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Letter to the Editors-in-Chief

Apixaban and rivaroxaban in patients with cerebral venous thrombosis

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Cerebral venous thrombosis (CVT) affects approximately 15 people per million annually and represents 0.5% of all stroke [1,2]. Initiation of anticoagulation with heparin followed by warfarin is currently the standard of care, after confirmation of diagnosis with computed tomography (CT) or magnetic resonance (MR) venography [3]. Apixaban and rivaroxaban have been shown to be non-inferior to warfarin for the treatment of deep vein thrombosis and pulmonary embolism [4,5]. However, only case reports and small case series have described their use in patients with CVT.

Given the paucity of reports we hereby summarize our experience using apixaban and rivaroxaban for treatment of CVT. We have used ICD-9 325 and ICD-10 G08 codes, and identified 236 patients who were diagnosed with CVT at Cleveland Clinic between December 2013 and February 2018. Manual chart review was performed for all patients using electronic medical records to confirm the diagnosis and exclude patients who underwent mechanical thrombectomy and patients who did not have follow-up MR or CT venography. Out of 72 patients who met these criteria, 63 (87%) were treated with either warfarin or enoxaparin. Whereas, 9 (13%) patients preferred either apixaban or rivaroxaban to avoid frequent blood tests and injections. All patients underwent MR or CT venography to establish the diagnosis, initially received therapeutic unfractionated heparin, and underwent thrombophilia workup including factor V Leiden mutation test, protein C and S, antithrombin activity, antiphospholipid antibody, and prothrombin gene mutation at diagnosis while on unfractionated heparin. Patient 3 and 4 underwent repeat thrombophilia testing in 3 months to confirm abnormal results. Clinically significant bleeding was defined as bleeding that associated with medical intervention such as temporary cessation of anticoagulation.

Nine subjects were identified, 7 (78%) were female and median age was 56 (range: 34 – 89). Patient 3, 4, and 7 were diagnosed with elevated factor VIII level, lupus anticoagulant, and heterozygous prothrombin G20210 mutation, respectively. Patient and treatment characteristics were summarized in Table 1. No patients had clinically significant bleeding while on apixaban or rivaroxaban and no thromboembolic event was occurred during median follow-up of 12 months.

Five patients (Patients 1 – 5) were committed to long-term anticoagulation with apixaban. Only patient 2 had lower gastrointestinal bleeding 15 days after being discharged with warfarin, then warfarin was switched to apixaban. All other patients were started on apixaban within median of 4 days after heparin and did not receive other oral anticoagulants. Follow-up MR/CT venography after median of 2 months (range: 1 – 18) from initiation of anticoagulation showed that no patient achieved complete recanalization, 2 (40%) patients achieved partial recanalization, and 3 (60%) patients did not have recanalization.

Four patients (Patients 6 – 9) received rivaroxaban. Patient 6 was started on rivaroxaban 30 days after being discharged with warfarin due to inability to maintain INR within therapeutic range. Other patients were solely treated with rivaroxaban after 1 to 3 days of heparin. Follow-up MR/CT venography after a median of 3 months (range: 1 – 7) from initiation of anticoagulation showed that 3 (75%) patients achieved complete recanalization, whereas 1 (25%) patient did not have recanalization.

Herweh et al. have analyzed 99 patients with CVT and did not find any association between recanalization status and outcome. Thirteen (13%) out of 99 patients received direct oral anticoagulants, however outcomes of these patients were not separately reported [6]. Efficacy of apixaban in CVT has been described only in two case reports/series and all 4 patients in both studies attained complete or partial recanalization [7,8]. Similarly, high recanalization rates have been reported in small case series for rivaroxaban [9,10]. Mendonca et al. have reported that 12 (80%) out of 15 CVT patients who were treated with dabigatran achieved partial or complete recanalization at follow-up imaging [11]. Currently, one randomized clinical trial to compare dabigatran with warfarin in patients with CVT has completed enrollment [12]. The median age was higher in our cohort compared to previous studies which may play a role for half of our patients who did not have recanalization. As previously noted, low recanalization rate was not predictive of worse outcome in this study, given that 8 (89%) patients had modified Rankin scale of 0 to 1 at six-month follow-up [13].

Our study has many limitations, mainly related to single-center retrospective nature of the study design with small number of patients. Heterogeneous timing of follow-up imaging may have influenced the rate of recanalization. Nevertheless, our data provide new insights into the use of apixaban and rivaroxaban for patients with CVT, especially in

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Table 1
Patient and treatment characteristics.

Characteristics	Patient no								
	1	2	3	4	5	6	7	8	9
Baseline characteristics									
Age at diagnosis	79	74	34	46	77	41	89	56	42
Female gender	N	Y	Y	Y	Y	Y	N	Y	Y
Body mass index at diagnosis	31	26	29	38	23	26	27	49	54
Smoking at any time	Y	N	Y	Y	N	Y	Y	N	Y
Creatinine clearance > 50 mL/min	Y	Y	Y	Y	Y	Y	Y	Y	Y
Antiplatelet therapy	Y	Y	Y	Y	N	N	Y	N	N
Risk factors for thrombosis									
Oral contraceptive use	N	N	N	Y	N	Y	N	N	N
Thrombophilia	N	N	Y	Y	N	N	Y	N	N
Active malignancy	N	Y	N	N	N	N	N	N	N
Meningitis	N	N	N	N	N	N	N	N	Y
Chronic inflammatory disorder	N	N	Y	N	N	N	N	N	N
Previous thromboembolic event	Y	N	N	N	N	N	N	Y	N
Clinical presentation									
Headache	Y	Y	Y	Y	N	Y	Y	Y	Y
Focal neurologic deficit	N	N	Y	N	Y	Y	Y	N	N
Visual problems	N	N	N	Y	Y	Y	N	Y	N
Seizures	N	N	N	N	Y	Y	N	N	N
Aphasia	N	N	N	N	Y	N	N	N	N
Affected vessel									
Transverse sinus	Y	Y	Y	Y	Y	Y	Y	N	Y
Internal jugular vein	Y	Y	Y	Y	N	Y	Y	N	N
Sigmoid sinus	Y	Y	Y	Y	N	N	Y	N	N
Superior sagittal sinus	N	N	Y	Y	Y	N	N	Y	N
Straight sinus	N	N	N	N	Y	N	N	Y	N
Brain lesion									
Hemorrhage	N	N	N	N	Y	Y	N	N	N
Venous infarction	N	Y	N	N	Y	Y	Y	Y	Y
Modified rankin scale on diagnosis	1	1	1	1	4	2	4	1	3
Modified rankin scale at discharge	0	0	1	1	4	1	0	1	0
Duration of hospital stay	3	3	4	4	24	3	3	7	4
Anticoagulation									
Time to start DOAC after diagnosis, day	1	18	1	4	7	30	1	3	1
Duration of DOAC, month	12	56	29	6	9	14	3	12	3
Clinically significant bleeding during anticoagulation	N	Y	N	N	N	N	N	N	N
Recanalization									
Time to follow-up imaging, month	2	1	18	3	1	3	7	3	1
Complete recanalization	N	N	N	N	N	Y	N	Y	Y
Partial recanalization	N	Y	N	Y	N	N	N	N	N
No recanalization	Y	N	Y	N	Y	N	Y	N	N

DOAC: direct oral anticoagulants, Y: yes, N: no.

elderly population. Larger, prospective studies are needed to verify these findings.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Author contributions

FC, HD contributed conception and design of study; FC, TK, OP, and MF collected the data; FC wrote the first draft of the manuscript. All authors contributed to manuscript revision and approved the submitted version.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

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