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Systematic Review

Efficacy and Safety of Long-Term Anticoagulation Therapy with Direct Oral Anticoagulants versus Vitamin K Antagonist in Patients with Cerebral Venous Thrombosis

Victor Febriant*, Tracy Solansa

General Practitioner, Department of Neurology Faculty of Medicine Pelita Harapan University, Tangerang, Indonesia

*Correspondence: Victor Febriant (drvictorfebriant@gmail.com)

Abstract: Introduction: Cerebral venous thrombosis is a rare type of stroke caused by partial or complete occlusion of cerebral venous sinuses. Current guidelines recommend the administration of Low Molecular Weight Heparin (LMWH) during the acute phase and oral Vitamin K antagonists (VKAs) such as warfarin for 3-12 months. Direct Oral Anticoagulants (DOACs) are an attractive alternative to VKAs as therapy for CVT, for its safety and efficacy as anticoagulation therapy for deep venous thrombosis or pulmonary embolism. **Method:** This systematic review is written based on PRISMA guidelines with electronic search performed on various databases for journals published from June 1, 2018 to June 1, 2023. **Results:** We found four studies fulfilling the inclusion criteria, with four randomized controlled studies presenting 179 CVT patients treated with DOAC and 150 patients treated with standard therapy. DOACs used in reviewed studies are Dabigatran and Rivaroxaban. **Discussion:** Administration of DOACs as anticoagulation therapy in patients with CVT presents better recanalization rate with no significant differences in efficacy compared with VKAs, along with a better safety profile through similar mortality rate across two groups. **Conclusion:** DOACs as long-term anticoagulation therapy in patients with CVT has better efficacy along with a similar safety profile compared to VKA.

Keywords: Cerebral Venous Thrombosis, DOAC, Vitamin K Antagonist

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1. Introduction

Cerebral venous thrombosis (CVT) is a rare cause of stroke caused by the partial or complete occlusion of the cerebral venous sinus. CVT causes approximately 0.5-1% of all stroke cases worldwide, with incidence of 3-4 per 1 million cases yearly [1, 2]. Current guidelines recommend the administration of Low Molecular Weight Heparin (LMWH) during the acute phase and oral Vitamin K antagonist (VKA) for 3-12 months [8], with an International Normalized Ratio (INR) target of 2.0-30 to prevent CVT recurrence.

Direct oral anticoagulants (DOACs) have shown greater benefits than warfarin as long-term treatment of thromboembolic diseases such as deep vein thrombosis (DVT) and pulmonary embolism (PE) [10]. Benefits of DOACs over warfarin have been reported various times, but as of this writing no guidelines or recommendations have been given for DOACs to be used in daily practice for CVT patients [1, 8]. This systematic review aims to provide further evidence regarding the efficacy and safety of long-term anticoagulation therapy with DOACs as treatment for CVT.

2. Methods

This systematic review is performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Figure 1).

Pubmed, PMC, Google Scholar, and the Cochrane Library are systematically searched with a timespan of June 1st, 2018 until June 30th, 2023. Keywords used during the search are "direct oral anticoagulants" and "cerebral venous thrombosis". (Figure 1)

Eligible studies admitted to this systematic review are in accordance to predetermined inclusion criterias as follows: 1) the studies conducted being randomized controlled trials (RCT); 2) subjects have a confirmed diagnosis of CVT; 3) studies in which patients receive direct oral anticoagulant drugs as anticoagulation treatment compared with warfarin; 4) studies on which the clinical/functional outcome is reported. The exclusion criteria were as follows a) case reports, conference abstracts or review articles; (b) case control, cross-sectional, retrospective or prospective cohort studies; c) studies that provided no outcomes of interest; d) studies written in languages other than English.

2.1. Data extraction and data analysis

Data extraction from selected studies for the purposes of being admitted to this review was done by two reviewers. Extracted data from studies included age, sex, and medical history; information regarding DOAC administered, dosage, time to initiation of anticoagulant, and duration of therapy. Safety outcomes assessed are recanalization rate after administration of DOAC, and occurrence of both intracranial or extracranial bleeding. Efficacy outcomes assessed are functional outcome after administration of DOAC or other anticoagulants during the follow up period, and mortality rate after intervention.

2.2. Quality Assessment (Risk of Bias Analysis)

The quality of studies included was assessed using the Cochrane Risk of Bias Tool 2.0 for randomized controlled trials. This tool evaluates five items: randomization process, deviations from intended intervention, missing outcome data, measurement of outcome, and selection of reported results.

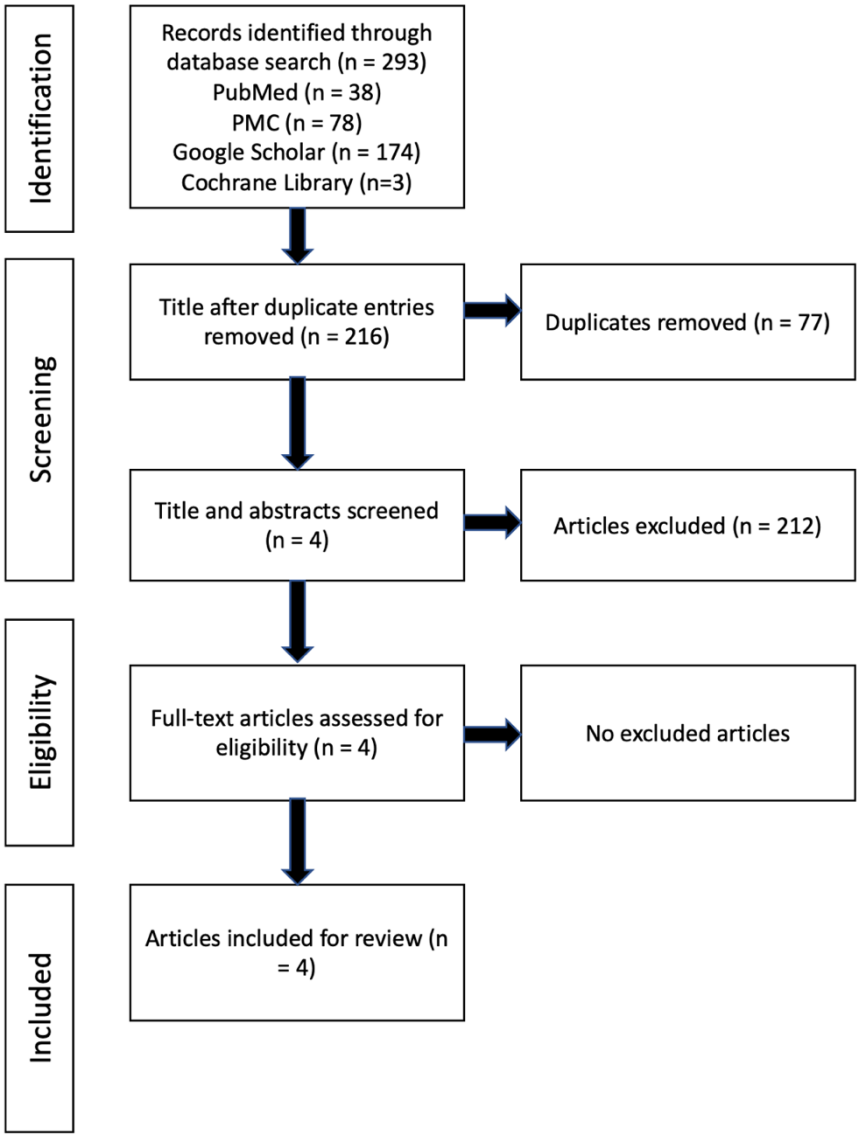

Figure 1. PRISMA flow diagram of studies included.

Study	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results
Ferro et al (2019)					
Connor et al (2020)					
Khorvash et al (2021)					
Masqood et al (2021)					

Figure 2. Risk of Bias of included studies

3. Results

3.1. Search Results

From 293 identified results, 4 randomized controlled trial (RCT) studies were included after fulfilling inclusion criteria, with 179 patients treated with DOAC and 150 patients treated with the standard therapy (Table 1). In four reviewed RCT studies, one study with 60 patients were administered dabigatran and 119 patients treated with rivaroxaban. Anticoagulants administered along with duration of administration, efficacy outcome, and safety are presented on Table 2.

Table 1. Characteristics of studies included in the review

Study (Year of Publication)	Study Design	Sample Size	Location	Age, years	Female (%)	Duration of Anticoagulation	Follow-up Duration
Ferro et al (2019)	Randomized Controlled Trial	60 Warfarin 60 Dabigatran	Multicenter	45,2 ± 13.8	33 (55%) 33 (55%)	5.15 months	3 months
Connor et al (2020)	Randomized Controlled Trial	41 Standard Anticoagulation 73 Rivaroxaban	Multicenter	Pediatric Population (<18 years)	18 (44%) 27 (37%)	3 months	3 months
Khorvash et al (2021)	Randomized Controlled Trial	25 Warfarin 25 Rivaroxaban	Iran	40.76 ± 11.72 41.20 ± 11.35	19 (76%) 17 (68%)	3 months	6 months
Masqood et al (2021)	Randomized Controlled Trial	24 Warfarin 21 Rivaroxaban	Pakistan	27 years 26 years	19 (79%) 18 (86%)	3-12 months	12 months

3.2. Dabigatran

A total of 60 patients with CVT diagnosis were administered Dabigatran. In a multicenter RCT study by Ferro et al,[4] patients with CVT were administered LMWH or unfractionated heparin (UFH) for 5-15 days, followed by the administration of dabigatran 150 mg BID for 24 weeks. During the three month follow up period, no new intracranial bleeding was found on the dabigatran group, whereas two new intracranial bleeding were found on the warfarin group. Recanalization rate is slightly better on the warfarin group with 35 patients (67%) compared with 33 patients (60%) on the dabigatran group. Functional outcome after the follow-up period was found to be better on the dabigatran group with mRS 0-2 found on 98,3% of patients (56 out of 59), compared with 96.6% of patients (56 out of 58) on the warfarin group. Regarding the safety of anticoagulants observed, no mortality was reported on both groups in the study conducted by Ferro *et al*. [4].

3.3. Rivaroxaban

Rivaroxaban was administered as anticoagulation therapy on three of the reviewed studies, with a total of 209 patients upon which 119 patients were administered rivaroxaban as anticoagulation therapy. In a multicenter RCT by Connor et al, patients with CVT were given an initial anticoagulation therapy of either UFH, LMWH, or fondaparinux for 5-9 days followed by the administration of rivaroxaban in a form of tablet or oral suspension. During the three-month follow-up period, no new intracranial bleeding was found on the rivaroxaban group, whereas one new intracranial bleeding was found on the heparin/VKA group. Recanalization rate is found to be better on the rivaroxaban group with 57 out of 73 patients (78%) achieving partial or complete recanalization post intervention.

During follow-up period, functional outcome assessed as the presence of recurrent CVT or new bleeding was found on 2 patients (4.9%) on the heparin/VKA group compared to zero occurrence on the rivaroxaban group. No mortality was reported on both groups in the study by Connor *et al*. [5].

Table 2. Characteristics of reviewed studies

Study (Year)	Anticoagulant	Time to initiation of AC (days)	Duration of AC	Recanalization	No Recanalization	Any Bleeding	New Intracranial Hemorrhage	Functional Outcome	Mortality
Ferro et al (2019)	Warfarin	5-15	5.15	35 (67%)	17 (33%)	12 (20%)	2(3.8%)	mRS 0-2: 56 (96.6%) mRS 3-5: 2 (2.3%)	0 (0%)
	Dabigatran			33 (60%)	22 (40%)	12 (20%)	0 (0%)	mRS 0-2 :58 (98.3%) mRS 3-5: 1 (1.7%)	0 (0%)
Connor et al (2020)	Heparin/VKA	5-9	3	30 (73%)	11 (27%)	1 (2.4%)	1 (2.4%)	Recurrent CVT/Hemorrhage: 2 (4.9%)	0 (0%)
	Rivaroxaban			57 (78%)	16 (22%)	5 (6.8%)	0 (0%)	Recurrent CVT/Hemorrhage: 0 (0%)	0 (0%)
Khorvash et al (2021)	Warfarin	2	3	NR	NR	0 (0%)	On Admission: 7 (28%) Month 3: 0 (0%) Month 6:0 (0%)	mRS On Admission: 3 (2.0, 4.0)[1] Month 3: 1 (0, 2.0)[1] Month 6: 0 (0, 2.0)[1]	0 (0%)
	Rivaroxaban					1 (4%)	On Admission::2 (8%) Month 3:1 (4%) Month 6:(0%)	mRS On Admission:: 3 (1.5, 4.0)[1] Month 3: 1 (0, 1.0)[1] Month 6: 0 (0, 1.0)[1]	0 (0%)
Masqood et al (2021)	Warfarin	5	3-12	Month 3 17 (71%) Month 6 20 (83%) Bulan ke-12 24 (100%)	Month 3 7 (29%) Month 6 4 (17%) Month 12 0 (0%)	6 (25%)	2 (8%)	NIHSS[2] Month 3 NIHSS 0: 21 (88%) NIHSS 1-4: 3 (12%) Month 6 NIHSS 0: 23 (96%) NIHSS 1-4: 1 (4%)	0 (0%)
	Rivaroxaban			Month 3 15 (71%) Month 6 18 (86%) Month 12 21 (100%)	Month 3 6 (29%) Month 6 3 (14%) Month 12 0 (0%)	2 (10%)	0 (0%)	Month 3 NIHSS 0: 20 (95%) NIHSS 1-4: 1 (5%) Month 6 NIHSS 0: 20 (95%) NIHSS 1-4: 1 (5%)	0 (0%)

[1] Data is shown as Median (first quartile, third quartile)

[2] Data is reported as NIHSS (National Institutes of Health Stroke Scale)

Abbreviations: AC, Anticoagulation; CVT: Cerebral Venous Thrombosis; LMWH: Low Molecular Weight Heparin; UFH, Unfractionated Heparin; mRS, Modified Rankin Scale; NR: Not Reported; VKA, Vitamin K Antagonist

A RCT study conducted by Khorvash et al in Iran [6], patients with CVT were administered enoxaparin 60mg subcutaneously BID on the first two days, continued with oral warfarin or rivaroxaban daily for the following three months. On initial anticoagulant administration, 2 occurrences (8%) of new intracranial bleeding were found on the rivaroxaban group whereas 7 (28%) new occurrences were found on the warfarin group. During the follow-up period of the sixth month, no new occurrences of intracranial bleeding was found on both groups. Recanalization rate was not reported by this study. Functional outcome reported as improvement of mRS was found to be similar on both groups of rivaroxaban and warfarin. No mortality was reported on both groups in the study by Khorvash *et al*. [6].

In a RCT study conducted by Masqood et al in Pakistan [7], patients with CVT were administered UFH or enoxaparin 1 mg/kg of weight for 5-12 days, continued with oral rivaroxaban 15 mg BID for three weeks continued with rivaroxaban 20 mg QD for 3-12 months in one group and warfarin titrated with INR target of 2-3 on the warfarin group. Recanalization rates on both rivaroxaban and warfarin groups were found to be similar after 12 months. No new intracranial bleeding was observed on the warfarin group and two occurrences of new intracranial bleeding was found on the rivaroxaban group during the follow up period. Functional outcome reported as NIHSS improvement was found to be similar on both groups, as well as no mortality was reported on both rivaroxaban and warfarin groups in the study by Masqood et al. [7].

4. Discussion

Administration of VKA such as warfarin is recommended by recent guidelines as treatment for CVT. Nevertheless, routine observation of INR, drug to drug interaction, food to drug interaction, as well as risk of hemorrhage presents a challenge to this treatment.[9] On the contrary, administration of DOAC does not need any routine checks of INR and dosing adjustments, while also providing a similar safety and efficacy profile in the treatment of venous thrombosis with comparable hemorrhage and mortality rate.[9] Therefore, administration of DOAC as a choice of treatment in CVT is being considered. However, due to low incidence rates of CVT, a large-scale RCT to compare between DOACs and VKA remains to be challenging.

From the four reviewed studies, initiation of anticoagulation therapy with LMWH or UFH during the acute phase for 2-15 days, followed by oral anticoagulation therapy with DOAC or VKA in the study by Khorvash et al after 2 days of acute phase anticoagulation therapy. Whereas three other studies (Ferro et al, Connor et al, Masqood et al) initiated oral anticoagulation within 5-15 days after acute phase therapy [4, 5, 7].

In our review, we found that recanalization rate is found to be better on the DOAC group with no significant differences between two groups in terms of functional outcome. In terms of safety assessed by incidence of new intracranial hemorrhage, DOAC has less incidence compared to the VKA group, as well as a similar low mortality rate on both groups.

Comparison between recanalization rate between dabigatran and rivaroxaban within the DOAC group, rivaroxaban shows a better recanalization rate when compared to dabigatran. Rivaroxaban itself is easier to administer when compared to dabigatran as once per day administration is required compared to twice daily with dabigatran. Nevertheless, further RCT with greater number of participants and scale is still needed to further assess the benefits of DOAC administration as long-term coagulation therapy on CVT.

5. Conclusion

In conclusion, our review found that administration of DOAC as long-term anticoagulation therapy on CVT patients to have similar efficacy and safety profile when com-

pared to VKA, along with a better recanalization rate and lower consequence new intracranial bleeding. Thus, DOAC can be used as a viable alternative therapy for CVT patients for long term anticoagulation therapy.

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