BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040212
Article Type:	Original research
Date Submitted by the Author:	12-May-2020
Complete List of Authors:	Bose, Gauruv; University of Ottawa, Neurology Graveline, Justin; University of Ottawa, Neurology Yogendrakumar, Vignan; The Ottawa Hospital Research Institute, Neurology Shorr , Risa; Ottawa Hospital Fergusson, Dean; Ottawa Hospital Research Institute, Medicine Le Gal, Gregoire; University of Ottawa, Hematology Coutinho, Jonathan; University of Amsterdam, Department of Neurology Mendonca, Marcelo; Centro Hospitalar de Lisboa Ocidental EPE, Neurology Viana-Baptista, Miguel; Centro Hospitalar de Lisboa Ocidental EPE, Neurology Nagel, Simon; University of Heidelberg, Neurology Dowlatshahi, Dar; The Ottawa Hospital, Neurology
Keywords:	Stroke < NEUROLOGY, Stroke medicine < INTERNAL MEDICINE, Anticoagulation < HAEMATOLOGY, EPIDEMIOLOGY

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

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Key words: Direct-Acting Oral Anticoagulants, Intracranial thrombosis, Systematic review, Venous Brain Infarction, Venous Thrombosis

Word count: Abstract (273), Total Manuscript (3071)

Tables: 2, Figures: 1, Supplemental information: Yes

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ABSTRACT

Objectives Cerebral venous thrombosis (CVT) can result in disability or death from venous infarct or intracranial hemorrhage. Anticoagulation improves outcomes, yet current guidelines do not recommend direct oral anticoagulants (DOAC) to treat CVT despite their benefits. We performed a systematic review to summarize published experience of DOAC therapy in CVT.

Data sources A systematic literature search of MEDLINE and EMBASE databases up to September 15, 2019 was conducted.

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

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, bleeding, or other DOAC related adverse events. Efficacy data included recanalization time and rates, disability by modified Rankin Scale (mRS), and discontinuation of DOAC therapy.

Results The search yielded 914 studies, with 22 meeting inclusion criteria. One randomized controlled trial, 2 retrospective cohorts, and 19 case series or studies contained 188 patients treated with DOAC for CVT. Ninety-three (49%) were treated with dabigatran, 85 (45%) with rivaroxaban, and 10 (5%) with apixaban, for 6 months median duration. DOAC was the initial treatment in 24 patients (12.7%). DOAC was discontinued in 9 (4.8%). One patient (0.5%) had worsening of their ICH and 3 (1.6%) had intestinal bleeding requiring intervention. Thirty-one patients (16%) had no recanalization, the median mRS was 0, with 8 patients (4%) having a score over 3, and 2 patients died (1%).

Conclusion The evidence for 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 determine optimal treatment regimen.

PROSPERO ID: CRD42017078398

Article Summary

Strengths and limitations of the study

- Cerebral venous thrombosis is a relatively uncommon diagnosis and there is limited reported use of direct oral anticoagulants.

- Real-world variability in timing, dosing, and follow-up of patients is highlighted in these reported studies.

- Given the heterogeneity of the literature, a risk of bias analysis was performed.

INTRODUCTION

Cerebral venous thrombosis (CVT) requires rapid treatment to prevent neurologic disability or death due to venous infarct and hemorrhage. 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 as standard practice.[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 RCT comparing warfarin with UFH or LMWH.

Direct oral anticoagulants (DOAC) were introduced to treat symptomatic VTE over the past 10 years and have advantages over warfarin: more predictable pharmacokinetics, no international normalized ratio (INR) monitoring requirement or daily dose adjustments, yet have similar efficacy in treatment of acute VTE and lower rates of intracerebral hemorrhage (ICH).[9] Guideline recommendations, however, do not support DOAC treatment for CVT given the paucity of evidence.[6] There has been recent larger studies on

CVT treatment with DOAC, thus assessment of the appropriateness of these anticoagulants for the treatment of CVT is warranted.[10]

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

METHODS

Search Strategy and Selection Criteria

The protocol for this systematic review was registered (PROSPERO ID: CRD42017078398)[11] and published[12], following the PRISMA-P[13] and PRISMA[14] guidelines where applicable, and is available in the supplement. The search strategy was iteratively developed with assistance of a research librarian (RS) and is available in the supplementary information (Appendix I). We searched Ovid MEDLINE, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials for original reports of patients with a diagnosis of CVT treated with a DOAC up to September 12, 2019. Given the expected low yield we included all available studies including RCT, prospective or retrospective cohorts, case series and case reports. Studies without follow-up data were excluded. Two authors (GB, JG) independently reviewed titles and abstracts for inclusion.

Data items

Type of study and number of patients were collected. Patient characteristic data included age, sex, and medical history. CVT diagnostic information included imaging modality, location of venous thrombosis, and other imaging findings such as edema or intracranial hemorrhage. Intervention data included type of DOAC therapy, dosage, initiation of DOAC after immediate therapy, and length of treatment. Outcome data were categorized into safety and efficacy data. Safety data included mortality, occurrence of intracranial and extracranial bleeding as defined by authors, and any other reported adverse events. The efficacy data extracted included recanalization time and rates, disability by the initial and final modified Rankin Scale (mRS), and the need to discontinue DOAC therapy. When applicable, authors were contacted for further data.

Risk of bias analysis

We used the Cochrane Risk of Bias Tool for randomized trials[15]; for observational cohorts, the Newcastle Ottawa Scale was used[16]; and for case reports and case series the appropriate Joanna Briggs Institute (JBI) Critical Appraisal Checklist was used.[17]

Statistical analysis

Data was reported as counts and proportions for dichotomous data, medians and inter-quartile ranges (IQR) for non-normally distributed continuous data, or means with standard deviation (SD) for normally distributed continuous data.

Patient and public involvement

No individual patient involvement.

RESULTS

Of 914 titles, 22 studies met inclusion criteria (Figure 1) reporting a total of 188 patients with CVT treated with a DOAC (Table 1).[18,19,28–37,20,38,39,21–27] There was one RCT consisting of 60 patients treated with dabigatran compared to 60 patients treated with warfarin; 2 retrospective cohorts consisting of patients treated with rivaroxaban (n=48), dabigatran (n=9), and apixaban (n=1); 4 case series consisting of patients treated with rivaroxaban (n=28), dabigatran (n=18), and apixaban (n=5); and 15 case reports consisting of patients treated with rivaroxaban (n=9), dabigatran (n=6), and apixaban (n=4). The clinical characteristics and outcomes of the 188 patients are listed (Table 2).

Dabigatran

A total of 93 patients (49%) were treated with dabigatran. There were 60 patients treated with dabigatran compared with 60 patients treated with warfarin reported in one multicenter open-label blinded end-point RCT by Ferro *et al*.[18] The patients were initially treated with LMWH or UFH for 5 -15 days, followed by dabigatran 150mg BID for 24 weeks. None of the patients treated with dabigatran had malignancy or inflammatory disorders. None of the patients died in the study. In total, 7 patients (11.7%) discontinued dabigatran: one due to worsening of their CVT-related baseline ICH, intestinal hematoma in another, and non-bleeding adverse events in the other 5. Of the 53 patients in DOAC group with follow-up data, 22 (41.5%) reportedly had no improvement of their CVT on repeat MRI. An mRS of 0 or 1 was reported in 54 (91.5%) patients, 4 (6.8%) had mRS of 2, and 1 patient (1.7%) had an mRS over 3. No patients had recurrent CVT or VTE.

Dabigatran was used in a case series of 15 patients reported by Mendonça *et al*. in addition to 3 patients with data that were acquired through contacting the authors.[35] These patients also were treated initially with UFH for a median 13 days followed by dabigatran for a median 6 months, 150mg BID in 16 patients (89%) and 110mg BID in 2 patients (11%). No deaths or new ICH was reported. One patient (6%) was switched from dabigatran to warfarin due to gastrointestinal complaints. One patient (6%) had a major intestinal bleed and one (6%) had minor intestinal bleed. There were 3 patients (17%) with no recanalization of their CVT. At 6 months, mRS of 0 or 1 was reported in 15 patients (83%) and one (6%) had mRS of 3.

There were six patients treated with dabigatran in case reports. One patient had a new ICH due to development of a dural arteriovenous fistula (DAVF) despite a reportedly complete recanalization of their CVT.[19] One patient was initially treated with rivaroxaban and was then switched to dabigatran due to drug-drug interaction concerns given concurrent phenytoin use.[25] No patient had reported mortality. All 6 patients had an mRS of 0 or 1 after treatment.

Rivaroxaban

A total of 85 patients (45%) were treated with rivaroxaban. Two retrospective cohorts, one by Wasay *et al*. and one by Herweh *et al*. reported a total of 48 patients treated with either 15mg BiD or 20mg daily rivaroxaban, 9 with dabigatran, and 1 with apixaban 5mg BiD, as well as 149 treated with warfarin and 3 with LMWH.[22,32] In the cohort by Wasay

et al, patients received 15-20mg of rivaroxaban and 2 (4.4%) died: one prior to discharge (2%) and one prior to 6-month follow-up (3%), compared to the warfarin group where 4 patients died (6%), 3 prior to discharge (5%), and 1 prior to 6-month follow-up (2%). The cause of death was not reported. No patient died in Herweh's cohort. No patients discontinued their therapy in either group. At follow-up, mRS was 0 or 1 in 25 patients (64%) in the cohort by Wasay *et al*, and 12 patients (92%) in the cohort from Herweh *et al*. More patients in the observational cohort by Wasay *et al*. had baseline ICH in the DOAC group compared with the warfarin group (55.6% vs 30.3%, p=0.01). The cohort by Herweh *et al.* suggested anticoagulation choice did not predict recanalization, rather site of thrombosis, specifically the superior-sagittal-sinus, was a predictor of successful recanalization on multivariate analysis (Odds ratio (OR) 16, 95% confidence interval (CI) 2-138).

A case series by Shankar Iyer *et al.*, reported use of rivaroxaban in 20 stable patients without the need for surgical intervention.[23] There was no initial treatment with LMWH or UFH in this series before initiating rivaroxaban 15mg BiD for 3 weeks followed by 20mg daily. At 6-month follow-up, no patient died or discontinued rivaroxaban. There was no ICH or adverse effects reported. There was recanalization of all patients. At 6-month follow-up, 19 patients (95%) reported mRS of 0 or 1, with only one patient (5%) having mRS of 2.

A further 13 patients in case reports were treated with rivaroxaban. No mortality or new ICH was reported, and all had mRS of 0 or 1 at follow-up. The dosing of rivaroxaban was

variable. The majority of patients received 20mg daily, with a minority first being treated with 15mg BID for 7 days. One patient was treated with a low dose of rivaroxaban 5mg daily, in conjunction with PLEX for concurrent anti-NMDA receptor encephalitis, with no recurrent thrombosis.[28] Another patient was treated with 10mg daily in conjunction with azathioprine for Crohn's disease[33], and one with 15 mg daily after initially being treated with warfarin for 3 months and switched after a recurrent stroke and diagnosis of anti-phospholipid antibody syndrome.[37]

Apixaban

Apixaban has been reported in 10 patients, one patient from the above cohort by Herweh *et al.*, 5 in a case series by Covut *et al.* that also reported 4 patients treated with rivaroxaban, as well as 4 additional case reports. In the series reported by Covut *et al*., all patients were initially treated with UFH and started on DOAC after a median 3 days, continuing for a median of 12 months.[20] 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 while 15 days after starting warfarin and one was switched onto rivaroxaban 30 days after starting warfarin due to INR fluctuations. There was no recanalization in 3 patients (60%) treated with apixaban and in 1 patient (25%) treated with rivaroxaban. The 6-month follow-up showed a good outcome of mRS 0 or 1 in 8 patients (89%), while one patient on apixaban had mRS of 4. The other case reports of apixaban indicate that all 4 patients had mRS of 0-1 after treatment, with no mortality or new ICH. Apixaban dosing was 5mg BiD for all patients, though one initially received

10mg BiD for 7 days in a patient with T cell acute lymphoblastic leukemia treated with pegylated asparaginase, a thrombogenic medication.[31]

Risk of bias

The risks of bias analyses are available in the supplementary information (Appendix II). The RCT had the lowest risk given utilization of a prospective randomized open blinded end-point (PROBE) design. The two observational cohorts did not control for confounders hence have inherent bias as per the Newcastle Ottawa Scale. The case series and case reports are moderately biased based on JBI Critical Appraisal given lack of reporting completeness.

DISCUSSION

We found that in nearly a decade since approval of DOAC for treatment of VTE, only 188 published patients have been treated with DOAC for CVT. The reported studies are mostly case reports, two retrospective cohorts, and one randomized controlled trial. Overall safety was reassuring, with one (0.5%) new ICH reported[19] and two (1%) patient mortalities reported[22], which is comparable to the expected overall mortality of treated CVT.[2] Efficacy is also promising with 80% of cases reporting an mRS of 0 or 1.

The most reported DOAC was dabigatran, used to treat 93 patients (49%). Most of these patients (65%) were enrolled in a recent RCT that showed similar safety and efficacy compared with warfarin at 6 months with 60% recanalization rate and median mRS of 0 or 1.[18] While dabigatran has the availability of a monoclonal antibody reversal agent, its

use was not reported in any patient. Rivaroxaban was second-most reported in 85 patients (45%), none of whom were in an RCT. The fact that nearly half of all reported DOAC treated CVT had rivaroxaban may indicate physician comfort with this medication. Results from ongoing RCTs comparing rivaroxaban with warfarin, SECRET investigating CVT, as well as EINSTEIN-JR investigating children with any acute VTE, including CVT, will help validate safety and efficacy.[40,41] The least reported DOAC in treatment of CVT is apixaban, with 10 patients (5%) published in case series and reports; this may relate to the comparatively short time since approval and availability. While the small sample precludes generalizability, no issues with safety have been reported with apixaban.

The timing of DOAC use is similar between studies, with initiation occurring between 5 and 15 days after treatment with LMWH or UFH. The average time from CVT diagnosis to initiation of DOAC was 9 days, similar to prospective trials initiating warfarin 7 days after diagnosis and initial treatment with UFH or LMWH.[42] In one case series of 20 patients, the initial anticoagulation was rivaroxaban at 15mg two times per day for 3 weeks followed by 20mg daily, and no safety concern was highlighted.[23] The ongoing RCT is utilizing once daily rivaroxaban dosing within 14 days of CVT diagnosis without initial higher dose. Future trials should help standardize how long initial therapy with LMWH or UFH is needed, if at all, prior to initiating a DOAC as well as if initial dosage adjustments are needed.

The prognostic value of recanalization has been investigated by a recent meta-analysis.[43] Recanalization occurred in up to 85% of patients and was associated with mRS 0-1 (OR 3.3, 95% CI, 1.7–6.3, p=0.001) and less likelihood of recurrent VTE (3.4% vs. 0.9%). Our systematic review showed a variable recanalization rate in patients treated with DOAC and no reported recurrent VTE. The RCT reported 31 of 53 patients (58%) with follow-up data to have recanalization at 6 months, similar to rates reported in randomized trials of LMWH and UFH to treat CVT.[3–5] In comparison, 119 of 128 patients (93%) reported outside of this RCT had recanalization after a median 6 months. The DOAC used in those with no recanalization was rivaroxaban (n=3), dabigatran (n=3), and apixaban (n=3).[20,32,35] This discrepancy is likely due to selection bias and the fact that in the RCT a blinded adjudication committee evaluated recanalization rates.

Overall, our systematic review suggests outside of randomized trial setting, there are physicians using DOAC for the treatment of CVT despite lack of guideline support. Currently, warfarin is supported by guidelines despite no RCT evidence of superior or non-inferiority to LMWH or UFH. A recent survey of Canadian neurologists and hematologists suggests interest in the utilization of DOAC for treatment of CVT.[44] 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 range of only 66.1% of the time[18], suggesting better anticoagulation may be achieved with DOAC.

The results of this systematic review should be interpreted with caution. The majority of studies were retrospective cohorts or case reports prone to selection bias, confounding, and lack of standardization in initiation of therapy and outcome ascertainment. Therefore, pooling and inferential statistical analysis was not prudent due to the clinical and methodological heterogeneity. The risk of bias analysis revealed that the RCT has the lowest bias risk given utilization of a PROBE design, and although the retrospective studies inherently have increased bias, most studies were appropriately informative; specific risks of bias analyses are available in the supplement. 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.

Physicians recognize the benefits of DOAC and are increasingly using these medications for treatment of CVT. Based on this review, no clear safety concerns are identified and available data on efficacy is promising, although a majority are from retrospective studies or case series and case reports. The ideal timing for initiation of DOAC after diagnosis of CVT, and the ideal length of therapy are remaining questions. The results future RCT may inform guidelines if no adverse safety signal and similar efficacy to warfarin are seen.

Authorship Details G. Bose, J. Graveline, D. Dowlatshahi and R. Shorr developed the search strategy; G. Bose, J. Graveline, and D. Dowlatshahi reviewed articles for inclusion; G. Bose, D. Fergusson, and D. Dowlatshahi performed data analysis; V. Yogendrakumar assessed articles for risk of bias; G. Bose wrote the manuscript; G. Le Gal, J. Coutinho, M. Mendonça, M. Viana-Baptista and S. Nagel contributed expert opinion and revised research question and discussion; and all authors revised the manuscript for intellectual content and approved the final manuscript.

Funding statement This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests

Dr. Bose: none

Dr. Graveline: none

Dr. Yogendrakumar: none

Ms. Shorr: none

Dr. Fergusson: none

Dr. Le Gal holds an Early Researcher Award from the Ontario Ministry of Research and Innovation (MRI); an Ontario Mid-Career Investigator Award from the Heart and Stroke Foundation of Canada; and a University of Ottawa, Faculty of Medicine Tier 1 Clinical Research Chair in Diagnosis of Venous Thromboembolism. He has indirectly received research funding from Portola, Boehringer-Ingelheim, Pfizer, Bristol-Myers Squibb, LEO

Pharma, Daiichi Sankyo, Bayer. He has received speaker honoraria from Bayer, Pfizer, LEO Pharma, Sanofi bioMérieux.

Dr. Coutinho: has received research funding from the following non-profit organizations: Dutch Heart Foundation, Dutch Brain Foundation and Amsterdam Neuroscience. He has also received research support from Bayer, Boehringer and Portola. All fees were paid to his institute and used to fund medical research.

Dr. Mendonça: none

Dr. Viana-Baptista received speaker fees from Boehringer Ingelheim, Portugal, is part of an advisory board of Daiichi Sankyo, Portugal, and received a travel grant from Boehringer Ingelheim, Portugal.

Dr. Nagel: received consulting fees from Brainomix and Böhringer Ingelheim and Honoria for lectures from Bayer, BMS Pfizer and Medtronic.

Dr. Dowlatshahi received a Heart & Stroke Foundation of Canada Clinician Scientist Award, and has received honoraria from Bayer, BMS, and Apopharma.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. Extra data can be accessed via the Dryad data repository at https://datadryad.org/stash, doi: 10.5061/dryad.37pvmcvgn

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FIGURE LEGEND

Figure 1. PRISMA flow diagram of studies included in systematic review. (N = number, CVT = cerebral venous thrombosis, DOAC = direct oral anticoagulant)

Table 1. Published patients with CVT treated with DOAC

Study	Year	Location	Anticoagulant	N	Study Type
Ferro *et al.* [18]	2019	Multicenter	Dabigatran	60	Randomized controlled trial
Huang *et al.* [19]	2019	China	Dabigatran	1	Case report
Covut *et al.* [20]	2019	USA	Rivaroxaban Apixaban	4 5	Case series
Hu *et al*. [21]	2019	China	Dabigatran	1	Case report
Wasay *et al.* [22]	2019	Multicenter	Rivaroxaban Dabigatran	36 9	Retrospective cohort
Shankar Iyer *et al.* [23]	2018	India	Rivaroxaban	20	Case series
Sui *et al.*[24]	2017	China	Rivaroxaban	1	Case report
Becerra *et al.* [25]	2017	Argentina	Rivaroxaban	1	Case report
Budhram *et al.* [26]	2017	Canada	Rivaroxaban	1	Case report
Cappellari *et al.* [27]	2017	Italy	Rivaroxaban	4	Case series
Hsu *et al.* [28]	2017	China	Rivaroxaban	1	Case report
Inche Mat *et al.* [29]	2017	Malaysia	Dabigatran	1	Case report
Rao *et al.* [30]	2017	United States	Apixaban	3	Case report
Talamo *et al.* [31]	2017	United States	Apixaban	1	Case report

Herweh *et al.* [32]	2016	Germany	Rivaroxaban Apixaban	12 1	Retrospective cohort
Cho *et al.* [33]	2016	South Korea	Rivaroxaban	1	Case report
Micieli *et al.* [34]	2016	Canada	Rivaroxaban	1	Case report
Mendonça *et al.* [35]*	2015	Portugal	Dabigatran	18	Case series
Mutgi *et al.* [36]	2015	United States	Rivaroxaban	2	Case report
Sugie *et al.* [37]	2015	Japan	Rivaroxaban	1	Case report
Mathew *et al.* [38]	2013	India	Dabigatran	1	Case report
Hon *et al.* [39]	2012	Hong Kong	Dabigatran	2	Case report
**. Three patients not included in original publication were included for analysis*					

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

Study	**RCT (N=60)**	**Retrospective cohorts (N=57)**		**Case Series and Reports (N=69)**		
	Ferro *et al.* (22)	Wasay *et al.* (38)	Herweh *et al.* (28)			
DOAC, N (%)	Dabigatran 60 (100%)	Rivaroxaban 36 (80%) / Dabigatran 9 (20%)	Rivaroxaban 12 (92%) / Apixaban 1 (8%)	Rivaroxaban 36 (57%)	Dabigatran 24 (26%)	Apixaban 9 (17%)
Female (%)	33 (55)	27 (60)	8 (62)	15 (42)	20 (83)	6 (67)
Age (SD)	45.2 (13.8)	36.5 (14.7)	41.7 (20.5)	37.3 (15.5)	40.2 (13.6)	46.8 (23.7)
Time to DOAC start, days (IQR)	5 to 15 (N/A)	7 (3-12)	6 (4-9)	0 (0-2.5)	14 (10.5-19.5)	4 (2-7)
Time on DOAC, months (range)	6 (N/A)	8 (6-13)	7 (1-14)	6 (1.5-12)	18.5 (2-41)	9 (1.5-56)
No recanal-ization (%)*	22 of 53 (41.5)	0 of 5 (0)	2 of 13 (15)	1 of 35 (3)	3 of 22 (14)	4 of 9 (44)
New ICH (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)
Any bleed (%)	12 (20)	2 (5)	3 (23)	0 (0)	3 (12.5)	1 (11)
mRS 0 or 1 (%)*	54 of 59 (91.5)	25 of 39 (64)	12 of 13 (92)	35 of 36 (97)	19 of 22 (86)	5 of 6 (83)
mRS 2 or 3 (%)*	4 of 59	12 of 39	1 of 13	1 of 36	3 of 22	0 of 6

	(6.7)	(31)	(8)	(3)	(14)	(0)
mRS >3 (%)*	1 of 59 (1.7)	3 of 39 (8)	0 of 13 (0)	0 of 36 (0)	0 of 22 (0)	1 of 6 (17)
Mortality (%)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)

*. Follow-up not available for all patients, denominator is shown

RCT = randomized controlled trial; DOAC = direct oral anticoagulant; ICH = intracranial hemorrhage; mRS = modified Rankin Scale;

N = number; SD = standard-deviation; IQR = inter-quartile range;

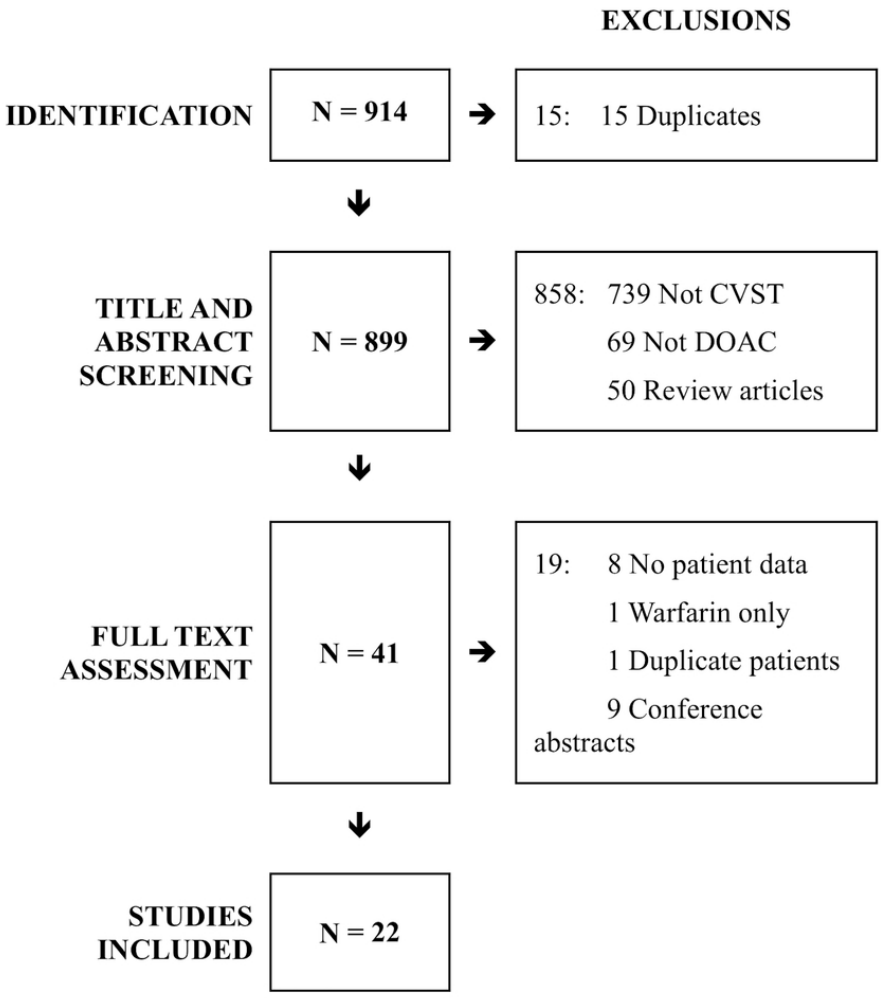

Figure 1. PRISMA flow diagram of studies included in systematic review. (N = number, CVT = cerebral venous thrombosis, DOAC = direct oral anticoagulant)

80x82mm (300 x 300 DPI)

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

SUPPLEMENTAL MATERIAL

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/
8. Factor Xa Inhibit*.tw.
9. exp *thrombin inhibitor/ or thrombin* inhibit*.tw.

10. or/1-9
11. exp cerebral sinus thrombosis/ or *occlusive cerebrovascular disease/
12. ((sinus* or sinovenous or cerebral or cavernous or sagittal venous or sagittal vein* or cerebrovenous or cerebro-venous or sigmoid) and thrombo*).tw.
13. (intracran* adj3 thrombo*).tw.
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

Appendix II: Risk of Bias Tables

I: 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

II: 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
Wasay *et al.*(4)	**2019**	⭐	⭐	⭐	⭐			⭐	⭐
Herweh *et al.*(5)	**2016**	⭐	⭐	⭐	⭐			⭐	⭐

III: 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.*(6)	2019	Y	N	N	Y	Y	Y	Y	Y	N	N
Shankar Iyer *et al.*(7)	2018	Y	Unclear	Unclear	Y	Y	Y	Y	Y	N	N
Cappellari *et al.*(8)	2017	Y	Unclear	Unclear	Unclear	Unclear	Y	Y	Y	N	Y
Mendonca *et al.*(9)	2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

IV: 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	Adverse Events	Takeaway Lesson?
Huang *et al.*(10)	2019	N	Y	Y	Y	Y	Y	Y	Y
Hu *et al.*(11)	2019	Y	Y	Y	Y	Y	Y	N	Y
Sui *et al.*(12)	2017	N	Y	Y	Y	Y	Y	N	Y
Becerra *et al.*(13)	2017	N	Y	Y	Y	Y	Y	Y	Y
Budhram *et al.*(14)	2017	Y	Y	Y	Y	Y	N	N	Y
Hsu *et al.*(15)	2017	N	Y	Y	Y	Y	Y	N	Y
Inche Mat *et al.*(16)	2017	Y	N	Y	N	Y	N	N	Y
Rao *et al.*(17)	2017	N	Y	Y	Y	Y	Y	N	Y
Talamo *et al.*(18)	2017	Y	Y	Y	Y	Y	Y	N	Y
Cho *et al.*(19)	2016	Y	Y	Y	Y	Y	Y	N	Y
Micieli *et al.*(20)	2016	Y	Y	N	Y	N	Y	N	N
Mutgi *et al.*(21)	2015	N	N	N	Y	N	Y	N	Y
Sugie *et al.*(22)	2015	Y	Y	Y	Y	Y	Y	N	Y
Mathew *et al.*(23)	2013	N	Y	Y	Y	Y	Y	N	Y
Hon *et al.*(24)	2012	Y	Y	Y	Y	Y	Y	N	Y

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Bose G, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review. *PRISMA Checklist*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study	4

		authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4 and 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Bose G, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review. *PRISMA Checklist*

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5 and Appendix II
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, table 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 and Appendix II
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of	n/a

		consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, Appendix II
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-

Bose G, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review. *PRISMA Checklist* Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040212.R1
Article Type:	Original research
Date Submitted by the Author:	08-Dec-2020
Complete List of Authors:	Bose, Gauruv; University of Ottawa, Neurology Graveline, Justin; University of Ottawa, Neurology Yogendrakumar, Vignan; The Ottawa Hospital Research Institute, Neurology Shorr , Risa; Ottawa Hospital Fergusson, Dean; Ottawa Hospital Research Institute, Medicine Le Gal, Gregoire; University of Ottawa, Hematology Coutinho, Jonathan; University of Amsterdam, Department of Neurology Mendonca, Marcelo; Centro Hospitalar de Lisboa Ocidental EPE, Neurology Viana-Baptista, Miguel; Centro Hospitalar de Lisboa Ocidental EPE, Neurology Nagel, Simon; University of Heidelberg, Neurology Dowlatshahi, Dar; The Ottawa Hospital, Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Evidence based practice, Epidemiology
Keywords:	Stroke < NEUROLOGY, Stroke medicine < INTERNAL MEDICINE, Anticoagulation < HAEMATOLOGY, EPIDEMIOLOGY

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

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Key words: Direct-Acting Oral Anticoagulants, Intracranial thrombosis, Systematic review, Venous Brain Infarction, Venous Thrombosis

Word count: Abstract (267), Total Manuscript (3707)

Tables: 2, Figures: 3, Supplemental information: Yes

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ABSTRACT

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

Data sources MEDLINE, EMBASE, and COCHRANE databases up to November 18, 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 hemorrhage (ICH), or other adverse events. Efficacy data included recurrent CVT, recanalization rates, and disability by modified Rankin Scales (mRS).

Results 33 studies met inclusion criteria. One randomized 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 0.29-15.59). 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: 1.02-1.25).

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.

PROSPERO ID: CRD42017078398

Article Summary

Strengths and limitations of the study

- We performed an all-encompassing review of patients treated with DOAC for CVT.
- Given the heterogeneity of the literature, a risk of bias analysis was performed.
- We compared DOAC and standard therapy in one RCT and 5 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 neurologic disability or death due to venous infarct and hemorrhage. 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 randomized controlled trial (RCT) comparing warfarin with UFH or LMWH.

Direct oral anticoagulants (DOAC) were introduced to treat symptomatic VTE over the past 10 years and have advantages over warfarin: more predictable pharmacokinetics, no international normalized ratio (INR) monitoring requirement or daily dose adjustments, while demonstrating similar efficacy in treatment of acute VTE with lower rates of intracranial hemorrhage (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 direct oral anticoagulants 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 PRISMA-P[15], PRISMA[16], and SWiM[17] guidelines where applicable. The search strategy was iteratively developed with assistance of a research librarian (RS) and is available in the supplement (Appendix I). 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 November 18, 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, 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 intracranial hemorrhage; 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, recanalization rates, and disability measured by the modified Rankin Scale (mRS). The mRS is a 6-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 randomized 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 utilized to assess the certainty of absolute treatment effects.[22]

Statistical analysis

Data was reported as counts and proportions for dichotomous data, medians and ranges for non-normally distributed continuous data, or means with standard deviation (SD) for normally distributed continuous data. We reported risk ratios (RR) with 95% confidence intervals (CI) 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 15.1 and RevMan 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]; 5 observational cohorts of 101 patients treated with rivaroxaban (n=80), dabigatran (n=11), and apixaban (n=10) compared to warfarin (n=301) or LMWH (n=14) [24–28]; 6 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 multicenter open-label blinded end-point RCT by Ferro *et al*., RE-SPECT CVT[23], patients were initially treated with LMWH or UFH for 5-15 days, followed by dabigatran 150mg BID 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 7 patients (11.7%) who discontinued dabigatran due to adverse events: one for worsening CVT-related baseline ICH, one intestinal hematoma, and 5 non-bleeding adverse events. None of the 4 (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 0.74-2.03, *p*=.44). At 24 weeks, a favourable mRS of 0 to 2 was reported in 58 of 59 (98.3%) in the dabigatran group and 56 of 58 (96.6%) in the warfarin group (*p*=.62).

Descriptive studies of dabigatran reported an additional 44 patients. A case series by Mendonça *et al*. provided patient-level data upon request for 18 patients treated initially with UFH for a median 13 days followed by dabigatran for a median 6 months, 150mg BID in 16 patients (89%) and 110mg BID in 2 patients (11%).[33] 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.* reported pooled data on 18 patients with dabigatran, 150mg BID in 16 and 110mg BID in 2, as well as rivaroxaban 20mg daily in 10, and apixaban 5mg BID in 8 patients treated for a median of 8.5 months.[31] During the 30-month follow-up, no death or ICH was reported but 3 (8.3%) had major bleeding. Recurrent CVT occurred in 2 (5.6%) at 5 and 20 months after DOAC completion. Complete recanalization 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 recanalization of their CVT[37], and one

myocardial infarction in the context of double thrombophilia from both 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 8 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 150mg BID, 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 4 patients treated with a DOAC compared with 6 on standard therapy (RR 2.12, 95%CI 0.29-15.59, p=.46, I^2 = 49%) (Figure 2). Hsu *et al*. reported two deaths after DOAC therapy (25%): one in hospital from respiratory failure post-aspiration in a patient treated with apixaban, and another due to metastatic lung cancer one year after CVT.[24] Wasay *et al*. reported 2 deaths in their DOAC group (4%): one prior to discharge and one prior to 6-month follow-up; and 4 deaths in their warfarin group (6%): 3 prior to discharge, and 1 prior to 6-month follow-up.[27] The causes of death were not reported. Herweh *et al*. reported two deaths in their cohort (2%), and upon request for patient-level data, none were treated with a DOAC.[28] No significant difference between DOAC or standard therapy was reported for ICH (1% vs. 2.5%, RR 0.72, 95%CI 0.18-2.85, p=.64, I^2=0%), recurrent CVT (5.7% vs. 11.7%, RR 0.45, 95%CI 0.05-4.40, p=.49, I^2=54%), or incomplete recanalization (35.8% vs. 26.5%, RR 0.84, 95%CI 0.58-1.21, p=.35, I^2=0%)

available in the supplement (Appendix II). A favourable functional outcome of mRS 0-2 was reported in 61 of 69 (88.4%) DOAC-treated patients compared to 126 of 156 (80.7%) on standard therapy (RR 1.13, 95%CI 1.02-1.25, p=.02, I^2=0%) (Figure 3).

Descriptive studies of rivaroxaban reported an additional 52 patients. A case series by Shankar Iyer *et al.* treated 20 stable patients with rivaroxaban acutely at 15mg BiD for 3 weeks followed by 20mg daily.[30] At 6-month follow-up, no patient died or discontinued rivaroxaban. There was no ICH or adverse effects reported. There was recanalization 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 20mg daily after initial standard therapy[32], one with antiphospholipid syndrome received 15mg daily after suffering a stroke with hemorrhagic transformation 3 months after starting warfarin for CVT[35], two received 10mg daily in the context of Crohn's disease[49] and pegylated asparaginase for acute lymphoblastic leukemia[48], and one was treated with 5mg daily, in conjunction with PLEX, for concurrent anti-NMDA receptor encephalitis.[50] One patient was initially treated with rivaroxaban 15mg BiD 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.*, 5 patients were treated with apixaban and 4 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 recanalization was reported in 3 patients (60%) on apixaban and 1 patient (25%) on rivaroxaban. At 6-month follow-up, mRS was 0 or 1 in 8 patients (89%) and 1 patient had persistent mRS of 4 (unable to walk unassisted). The other case studies of apixaban indicate that all 4 patients had mRS of 0-1 after treatment, with no mortality or new ICH. Apixaban dosing was 5mg BiD for all patients, though one received 10mg BiD initially for 7 days in the context of T cell acute lymphoblastic leukemia treated with pegylated asparaginase.[40]

Edoxaban

Edoxaban was reported in case studies of 5 patients (1.8%).[37–41] No death, ICH, recurrent CVT or incomplete recanalization was reported and all patients had a good functional outcome. Two of the reported patients developed CVT in the context of Coronavirus Disease 2019 (COVID-19) infection and recovered without neurologic sequelae.[45,46]

Risk of bias

The risks of bias analyses are available in the supplement (Appendix III). 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

standardized.[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 hematologists suggests interest in the utilization 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, 2 of 4 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, utilization 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*. showed similar results to our review with no difference between DOAC or warfarin for recanalization rates or major bleeding, however their review analyzed an "excellent" mRS outcome of 0 to 1 and found no difference, while our study analyzed a "favourable" mRS of 0 to 2 and found a difference in the observational cohorts.[57] The dichotomy of a favourable mRS has been debated, with mRS greater than 2 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 analyzed observational cohort studies (Geisbüsch *et al*. and Herweh *et al*.) potentially including patients from the same institution during overlapping time periods (January 2012 to December 2013 and January 1998 to September 2014, respectively).[28,61] 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.* 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, NCT 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 randomized 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 75mg to 150mg BiD in the cohort by Wasay *et al.*, and rivaroxaban dosing between 5mg daily to 20mg daily depending on the study. Both ongoing RCTs utilize rivaroxaban after initial acute therapy with LMWH or UFH, for SECRET 20mg daily within 14 days of CVT diagnosis, and for RWCVT 20mg or 15mg, depending on creatinine clearance, after a non-specified duration of acute therapy. These and future trials should help standardize 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 hematoma and worsening of the hemorrhagic component of their baseline intracranial lesion.[23] Bleeding events on rivaroxaban were only reported in the series by Rusin *et al*. in 3 patients (8.3%), two on 20mg daily rivaroxaban and one on 110mg BID dabigatran, who had heavy menstrual bleedings in two and upper gastrointestinal bleeding in one.[31] 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 dural arteriovenous fistulae (dAVF) formation 3 months after CVT despite complete recanalization 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 4 patients overall (1.5%), 2 patients from the cohort Powell *et al.* (11%), and 2 in the case series Rusin *et al*. (5.6%) after discontinuation of DOAC.[25,31] 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] Recanalization rates varied between DOAC treatment at similar rates reported in randomized 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 recanalization has been investigated by a meta-analysis of standard therapy, which showed recanalization occurred in up to 85% of patients and was associated with mRS 0 or 1 (odds ratio 3.3, 95% CI, 1.7–6.3, *p*=.001).[68] Further high quality studies will be required to determine if recanalization 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 standardization 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 utilization of a 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, EINSTEIN-JR, investigated pediatric cases of any acute VTE and randomized to weight-based rivaroxaban or standard anticoagulation showed potentially improved thrombotic burden (OR 1.70, p=.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, idaricizumab, 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, enrollment in these large randomized studies is slow, so review of observational cohorts and smaller studies provide needed information. Physicians recognize 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 future RCTs may inform guidelines if no adverse safety signal and a similar efficacy to standard therapy is seen.

Authorship Details G. Bose, J. Graveline, D. Dowlatshahi and R. Shorr developed the search strategy; G. Bose, J. Graveline, and D. Dowlatshahi reviewed articles for inclusion; G. Bose, D. Fergusson, and D. Dowlatshahi performed data analysis; V. Yogendrakumar assessed articles for risk of bias; G. Bose wrote the manuscript; G. Le Gal, J. Coutinho, M. Mendonça, M. Viana-Baptista and S. Nagel contributed expert opinion and revised research question and discussion; and all authors revised the manuscript for intellectual content and approved the final manuscript.

Funding statement This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests

Dr. Bose: none

Dr. Graveline: none

Dr. Yogendrakumar: none

Ms. Shorr: none

Dr. Fergusson: none

Dr. Le Gal holds an Early Researcher Award from the Ontario Ministry of Research and Innovation (MRI); an Ontario Mid-Career Investigator Award from the Heart and Stroke Foundation of Canada; and a University of Ottawa, Faculty of Medicine Tier 1 Clinical Research Chair in Diagnosis of Venous Thromboembolism. He has indirectly received research funding from Portola, Boehringer-Ingelheim, Pfizer, Bristol-Myers Squibb, LEO

Pharma, Daiichi Sankyo, Bayer. He has received speaker honoraria from Bayer, Pfizer, LEO Pharma, Sanofi bioMérieux.

Dr. Coutinho: has received research funding from the following non-profit organizations: Dutch Heart Foundation, Dutch Brain Foundation and Amsterdam Neuroscience. He has also received research support from Bayer, Boehringer and Portola. All fees were paid to his institute and used to fund medical research.

Dr. Mendonça: none

Dr. Viana-Baptista received speaker fees from Boehringer Ingelheim, Portugal, is part of an advisory board of Daiichi Sankyo, Portugal, and received a travel grant from Boehringer Ingelheim, Portugal.

Dr. Nagel: received consulting fees from Brainomix and Böhringer Ingelheim and Honoria for lectures from Bayer, BMS Pfizer and Medtronic.

Dr. Dowlatshahi received a Heart & Stroke Foundation of Canada Clinician Scientist Award, and has received honoraria from Bayer, BMS, and Apopharma.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.37pvmcvgn

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FIGURE LEGEND

Figure 1. PRISMA flow diagram of studies included in systematic review. (N = number, CVT = cerebral venous thrombosis, DOAC = direct oral anticoagulant)

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

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

Table 1. Published patients with CVT treated with DOAC

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

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 recanali-zation	Recurrent CVT	New ICH	Any bleed	mRS 0-2	mRS 3-5	Mortality
Randomized controlled trial													
Ferro 2019 [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 2020 [24]	Apixaban Rivaroxaban	1 (2%) 7 (15%)	5 (62%)	51 (18-92)	N/A	N/A	N/A	0 (0%)	0 (0%)	N/A	N/A		2 (25%)
	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 2020 [25]	Apixaban Rivaroxaban	7 (6%) 12 (10%)	8 (42%)	48.1	5.3	11.03	6 (31.6%)	2 (11%)	0 (0%)	1 (5.3%)	0.78 [a]		0 (0%)
	LMWH Warfarin	11 (9%) 89 (75%)	64 (64%)	43.8	11.2	13.48	31 (31%)	10 (10%)	3 (3%)	10 (10%)	1.32 [a]		0 (0%)
Lurkin 2019 [26]	Dabigatran Apixaban Rivaroxaban	2 (5%) 1 (2%) 13 (32%)	10 (62%)	39.9 (16-74)	N/A	6	10 (62%)	0 (0%)	1 (6.2%)	N/A	13 (81%)	3 (19%)	0 (0%)
	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 2019 [27]	Dabigatran Rivaroxaban	9 (8%) 36 (32%)	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%)
	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 2016 [b] [28]	Apixaban Rivaroxaban	1 (1%) 12 (12%)	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%)
	LMWH Warfarin	3 (3%) 83 (84%)	73 (85%)	37.4	N/A		11 (13%)	0 (0%)	1 (1%)	2 (2.3%)	76 (88%)	8 (9.3%)	2 (2.3%)

Table 2 (continued). Summary of published patients with CVT treated by a DOAC

Study	AC	N (%)	Female	Age, years	Time to AC start, days	AC duration, months	No recanali-zation	Recurrent CVT	New ICH	Any bleed	mRS 0-2	mRS 3-5	Mortality
Case series													
Covut 2019 [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 2019 [31]	Dabigatran Apixaban Rivaroxaban	18 (50%) 8 (22%) 10 (28%)	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%)
Shankar Iyer 2018 [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 2017 [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 2016 [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 2015 [c] [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 (±standard deviation), unless otherwise stated
If data is not available for all patients, the denominator is shown

A. Mean mRS at follow-up reported
B. Patient level data was acquired from contacting authors
C. Data from three additional patients were included from contacting authors

AC = anticoagulation, CVT = cerebral venous thrombosis, ICH = intracranial hemorrhage, IQR = interquartile range, LMWH = low molecular-weight heparin, mRS = modified Rankin Scale, N = number

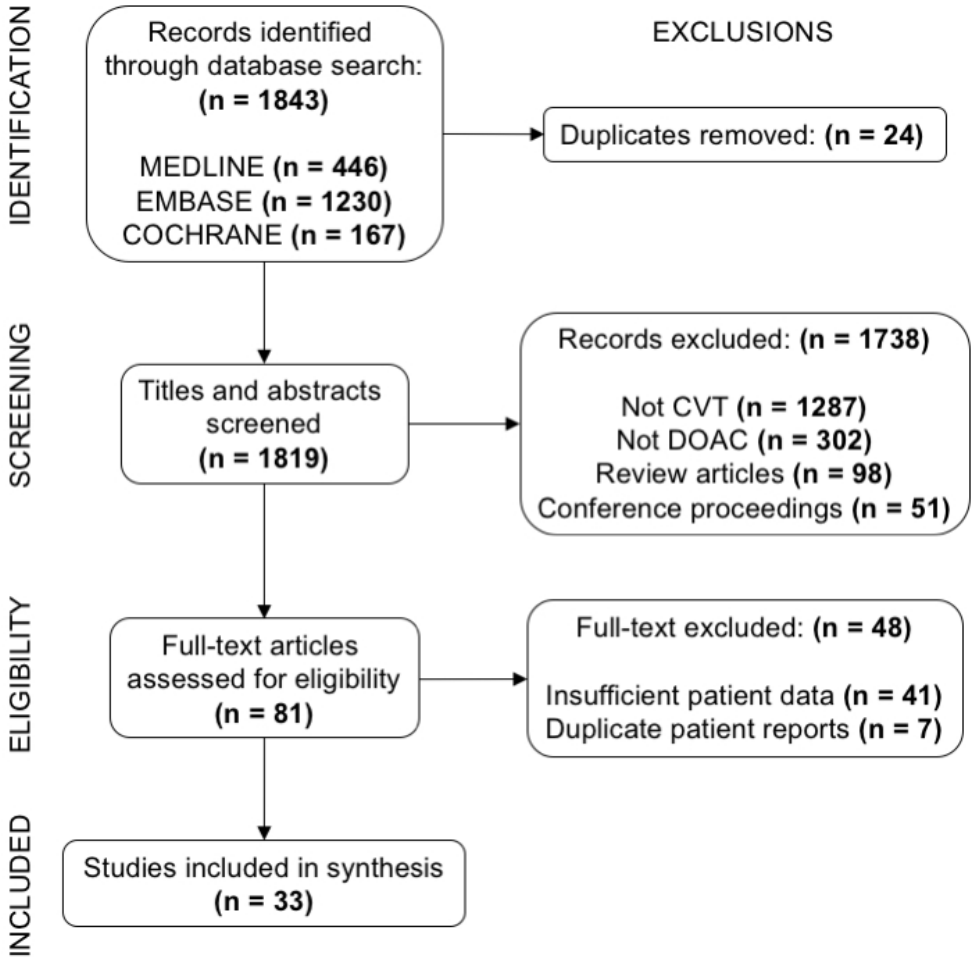

Figure 1. PRISMA flow diagram of studies included in systematic review. (N = number, CVT = cerebral venous thrombosis, DOAC = direct oral anticoagulant)

149x149mm (122 x 122 DPI)

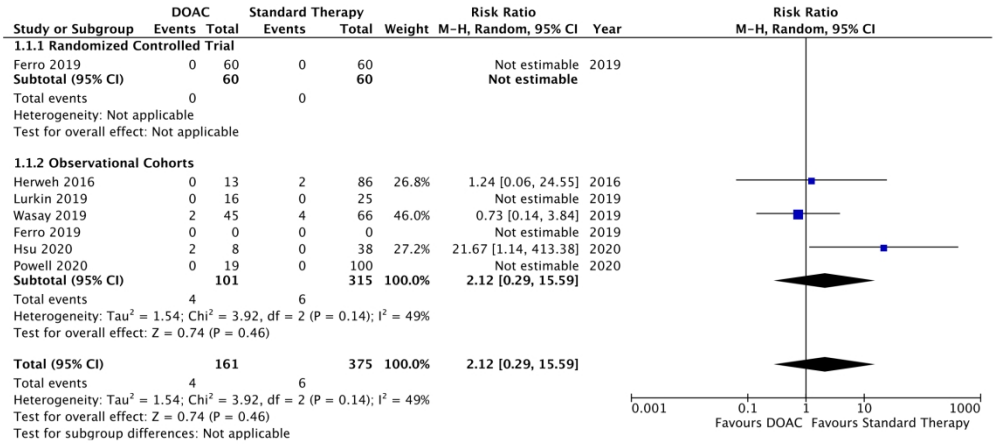

Figure 2. Forest plot comparing all-cause mortality between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin) for cerebral venous thrombosis

197x92mm (300 x 300 DPI)

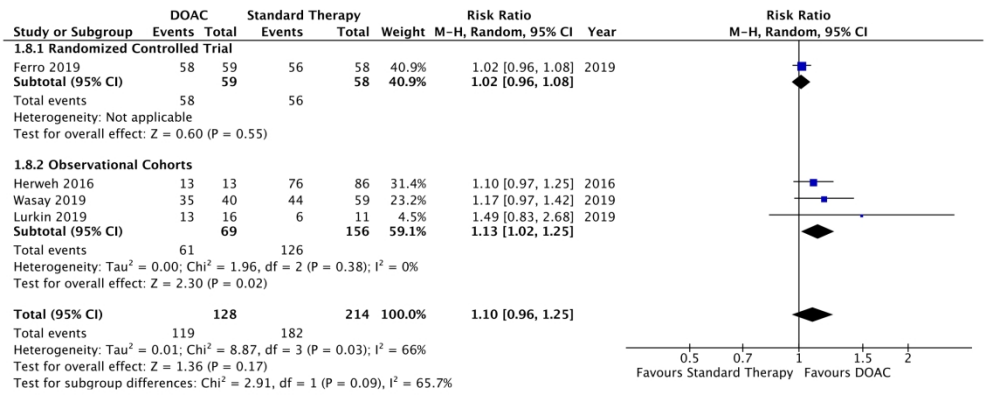

Figure 3. Forest plot comparing favourable functional outcome of modified Rankin Scale (mRS) of 0 to 2 between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin) for cerebral venous thrombosis

199x78mm (300 x 300 DPI)

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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4. Department of Neurology, University Hospital, University of Heidelberg, Heidelberg, Germany

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/
8. Factor Xa Inhibit*.tw.
9. exp *thrombin inhibitor/ or thrombin* inhibit*.tw.
10. or/1-9
11. exp cerebral sinus thrombosis/ or *occlusive cerebrovascular disease/
12. ((sinus* or sinovenous or cerebral or cavernous or sagittal venous or sagittal vein* or cerebrovenous or cerebro-venous or sigmoid) and thrombo*).tw.
13. (intracran* adj3 thrombo*).tw.

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

Appendix II: Forest Plots

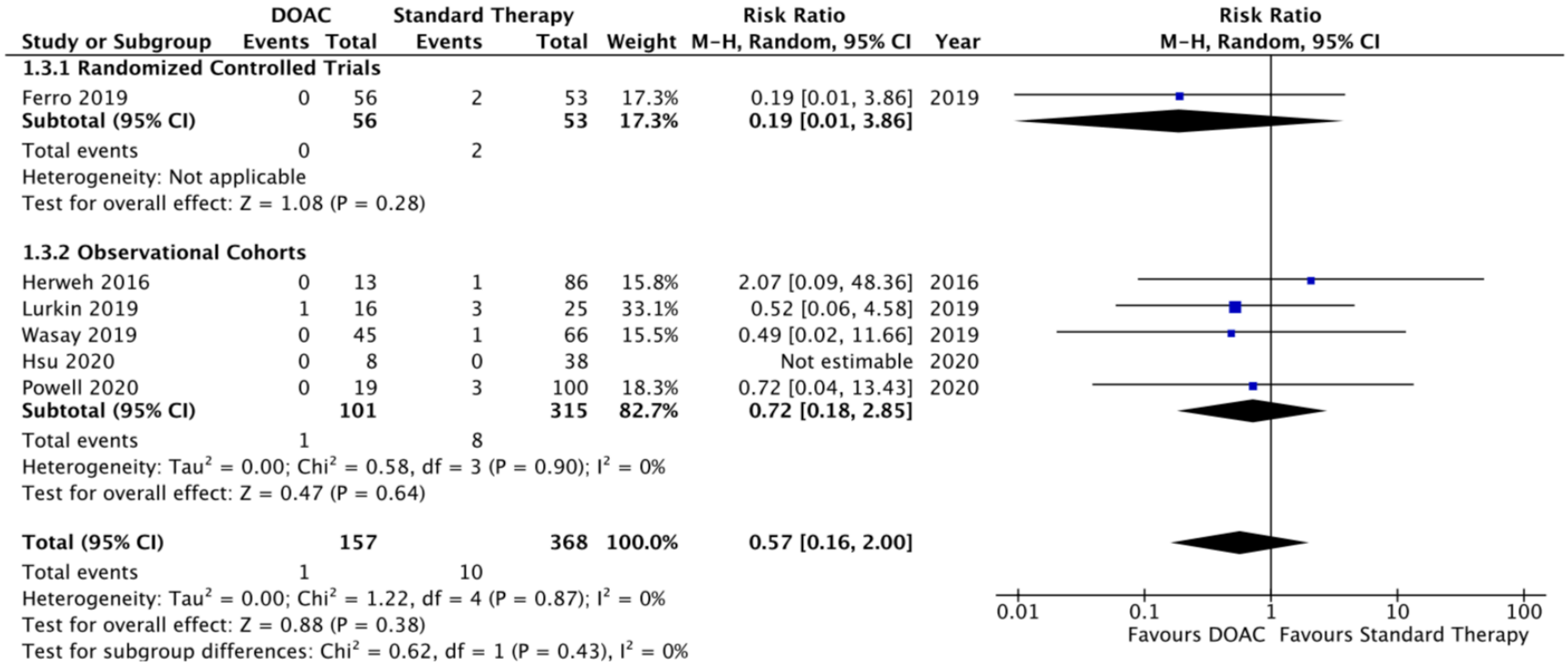

Figure s1. Forest plot comparing intracranial hemorrhage (ICH) between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin) for cerebral venous thrombosis

Appendix II: Forest Plots

Study or Subgroup	DOAC Events	DOAC Total	Standard Therapy Events	Standard Therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.7.1 Randomized Controlled Trial							
Ferro 2019	0	60	0	60		Not estimable	2019
Subtotal (95% CI)		**60**		**60**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.7.2 Observational Cohorts							
Herweh 2016	0	0	0	0		Not estimable	2016
Lurkin 2019	0	16	3	11	36.3%	0.10 [0.01, 1.78]	2019
Wasay 2019	0	0	0	0		Not estimable	2019
Powell 2020	2	19	10	100	63.7%	1.05 [0.25, 4.43]	2020
Hsu 2020	0	0	0	0		Not estimable	2020
Subtotal (95% CI)		**35**		**111**	**100.0%**	**0.45 [0.05, 4.40]**	
Total events	2		13				
Heterogeneity: $Tau^2 = 1.59$; $Chi^2 = 2.19$, df = 1 (P = 0.14); $I^2 = 54\%$							
Test for overall effect: Z = 0.69 (P = 0.49)							
Total (95% CI)		**95**		**171**	**100.0%**	**0.45 [0.05, 4.40]**	
Total events	2		13				
Heterogeneity: $Tau^2 = 1.59$; $Chi^2 = 2.19$, df = 1 (P = 0.14); $I^2 = 54\%$							
Test for overall effect: Z = 0.69 (P = 0.49)							
Test for subgroup differences: Not applicable							

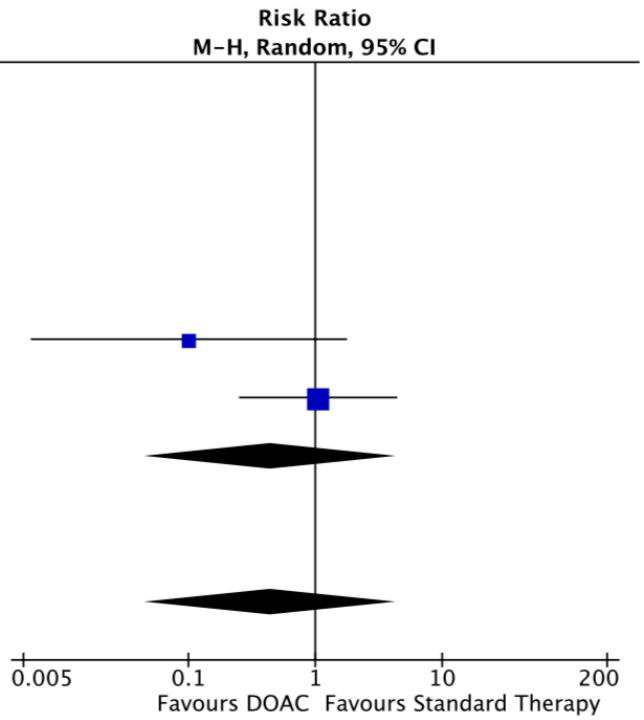

Figure s2. Forest plot comparing recurrent cerebral venous thrombosis (CVT) between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin)

Appendix II: Forest plots

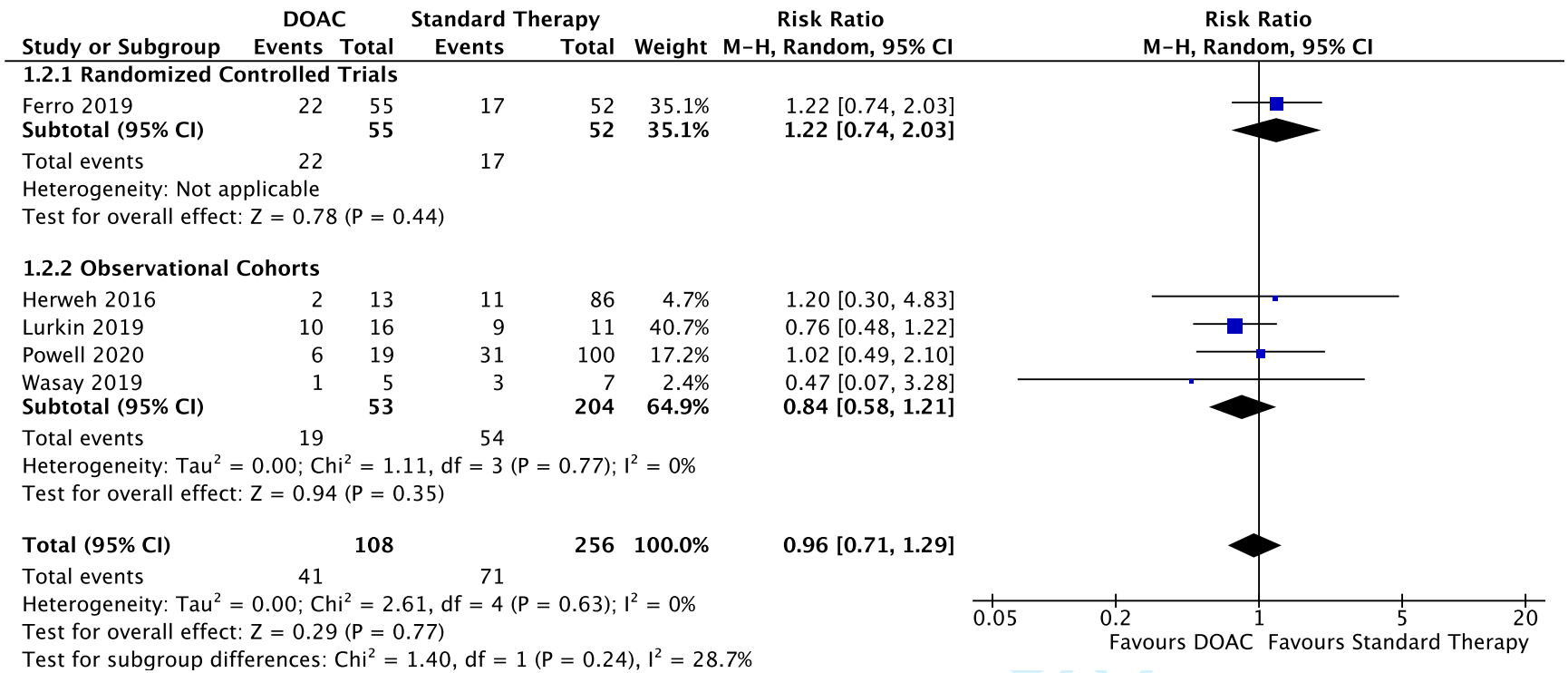

Figure s3. Forest plot comparing incomplete recanalization for cerebral venous thrombosis (CVT) between direct oral anticoagulant (DOAC) and standard therapy (warfarin, low molecular-weight heparin, or unfractionated heparin)

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

Supplemental references

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Bose G, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review. *PRISMA Checklist*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study	5

		authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 and 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6 and 7

Bose G, et al. Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review. *PRISMA Checklist*

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6 and Appendix II
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-12, table 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13 and Appendix II
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-12, Figure 2-3, and

			supp. Figure s1-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10 and figures.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11, Appendix II
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data);	19

		role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Synthesis Without Meta-analysis (SWiM) reporting items

The citation for the Synthesis Without Meta-analysis explanation and elaboration article is: Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020;368:l6890 http://dx.doi.org/10.1136/bmj.l6890

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	5 & 6	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	5	Protocol search date was updated
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	6& 7	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	6 (risk of bias & pooling descriptive statistics) 14 (no meta-analysis comparison for DOAC treatment)	
4 Criteria used to prioritise results for	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	5 search criteria 6 (risk of bias & pooling descriptive statistics)	

Synthesis Without Meta-analysis (SWiM) reporting items

summary and synthesis			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	6	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	6	
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	6	
Results			
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	7-12	
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	16-17	

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Synthesis Without Meta-analysis (SWiM) reporting items

*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL)).