, and all eight case studies reported an mRS of 0 or 1 after treatment.[37–39 52–55]

Rivaroxaban

A total of 132 patients (47.3%) were treated with rivaroxaban. Five observational cohorts pooled 101 DOAC-treated patients, 80 (79%) on rivaroxaban, 11 (11%) on dabigatran 150 mg twice daily and 10 (10%) on apixaban, compared with 315 on standard therapy with 301 (96%) warfarin and 14 (4%) LMWH.[24–28] Patients were treated with DOAC for an average 8.1 months and with standard therapy for 9.8 months. Deaths were reported in four patients treated with a DOAC compared with six on standard therapy (RR 2.12, 95% CI 0.29 to 15.59, p=0.46,

Table 1 Published patients with CVT treated with DOAC

Study	Year	Location	Anticoagulant	N	Study type
Bando *et al*[43]	2020	Japan	Edoxaban	1	Case report
Hsu *et al*[24]	2020	USA	Rivaroxaban Apixaban	1 7	Observational cohort
Saito *et al*[44]	2020	Japan	Edoxaban	1	Case report
Sugiyama *et al*[45]	2020	Japan	Edoxaban	1	Case report
Chiu *et al*[39]	2020	USA	Dabigatran	1	Case report
Powell *et al*[25]	2020	USA	Rivaroxaban Apixaban	12 7	Observational cohort
Bolaji *et al*[46]	2020	UK	Edoxaban	1	Case report
Ferro *et al*[23]	2019	Multicentre	Dabigatran	60	Randomised controlled trial
Lurkin *et al*[26]	2019	France	Dabigatran Rivaroxaban Apixaban	2 13 1	Observational cohort
Wasay *et al*[27]	2019	Multicentre	Rivaroxaban Dabigatran	36 9	Observational cohort
Huang *et al*[37]	2019	China	Dabigatran	1	Case report
Covut *et al*[29]	2019	USA	Rivaroxaban Apixaban	4 5	Case series
Hu *et al*[38]	2019	China	Dabigatran	1	Case report
Rusin *et al*[31]	2019	Poland	Dabigatran Rivaroxaban Apixaban	18 10 8	Case series
Shankar Iyer *et al*[30]	2018	India	Rivaroxaban	20	Case series
Yasushi[42]	2017	Japan	Edoxaban	1	Case report
Sui *et al*[48]	2017	China	Rivaroxaban	1	Case report
Becerra *et al*[52]	2017	Argentina	Dabigatran	1	Case report
Budhram *et al*[51]	2017	Canada	Rivaroxaban	1	Case report
Cappellari *et al*[32]	2017	Italy	Rivaroxaban	4	Case series
Hsu *et al*[50]	2017	China	Rivaroxaban	1	Case report
Inche Mat *et al*[55]	2017	Malaysia	Dabigatran	1	Case report
Rao *et al*[41]	2017	USA	Apixaban	3	Case report
Talamo *et al*[40]	2017	USA	Apixaban	1	Case report
Herweh *et al*[28]	2016	Germany	Rivaroxaban Apixaban	12 1	Observational cohort
Anticoli *et al*[34]	2016	Italy	Rivaroxaban	6	Case series
Cho *et al*[49]	2016	South Korea	Rivaroxaban	1	Case report
Micieli *et al*[47]	2016	Canada	Rivaroxaban	1	Case report
Mendonça *et al*[33]	2015	Portugal	Dabigatran	18	Case series
Mutgi *et al*[36]	2015	USA	Rivaroxaban	2	Case report
Sugie *et al*[35]	2015	Japan	Rivaroxaban	1	Case report
Mathew *et al*[54]	2013	India	Dabigatran	1	Case report
Hon *et al*[53]	2012	Hong Kong	Dabigatran	2	Case report

CVT, cerebral venous thrombosis; DOAC, direct oral anticoagulants.

I^2=49%) (figure 2). Hsu *et al*[24] reported two deaths after DOAC therapy (25%): one in hospital from respiratory failure postaspiration in a patient treated with apixaban, and another due to metastatic lung cancer 1 year after CVT. Wasay *et al*[27] reported two deaths in their DOAC group (4%): one prior to discharge and one prior to 6-month follow-up, and four deaths in their warfarin group (6%): three prior to discharge and one prior to

Table 2 Summary of published patients with CVT treated by a DOAC

Study	Anticoagulant	N (%)	Female	Age, years	Time to AC start, days	AC duration, months	No recanalisation	Recurrent CVT	New ICH	Any bleed	mRS 0–2	mRS 3–5	Mortality
Randomised controlled trial													
Ferro *et al*[23]	Dabigatran	60 (50)	33 (55)	45.2 (±13.8)	5–15	5.15 (±1.4)	22/55 (40)	0 (0)	0/56 (0)	12 (20)	58/59 (98.3)	1/59 (1.7)	0 (0)
	Warfarin	60 (50)	33 (55)	45.2 (±13.8)		5.3 (±1.2)	17/52 (33)	0 (0)	2/53 (3.8)	12 (20)	56/58 (96.6)	2/58 (2.3)	0 (0)
Observational cohorts													
Hsu *et al*[24]	Apixaban	1 (2)	5 (62)	51 (18–92)	N/A	N/A	N/A	0 (0)	0 (0)	N/A	N/A		2 (25)
	Rivaroxaban	7 (15)											
	Warfarin	38 (83)	22 (58)	43 (19–83)	N/A	N/A	N/A	0 (0)	0 (0)	N/A	N/A		0 (0)
Powell *et al*[25]	Apixaban	7 (6)	8 (42)	48.1	5.3	11.03	6 (31.6)	2 (11)	0 (0)	1 (5.3)	0.78*		0 (0)
	Rivaroxaban	12 (10)											
	LMWH Warfarin	11 (9) 89 (75)	64 (64)	43.8	11.2	13.48	31 (31)	10 (10)	3 (3)	10 (10)	1.32*		0 (0)
Lurkin *et al*[26]	Dabigatran	2 (5)	10 (62)	39.9 (16–74)	N/A	6	10 (62)	0 (0)	1 (6.2)	N/A	13 (81)	3 (19)	0 (0)
	Apixaban	1 (2)											
	Rivaroxaban	13 (32)											
	Warfarin	25 (61)	15 (60)	47.7 (16–83)	N/A	8	9/11 (82)	3/11 (27)	3 (12)	N/A	6/11 (55)	5/11 (45)	0 (0)
Wasay *et al*[27]	Dabigatran	9 (8)	27 (60)	36.5 (±14.7)	7 (3–12)	8 (6–13)	1/5 (20)	0 (0)	0 (0)	2 (4)	35/39 (90)	4/39 (10)	2 (4)
	Rivaroxaban	36 (32)											
	Warfarin	66 (59)	37 (56)	41.3 (±14.8)	5 (3–10)		3/7 (43)	0 (0)	1 (1.5)	6 (9)	44/56 (79)	12/56 (21)	4 (6)
Herweh *et al*[28]†	Apixaban	1 (1)	8 (62)	41.7 (±20.5)	6 (4-9)	7 (1–84)	2 (15)	0 (0)	0 (0)	3 (23)	13 (100)	0 (0)	0 (0)
	Rivaroxaban	12 (12)											
	LMWH	3 (3)	73 (85)	37.4	N/A		11 (13)	0 (0)	1 (1)	2 (2.3)	76 (88)	8 (9.3)	2 (2.3)
	Warfarin	83 (84)											
Case series													
Covut *et al*[29]	Apixaban	5 (56)	4 (80)	62 (±21)	1 (1–18)	12 (6–56)	3 (60)	0 (0)	0 (0)	0 (0)	4 (80)	1 (20)	0 (0)
	Rivaroxaban	4 (44)	3 (75)	57 (±22)	2 (1–30)	8 (3–14)	1 (25)	0 (0)	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)
Rusin *et al*[31]	Dabigatran	18 (50)	21 (58.3)	40.3 (±9.2)	6 (IQR 5–8.8)	8.5 (IQR 6.2–12)	2 (5.6)	2 (5.6)	0 (0)	3 (8.3)	34 (94.4)	2 (5.6)	0 (0)
	Apixaban	8 (22)											
	Rivaroxaban	10 (2)											
Shankar Iyer *et al*[30]	Rivaroxaban	20 (100)	4 (20)	34.2 (±13.2)	0 (0–0)	6	0 (0)	N/A	0 (0)	0 (0)	20 (100)	0 (0)	0 (0)
Cappellari *et al*[32]	Rivaroxaban	4 (100)	4 (100)	31.2 (±7.1)	4 (3–8)	4.5 (3–6)	0 (0)	N/A	0 (0)	N/A	4 (100)	0 (0)	0 (0)
Anticoli *et al*[34]	Rivaroxaban	6 (100)	6 (100)	36.5 (16–46)	7 (4–90)	4 (3–5)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)	0 (0)	0 (0)
Mendonça *et al*[33]‡	Dabigatran	18 (100)	15 (83.3)	41.2±13.8	13 (4–58)	7 (3–41)	3 (16.7)	0 (0)	0 (0)	0 (0)	17 (94.4)	1 (5.6)	0 (0)
Pooled case studies													
Dabigatran[37–39 52–55]		8 (32)	5 (62)	37.9	13/7	3.7	0 (0)	0 (0)	1 (12)	1 (12)	100	0	0
Apixaban[40 41]		4 (16)	2 (50)	27.7	6	5.6	0 (0)	0 (0)	0 (0)	0 (0)	100	0	0
Rivaroxaban[35 36 47–51]		8 (32)	4 (50)	38.4	37/4	6.6	0 (0)	0 (0)	0 (0)	0 (0)	100	0	0
Edoxaban[42–46]		5 (20)	2 (40)	56.6	12/2	6.7	0 (0)	0 (0)	0 (0)	0 (0)	100	0	0

Data is shown as a number (%), median (range) or mean (±SD), unless otherwise stated.
*If data are not available for all patients, the denominator is shown: mean mRS at follow-up reported.
†If data are not available for all patients, the denominator is shown: patient level data were acquired from contacting authors.
‡If data are not available for all patients, the denominator is shown: data from three additional patients were included from contacting authors.
AC, anticoagulation; CVT, cerebral venous thrombosis; DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; mRS, modified Rankin Scale.

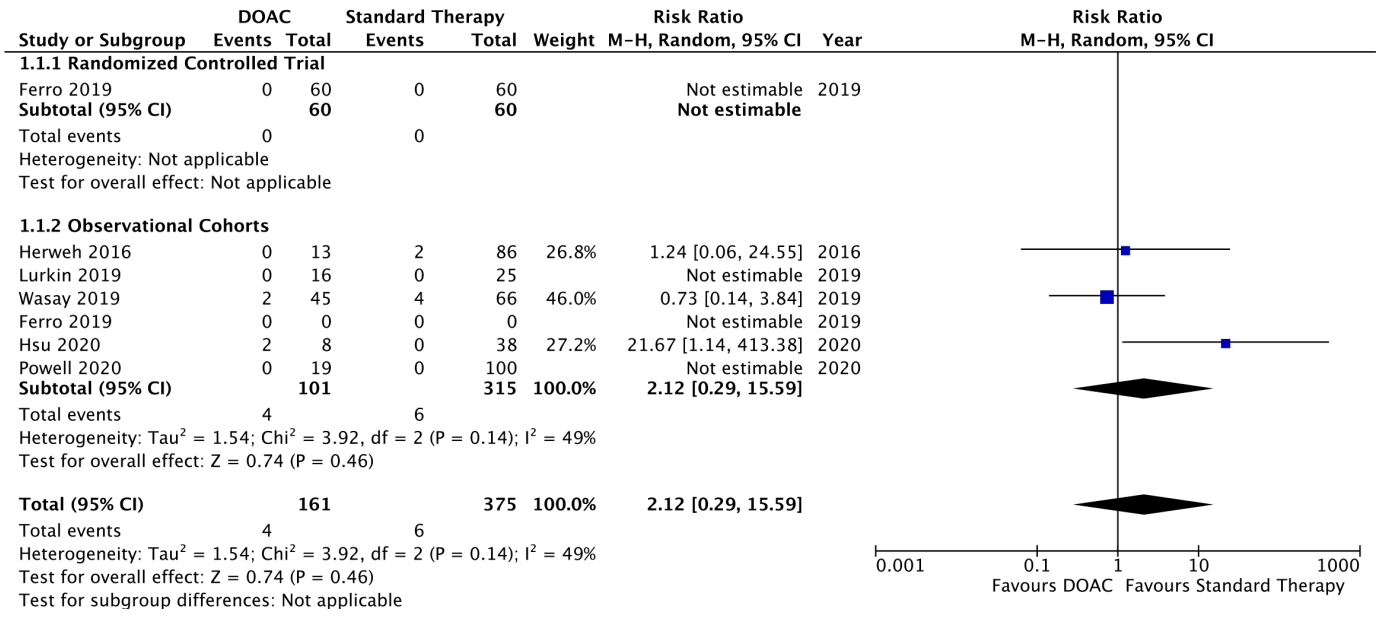

Figure 2 Forest plot comparing all-cause mortality between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular weight heparin or unfractionated heparin) for cerebral venous thrombosis.

6-month follow-up. The causes of death were not reported. Herweh *et al*[28] reported two deaths in their cohort (2%), and on request for patient-level data, none were treated with a DOAC. No significant difference between DOAC or standard therapy was reported for ICH (1% vs 2.5%, RR 0.72, 95% CI 0.18 to 2.85, p=0.64, I^2=0%), recurrent CVT (5.7% vs 11.7%, RR 0.45, 95% CI 0.05 to 4.40, p=0.49, I^2=54%) or incomplete recanalisation (35.8% vs 26.5%, RR 0.84, 95% CI 0.58 to 1.21, p=0.35, I^2=0%) available in the supplement (online supplemental appendix 2). A favourable functional outcome of mRS 0–2 was reported in 61 of 69 (88.4%) DOAC-treated patients compared with 126 of 156 (80.7%) on standard therapy (RR 1.13, 95% CI 1.02 to 1.25, p=0.02, I^2=0%) (figure 3).

Descriptive studies of rivaroxaban reported an additional 52 patients. A case series by Shankar Iyer *et al*[30] treated 20 stable patients with rivaroxaban acutely at 15 mg twice daily for 3 weeks followed by 20 mg daily. At 6-month follow-up, no patient died or discontinued rivaroxaban. There was no ICH or adverse effects reported. There was recanalisation in all patients and 19 (95%) reported mRS of 0 or 1, with mRS of 2 in only one (5%). Other case series and studies of rivaroxaban reported no mortality or ICH, and all had mRS 0 or 1 at follow-up.[32 34–36 47–51] The dosing of rivaroxaban was variable: most received 20 mg daily after initial standard therapy,[32] one with antiphospholipid syndrome received 15 mg daily after suffering a stroke with haemorrhagic transformation 3 months after

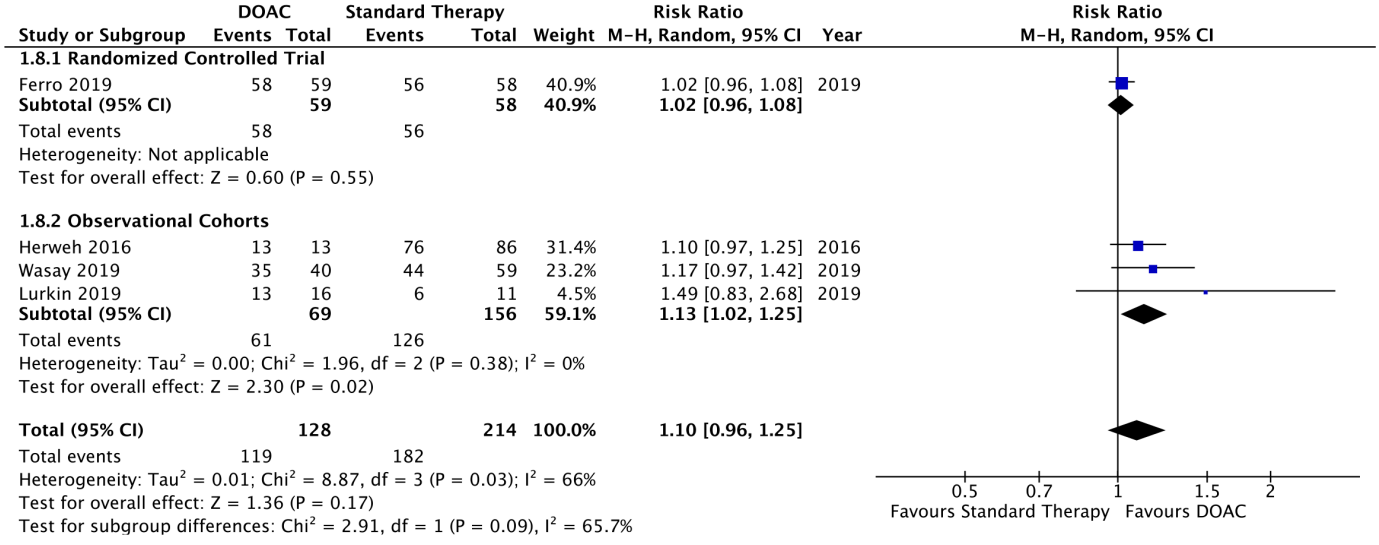

Figure 3 Forest plot comparing favourable functional outcome of modified Rankin Scale (mRS) of 0–2 between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular weight heparin or unfractionated heparin) for cerebral venous thrombosis.

starting warfarin for CVT,[35] two received 10 mg daily in the context of Crohn's disease[49] and pegylated asparaginase for acute lymphoblastic leukaemia,[48] and one was treated with 5 mg daily, in conjunction with plasma exchange (PLEX), for concurrent anti-N-methyl-D-aspartate (NMDA) receptor encephalitis.[50] One patient was initially treated with rivaroxaban 15 mg twice daily and was then switched to dabigatran due to low anti-Xa levels in the context of concurrent phenytoin use for seizures secondary to CVT.[52]

Apixaban

Apixaban has been reported in 27 patients (9.7%).[29 40 41] In the series reported by Covut *et al*[29], five patients were treated with apixaban and four patients with rivaroxaban after a median 3 days of UFH and continued for a median of 12 months. No patient died or had new ICH during the follow-up, nor switched off their DOAC. One patient was switched onto apixaban due to gastrointestinal bleeding on warfarin and another was switched onto rivaroxaban 30 days after starting warfarin due to INR fluctuations. No recanalisation was reported in three patients (60%) on apixaban and one patient (25%) on rivaroxaban. At 6-month follow-up, mRS was 0 or 1 in eight patients (89%) and one patient had persistent mRS of 4 (unable to walk unassisted). The other case studies of apixaban indicate that all four patients had mRS of 0–1 after treatment, with no mortality or new ICH. Apixaban dosing was 5 mg twice daily for all patients, though one received 10 mg twice daily initially for 7 days in the context of T cell acute lymphoblastic leukaemia treated with pegylated asparaginase.[40]

Edoxaban

Edoxaban was reported in case studies of five patients (1.8%).[37–41] No death, ICH, recurrent CVT or incomplete recanalisation was reported, and all patients had a good functional outcome. Two of the reported patients developed CVT in the context of COVID-19 infection and recovered without neurological sequelae.[45 46]

Risk of bias

The risks of bias analyses are available in the supplement (online supplemental appendix 3). In RE-SPECT CVT, patients and treating teams were aware of treatment allocation.[23] No observational cohort controlled for confounders. Treatment initiation time was not reported in two observational cohorts, and follow-up duration was not standardised.[24 26] The case series and case studies are moderately biased based on JBI Critical Appraisal, given lack of reporting completeness. Based on the currently available studies, the GRADE certainty is low for the absolute treatment effect.

DISCUSSION

We found that since the approval of DOAC for treatment of VTE, 279 patients treated with DOAC for CVT have been published with follow-up data. Of these patients, 42% are reported in case studies or case series, 36% in five observational cohorts and 22% in one RCT. There were 200 patients (72%) published in 2019 and 2020, suggesting that practitioner comfort for DOAC use in CVT is improving despite a lack of guideline recommendations.[6] A recent survey of Canadian neurologists and haematologists suggests interest in the utilisation of DOAC for treatment of CVT, and the increasing reports support this trend.[56]

Outcomes of DOAC compared with standard therapy

Currently, warfarin is supported by guidelines despite no RCT evidence of superiority or non-inferiority to LMWH or UFH. The benefits of the DOAC over warfarin include reduced dose adjustments due to drug and food interactions, no need for INR monitoring to ensure therapeutic range and, in the case of dabigatran, the availability of a reversal agent. Furthermore, even when closely monitored in a clinical trial setting, patients on warfarin for CVT were in the therapeutic INR range only 66% of the time,[23] suggesting better anticoagulation may be achieved with DOAC. Overall safety of DOAC was reassuring, with recurrent CVT, new ICH and death only reported in observational cohorts at rates similar to standard therapy and within the expected range of treated CVT.[2] Furthermore, of the DOAC-treated patients who died, two of four deaths occurred after discharge, including one related to underlying metastatic cancer that would not suggest DOAC-related mortality.[24] Efficacy was also promising with 93% of DOAC-treated patients attaining a favourable outcome of mRS from 0 to 2 compared with 85% of those on standard therapy. Compared with standard therapy in the observational cohorts, this value was higher for DOAC-treated patients. However, utilisation of DOAC in less severe CVT cannot be ruled out as a confounding factor since the observational cohorts did not have comparable standard treatment groups.

A meta-analysis published by Lee *et al*[57] showed similar results to our review with no difference between DOAC or warfarin for recanalisation rates or major bleeding; however, their review analysed an 'excellent' mRS outcome of 0–1 and found no difference, while our study analysed a 'favourable' mRS of 0–2 and found a difference in the observational cohorts. The dichotomy of a favourable mRS has been debated, with mRS greater than two shown to be related to 1-year mortality, as well as being an independence cut-off for entry to certain endovascular trials.[58–60] The apparent discrepancy may also relate to two of their analysed observational cohort studies (Geisbüsch *et al*[61] and Herweh *et al*[28]) potentially including patients from the same institution during overlapping time periods (January 2012–December 2013 and January 1998–September 2014, respectively). To clarify, we were able to contact the authors from these studies and obtain patient-level data, which led to the exclusion of Geisbüsch *et al*[61] due to duplicate patient data. Furthermore, we have

updated the search to include an additional two cohorts published in 2020.

An ongoing RCT out of University of British Columbia, the 'Study of Rivaroxaban for CeREbral Venous Thrombosis' (SECRET, NCT03178864), is currently recruiting an estimated 50 participants comparing rivaroxaban with standard anticoagulation of LMWH, UFH or warfarin, expected to be completed December 2021.[62] Another RCT, 'Rivaroxaban vs Warfarin in CVT Treatment' (RWCVT, NCT04569279) out of Damascus University has completed enrollment of 71 patients though not yet published results.[63] Results of these studies will be useful for future guideline recommendations for DOAC use in CVT compared with standard therapy.[6]

Comparison between different DOAC

Our search yielded no randomised trials comparing different DOAC against each other, thus no formal meta-analysis comparing different DOAC was possible. Dabigatran was compared against warfarin in the only published RCT specifically looking at CVT to date; however, the most commonly reported DOAC was rivaroxaban, possibly suggesting physician comfort with this medication. Results from RWCVT and SECRET will help validate safety and efficacy of rivaroxaban and allow more definitive comparison with dabigatran from RE-SPECT CVT.[62]

The timing of DOAC initiation after acute treatment with LMWH or UFH ranged from 5 to 15 days for the RCT and from 3 to 12 days for the observational cohorts. The descriptive studies had more variability in DOAC initiation, ranging from acutely after CVT diagnosis, to as far as 3 months, making comparisons challenging. The dosage of DOAC was also inconsistent, with dabigatran dose ranging from 75 mg to 150 mg twice daily in the cohort by Wasay *et al*[27] and rivaroxaban dosing between 5 mg daily and 20 mg daily depending on the study. Both ongoing RCTs use rivaroxaban after initial acute therapy with LMWH or UFH, for SECRET 20 mg daily within 14 days of CVT diagnosis, and for RWCVT 20 mg or 15 mg, depending on creatinine clearance, after a non-specified duration of acute therapy. These and future trials should help standardise how long initial therapy with LMWH or UFH is needed, if at all, prior to using DOAC, as well as if initial dosage adjustments are needed.

There were rare adverse events with each DOAC therapy. For dabigatran, no deaths were reported, and of the patients who experienced bleeding, none were given the reversal agent. However, in RE-SPECT CVT, dabigatran was stopped in two patients due to intestinal haematoma and worsening of the haemorrhagic component of their baseline intracranial lesion.[23] Bleeding events on rivaroxaban were only reported in the series by Rusin *et al*[31] in three patients (8.3%), two on 20 mg daily rivaroxaban and one on 110 mg twice daily dabigatran, who had heavy menstrual bleedings in two and upper gastrointestinal bleeding in one. Other rare adverse events include the in-hospital death of a patient treated with apixaban who had an aspiration event and respiratory failure,[24] myocardial infarction while on dabigatran[39] and DAVF formation 3 months after CVT despite complete recanalisation with dabigatran.[37] A post hoc analysis of the RE-SPECT CVT showed no DAVF formation at 6 months.[64] Two case studies of edoxaban treated patients with CVT in the context of COVID-19.[45 46] Thrombotic complications of COVID-19 has been reported, but the safety and efficacy of DOAC in COVID-19 related thrombosis specifically has yet to be confirmed.[65 66]

The efficacy of each DOAC was good for treatment of CVT. Recurrent CVT was only reported in four patients overall (1.5%), two patients from the cohort Powell *et al*[25] (11%) and two in the case series Rusin *et al*[31] (5.6%) after discontinuation of DOAC. An international long-term cohort found the rate of recurrent CVT is as high as 4.4% at median 40 months; therefore, long-term follow-up of DOAC-treated CVT is needed to determine the ideal treatment duration.[67] Recanalisation rates varied between DOAC treatment at similar rates reported in randomised trials of LMWH and UFH to treat CVT[3–5] without clear reduction of a favourable functional outcome, as previously demonstrated.[28] However, the prognostic value of recanalisation has been investigated by a meta-analysis of standard therapy, which showed recanalisation occurred in up to 85% of patients and was associated with mRS 0 or 1 (OR 3.3, 95% CI 1.7 to 6.3, p=0.001).[68] Further high-quality studies will be required to determine if recanalisation rates differ between DOACs, as well as if they are related to functional outcome.

Limitations

The results of this systematic review should be interpreted with caution. The majority of patients were reported in retrospective observational cohorts or case studies prone to selection bias, confounding and lack of standardisation in timing of therapy initiation and follow-up duration. Therefore, pooling and inferential statistical analysis was not prudent due to the clinical and methodological heterogeneity and conclusions as to how DOAC therapies perform against each other could not be made. The risk of bias analysis revealed that RE-SPECT CVT has the lowest bias risk given utilisation of a Prospective Randomized Open, Blinded End-point (PROBE) design, and although the retrospective studies inherently have increased bias, most studies were appropriately informative. Finally, follow-up data and treatment duration were limited to a median 6 months; longer term registries for safety will be needed to estimate rates of recurrent CVT in patients treated with a DOAC.

Unanswered questions and future research

Our systematic review suggests physicians are increasingly using DOAC for the treatment of CVT; however, several remaining questions require further study. The ideal time to start a DOAC after diagnosis of CVT is not known. Certain studies first use LMWH or UFH treatment, while others used a DOAC acutely. The safety of DOAC use in children is not known. The recently published RCT,

'Oral Rivaroxaban in Children With Venous Thrombosis' (EINSTEIN-JR, NCT02234843), investigated paediatric cases of any acute VTE and randomised to weight-based rivaroxaban or standard anticoagulation showed potentially improved thrombotic burden (OR 1.70, p=0.012) and similar safety as adult studies.[69] Specific outcomes were not reported based on VTE location; however, 74 of 335 (22%) patients treated with rivaroxaban had CVT, and no clear safety concern was identified. Finally, the ideal DOAC to use for CVT also requires further study. Results from RWCVT and SECRET will help validate safety and efficacy of rivaroxaban and allow more definitive comparison with dabigatran from RE-SPECT CVT.[62] Although dabigatran has the advantage of having a reversal agent, idarucizumab, its use in CVT has not been published at the current time, so any unique risks in this population is unknown.[70] Extrapolating conclusions for apixaban or edoxaban from studies of different DOAC may give an inaccurate risk–efficacy profile, and thus high-quality RCT of these treatments are also needed.

Given that CVT is a rare disease, enrolment in these large randomised studies is slow, so review of observational cohorts and smaller studies provide needed information. Physicians recognise the benefits of DOACs and are increasingly using these medications for treatment of CVT despite the lack of guideline recommendations. Based on this review, no clear safety concerns are identified for any particular DOAC, and the available data on efficacy is promising. The ideal timing for initiation of DOAC after diagnosis of CVT, and the ideal DOAC to use for CVT, are remaining questions. The results of future RCTs may inform guidelines if no adverse safety signal and a similar efficacy to standard therapy is seen.

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SUPPLEMENTAL MATERIAL

Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review

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Appendix I: Search Strategy

The complete protocol is previously published[1] and is hosted on PROSPERO (ID: CRD42017078398).[2]

Ovid MEDLINE(R) ALL
Strategy:

1. apixaban.mp.
2. edoxaban.mp.
3. Dabigatran.mp.
4. Rivaroxaban.mp.
5. (doac* or noac*).tw,kw.
6. ((direct oral or novel) adj3 (anticoagul* or anti coagulat*)).tw.
7. exp Factor Xa Inhibitors/
8. Factor Xa Inhibit*.mp.
9. Antithrombins/ or thrombin inhibit*.mp.
10. or/1-9
11. "intracranial embolism and thrombosis"/ or intracranial thrombosis/ or exp sinus thrombosis, intracranial/
12. cvt.tw,kw.
13. (cerebral veins/ or exp cranial sinuses/) and (thrombosis/ or venous thrombosis/)
14. ((sinus* or sinovenous or cerebral or cavernous or sagittal venous or sagittal vein* or cerebrovenous or cerebro-venous or sigmoid) and thrombo*).tw,kw.
15. intracran* thrombo*.kw. or (intracran* adj3 thrombo*).tw.
16. 11 or 12 or 13 or 14 or 15
17. 10 and 16

Database: Embase Classic+Embase
Strategy:

1. apixaban.mp.
2. edoxaban.mp.
3. Dabigatran.mp.
4. Rivaroxaban.mp.
5. (doac* or noac*).tw.
6. ((direct oral or novel) adj3 (anticoagul* or anti coagulat*)).tw.
7. exp *Factor Xa Inhibitors/

14. cvt.tw.
15. or/11-14
16. 10 and 15

Database: EBM Reviews - Cochrane Central Register of Controlled Trials Search Strategy:

1. apixaban.mp.
2. edoxaban.mp.
3. Dabigatran.mp.
4. Rivaroxaban.mp.
5. (doac* or noac*).tw,kw.
6. ((direct oral or novel) adj3 (anticoagul* or anti coagulat*)).tw.
7. exp Factor Xa Inhibitors/
8. Factor Xa Inhibit*.mp.
9. Antithrombins/ or thrombin inhibit*.mp.
10. or/1-9
11. "intracranial embolism and thrombosis"/ or intracranial thrombosis/ or exp sinus thrombosis, intracranial/
12. cvt.tw,kw.
13. (cerebral veins/ or exp cranial sinuses/) and (thrombosis/ or venous thrombosis/)
14. ((sinus* or sinovenous or cerebral or cavernous or sagittal venous or sagittal vein* or cerebrovenous or cerebro-venous or sigmoid) and thrombo*).tw,kw.
15. intracran* thrombo*.kw. or (intracran* adj3 thrombo*).tw.
16. 11 or 12 or 13 or 14 or 15
17. 10 and 16

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SUPPLEMENTAL MATERIAL

Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review

Gauruv Bose[1], Justin Graveline[1], Vignan Yogendrakumar[1], Risa Shorr[1], Dean Fergusson[1], Gregoire Le Gal[1], Jonathan M. Coutinho[2], Marcelo Mendonça[3], Miguel Viana-Baptista[3], Simon Nagel[4], and Dar Dowlatshahi[1]

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Appendix II: Forest Plots

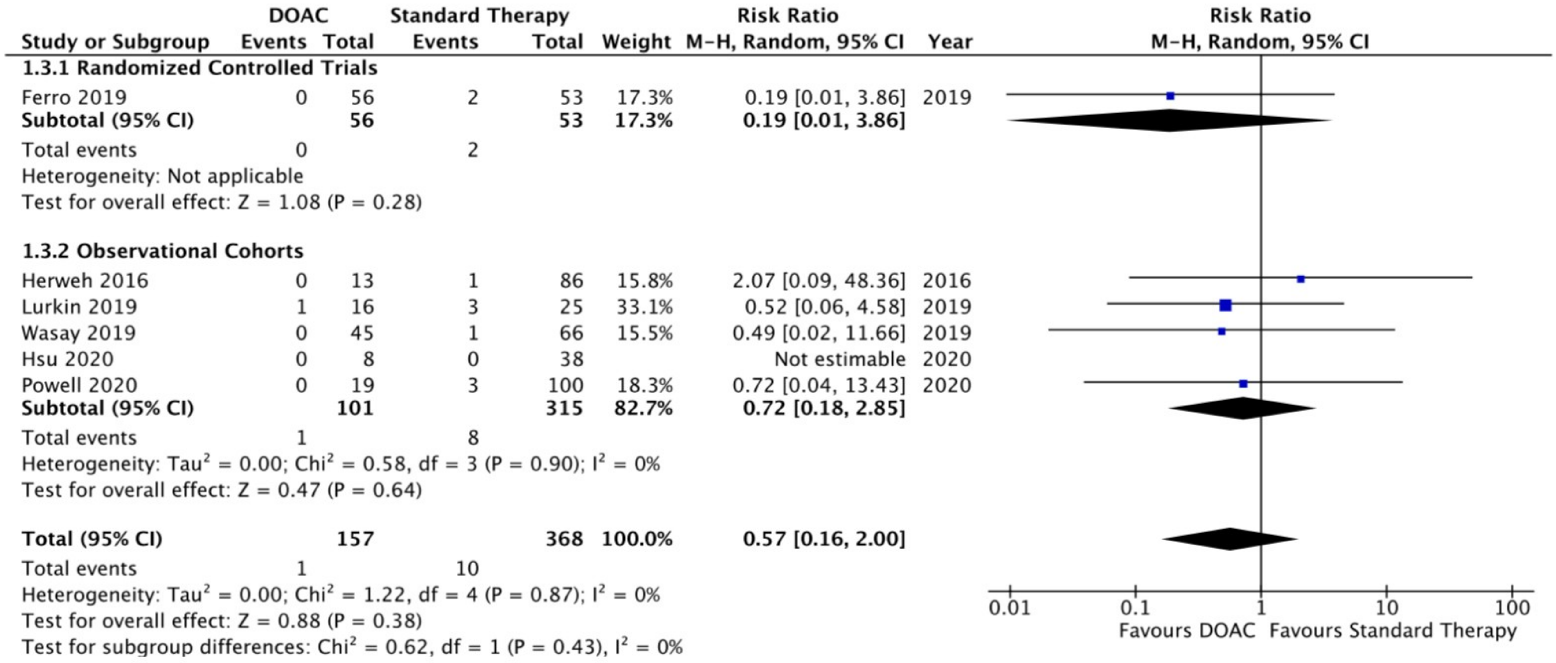

Figure s1. Forest plot comparing intracranial hemorrhage (ICH) between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin) for cerebral venous thrombosis

Appendix II: Forest Plots

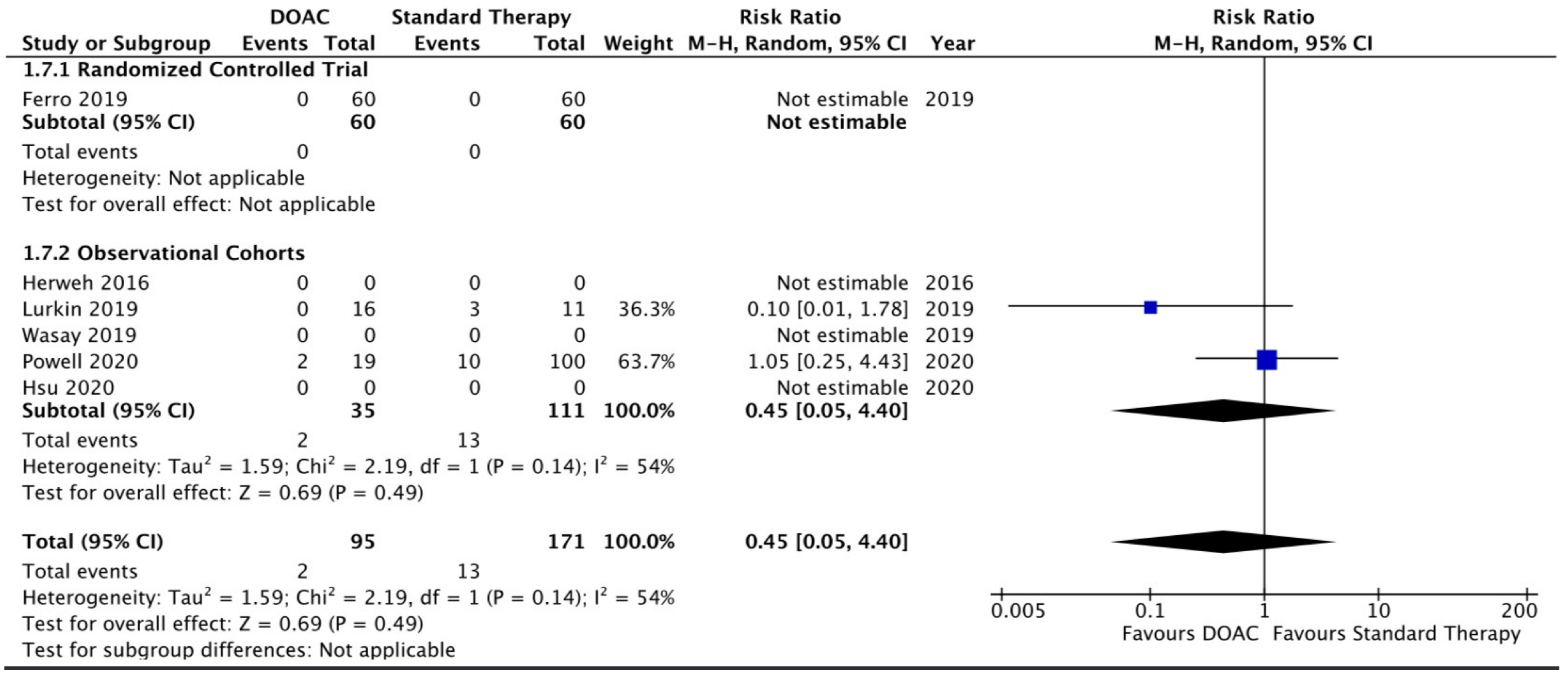

Figure s2. Forest plot comparing recurrent cerebral venous thrombosis (CVT) between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin)

Appendix II: Forest plots

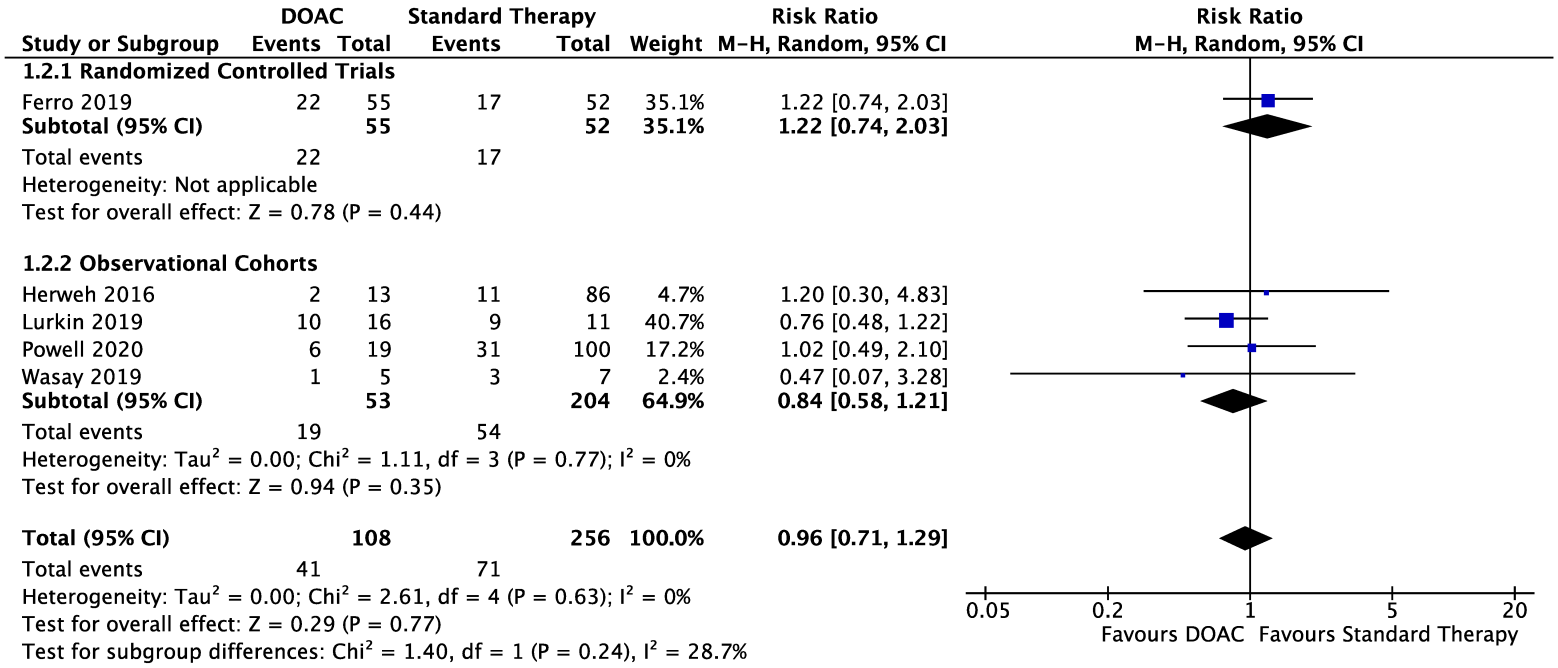

Figure s3. Forest plot comparing incomplete recanalization for cerebral venous thrombosis (CVT) between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin)

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SUPPLEMENTAL MATERIAL

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Appendix III: Risk of Bias Tables

Table s1: Randomized Controlled Trials; Cochrane Risk of Bias Tool

	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Ferro et al.[3]	2019	**Low Risk:** Patients were randomized using an online 24-hour telephone service	**Low Risk:** Concealment maintained using the telephone service	**High Risk:** Patients and treating teams were aware of treatment allocation.	**Low Risk:** All outcomes were adjudicated in a blinded manner by an adjudication committee	**Low Risk:** All missing/excluded patients were disclosed by study authors. Reasons for exclusion were provided. 11 patients lost to follow-up overall.	**Low Risk** all outcomes that were pre-specified were reported	**Unclear** exploratory trial with no formal hypothesis statistical testing

Appendix III: Risk of Bias Tables

Table s2: Observational Cohorts; NewCastle Ottawa Scale

	Year	Selection (Max☆☆☆☆)				Comparability (Max☆☆)	Outcome Max (☆☆☆)		
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome absent at study start	Comparable cohorts (design or analysis)	Assessment of outcome	Appropriate follow-up time	Adequate follow-up of cohorts
Hsu et al.[4]	2020	☆	☆	☆	☆		☆	☆	☆
Powell et al.[5]	2020	☆	☆	☆	☆		☆	☆	☆
Lurkin et al.[6]	2019	☆	☆	☆	☆		☆	☆	☆
Wasay et al.[7]	2019	☆	☆	☆	☆		☆	☆	☆
Herweh et al.[8][a]	2016	☆	☆	☆	☆		☆	☆	☆
A. Additional patient level information was provided upon request to authors.									

Appendix III: Risk of Bias Tables

Table s3: Case Series; Johanna Briggs Institute Critical Appraisal for Case Series

	Year	Clear Inclusion Criteria	Condition Measured in Reliable Way	Valid Method to ID condition	Consecutive Inclusion	Complete Inclusion	Demographics	Clinical Information	Outcomes	Presenting Site, Clinical Demographics	Stat Analysis
Covut et al.[9]	2019	Y	N	N	Y	Y	Y	Y	Y	N	N
Rusin et al.[10]	2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Shankar Iyer et al.[11]	2018	Y	Unclear	Unclear	Y	Y	Y	Y	Y	N	N
Cappellari et al.[12]	2017	Y	Unclear	Unclear	Unclear	Unclear	Y	Y	Y	N	Y
Anticoli et al. [13]	2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Mendonca et al.[14]	2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

Appendix III: Risk of Bias Tables

Table s4: Case Reports; Johanna Briggs Institute Critical Appraisal

	Year	Patient Demographics Clearly Described	Patient History Clearly Described	Clinical Condition Clearly Described	Diagnostic Tests Well Described	Intervention or Treatment Well Described	Post-Intervention Clinical Condition Described	Adverse Events	Takeaway Lesson?
Bando et al[15]	2020	Y	Y	Y	Y	Y	Y	N	Y
Saito et al[16]	2020	Y	N	Y	Y	N	Y	N	Y
Sugiyama et al[17]	2020	Y	N	Y	Y	Y	Y	Y	Y
Chiu et al[18]	2020	Y	N	Y	Y	N	Y	Y	Y
Bolaji et al[19]	2020	Y	Y	Y	Y	N	N	N	N
Huang et al[20]	2019	N	Y	Y	Y	Y	Y	Y	Y
Hu et al[21]	2019	Y	Y	Y	Y	Y	Y	N	Y
Yasushi [22]	2017	Y	Y	Y	Y	Y	Y	N	Y
Sui et al[23]	2017	N	Y	Y	Y	Y	Y	N	Y
Becerra et al[24]	2017	N	Y	Y	Y	Y	Y	Y	Y
Budhram et al[25]	2017	Y	Y	Y	Y	Y	N	N	Y
Hsu et al[26]	2017	N	Y	Y	Y	Y	Y	N	Y
Inche Mat et al[27]	2017	Y	N	Y	N	Y	N	N	Y
Rao et al[28]	2017	N	Y	Y	Y	Y	Y	N	Y
Talamo et al[29]	2017	Y	Y	Y	Y	Y	Y	N	Y
Cho et al[30]	2016	Y	Y	Y	Y	Y	Y	N	Y
Micieli et al[31]	2016	Y	Y	N	Y	N	Y	N	N
Mutgi et al[32]	2015	N	N	N	Y	N	Y	N	Y
Sugie et al[33]	2015	Y	Y	Y	Y	Y	Y	N	Y
Mathew et al[34]	2013	N	Y	Y	Y	Y	Y	N	Y
Hon et al[35]	2012	Y	Y	Y	Y	Y	Y	N	Y

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