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ORIGINAL ARTICLE



# Use of oral rivaroxaban in cerebral venous thrombosis

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**ABSTRACT**

**Background:** Cerebral venous thrombosis (CVT) is an uncommon cause of stroke in humans and the mainstay of treatment is anticoagulation unless contraindicated. Non-vitamin K oral anticoagulants have not been duly evaluated in randomized controlled trials in CVT.

**Objective:** To compare the efficacy and safety of oral rivaroxaban with vitamin K anticoagulant (warfarin) in preventing recurrent venous thromboembolism (VTE) in patients with CVT.

**Methods:** Adult patients with CVT, who were stable after 5–12 days of treatment with parenteral heparin 1 mg/kg, were screened for eligibility. The patients were randomly divided into two groups to receive oral rivaroxaban 20–30 mg daily or warfarin 1, 3 or 5 mg daily (with the dose adjusted to maintain an INR of 2–3), for 3–12 months. Recanalization rates, periprocedural complications, and clinical outcomes were assessed by Magnetic Resonance Venography (MRV) and National Institutes of Health Stroke Scale (NIHSS) at 3rd, 6th and 12th month follow-ups.

**Results:** In total, 45 patients with CVT were randomized to the two treatment groups (21 to rivaroxaban and 24 to warfarin). Overall recanalization was achieved by 18 (86%) and 20 (83%) cases from rivaroxaban and warfarin group, respectively at 6th month follow-up; and by all 45 (100%) cases from the both groups at 12th month follow-up. Excellent outcome (NIHSS score 0) was obtained by 20 (95%) cases from rivaroxaban group at 3rd to 12th month follow-ups; and by 23 (96%) cases at 6th to 12th month follow-ups. There were no major bleeding events during the trial. None of the patients developed recurrence of thrombosis. Statistically, no significant difference between the two treatment groups in terms of recanalization and clinical outcomes could be observed.

**Conclusion:** Rivaroxaban is a safe option in CVT however; larger randomized controlled studies will impact the results validity.

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**KEYWORDS**
Rivaroxaban; cerebral venous thrombosis; anticoagulation; recanalization; vitamin K antagonist

## Introduction

Cerebral venous thrombosis (CVT) is a rare cause of stroke in the general population, accounting for about 0.5–1% of all strokes[1]. Annual occurrence is estimated to be 3–4 cases per one million. It occurs three times more frequently in women, especially during pregnancy and with use of hormonal contraceptives, reaching up to 12 cases per one million deliveries[2]. Risk factors of CVT are different from that of ischemic stroke, with pregnant or postpartum women having 3.5 times higher risk of developing CVT than non-pregnant or postpartum women of similar age[3,4]. Recommended treatment of CVT is anticoagulation unless contraindicated, initially with intravenous unfractionated heparin (UFH) or low molecular weight heparin (LMWH) i.e. enoxaparin, subcutaneously. Subsequently, long term treatment is oral vitamin k antagonist (VKA) warfarin for 3–12 months[5–7]. Warfarin is a conventional oral anticoagulant, commonly used to treat blood clots such as deep vein thrombosis and pulmonary embolism, and to prevent stroke in people who have atrial fibrillation, valvular heart disease or artificial heart valves[8]. Warfarin is contraindicated in pregnancy, as it passes through the placental barrier and may cause bleeding in the fetus leading to spontaneous abortion, stillbirth, neonatal death, and preterm birth[9]. Nevertheless, in order to achieve maximal protection against stroke and to minimize bleeding complications, warfarin therapy must be tightly controlled and maintained within a narrow therapeutic range of international normalized ratio (INR) values between 2 and 3. This task is not easy to achieve as INR levels are known to be influenced by several factors including patient's age, concurrent medications, genetic makeup, herb consumption, and diet[10,11]. As a result, oral anticoagulant therapy requires regular monitoring, which can be inconvenient for patients and healthcare providers. The large inter-and intra-individual variability in patients' responses makes warfarin therapy difficult to control, and this increases the risk of bleeding or thrombosis[12]. Rivaroxaban is a new oral anticoagulant that directly inhibits factor Xa and it may give more predictable and consistent anticoagulation than warfarin[13,14].

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Rivaroxaban has been reported to prevent venous thromboembolism more effectively than enoxaparin followed by warfarin in orthopedic surgery, in studies conducted on established venous thrombosis patients[15,16]. In acute phases, it is necessary to balance the risk of hemorrhage and thrombosis, as venous infarct is commonly associated with hemorrhage[17]. Information regarding the use of newer oral anticoagulant i.e. rivaroxaban in CVT is meager and mostly based on studies of small sample size[18–20]. Patel et al. documented the use of rivaroxaban in atrial fibrillation, indicating its better effect in lowering the rate of major & minor bleeding and intracranial hematoma, as compared to warfarin[21]. A couple of other reports have presented encouraging data on the use of rivaroxaban in CVT[19,22].

At our institute (Lahore General Hospital, Pakistan), a significant number of patients are enrolled with CVT. This study was aimed to systematically review, in patients with CVT, the recanalization rate and its association with clinical outcome and CVT recurrence.

## Methods

### Study participants

A single-center prospective study on the efficacy and safety of oral rivaroxaban for the treatment of recurrent venous thromboembolism (VTE) was performed at Lahore General Hospital (LGH), Lahore, Pakistan. The study participants included patients diagnosed with thrombosis of the dural sinus and/or cerebral veins, enrolled from May, 2017 to May, 2018. The study was approved by the ethical committee of the institute. All patients provided written informed consent prior to enrollment in the trial. The patients were between 18 and 60 years of age and fulfilling the inclusion criteria of the study i.e. patients were clinically stable after the initial treatment with parenteral heparin. The exclusion criteria were: unable to take oral medication, major or life threatening bleeding in last 6 months, preceding episode of VTE which required treatment with an anticoagulant, current or active malignancy, CVT associated with sepsis or central nervous system infection, planned surgical procedure for CVT, kidney disease with creatinine clearance rate below 30 ml/min, traumatic patients and comorbid conditions including renal failure, heart failure and cirrhosis. Screening and randomization was done after initial parenteral anticoagulation (from 5 to 12 days, keeping in view the patients' clinical stability) with unfractionated or low molecular weight heparin (enoxaparin 1 mg/kg body wt.), as shown in Table 1. The patients were divided into two groups randomly i.e. (1) patients admitted on odd date were enrolled in rivaroxaban or non-vitamin K oral anticoagulant (NOAC) group; and (2) those admitted on even date, in vitamin K oral anticoagulant (VKA) group. NOAC group patients were given oral rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily for 3–12 months. VKA group patients were treated with warfarin at a dose to maintain INR between 2 and 3. Warfarin was apportioned in 1 mg, 3 mg or 5 mg tablets and taken once daily for 3–12 months. Bleeding complications were managed according to the standard protocols. Patients from NOAC group who developed bleeding, were given half dose (i.e. 10 mg once daily) throughout the treatment period. Diagnosis was made with a clinical presentation consistent with CVT, and confirmed by Magnetic Resonance Imaging (MRI) and Magnetic Resonance Venography (MRV) of the brain. At screening, MRI and MRV neuroimaging was performed for the diagnosis of CVT and baseline brain lesions i.e. hemorrhage, brain edema and venous infarct. MRI and MRV neuroimaging was repeated at 3rd, 6th and 12th months during follow-up period. All the neuroimaging was reviewed by two consultant radiologist, blind to the treatment groups and clinical data.

### Outcome and relevant variables

The primary outcome was recanalization rate that was assessed by MRV at 3, 6 and 12-month follow-ups, by two expert consultant radiologists who were blind to the intervention. The secondary outcome (i.e. clinical outcome, recurrence of thrombosis and complications of the treatment) was assessed by "National Institute of Health Stroke Scale (NIHSS)" scoring, which ranges from 0 (minimum) to 42 (maximum). The 0 score represents for no stroke symptoms (defined as an excellent clinical outcome); 1–4 score represents minor stroke; 5–15 shows moderate stroke; 16–20 represents moderate to severe stroke; and 21–42 represents severe stroke at admission, discharge, and follow-up visits (i.e. 3 months, 6 months and 1 year). Complications like allergy or urticaria, abdominal discomfort, skin necrosis, alopecia, elevated liver enzyme, thrombocytopenia and bleedings events (major or minor) were monitored. Major bleeding is defined as the bleeding that is fatal or overt bleeding with a drop in hemoglobin level to at least 20 g/L or requiring transfusion of at least 2 units packed blood cells, or hemorrhage into a critical anatomical site (e.g. intracranial, retroperitoneal)[23]. Minor bleeding can be divided into two categories i.e. clinically relevant non–major bleeding; and clinically non-relevant non–major bleeding. Clinically relevant non-major bleeding is further defined as overt bleeding, not meeting the standards of major bleeding but associated with medical intervention. All relevant clinical data, symptoms, neurological deficit, demographic profile, risk factors and affected vessels were also recorded. All patients were screened for acquired and congenital thrombophilia, including: Factor V Leiden mutation, protein S, protein C and antithrombin III deficiency, lupus anticoagulant (LAC), anticardiolipin antibodies and hyperhomocysteinemia. Use of oral contraceptive pills (OCPs) was carefully noted and considered if the patients were currently on hormone therapy or had been taking for one month before enrollment. Hydration status was checked with skin turgor, mucous membrane, exposure to excessive sunlight, blood pressure, sitting and lying position, and weight of patient before and after rehydration.

### Statistical analysis

SPSS (v.22) software was used for all statistical analyses. Percentage of recanalization in terms of partial or complete,

**Table 1.** Demographic, clinical, and imaging features of the study participants.

| Baseline characteristics | All patients $N = 45$ | Rivaroxaban $N = 21$ | Warfarin $N = 24$ | $p$-Value |
|---|---|---|---|---|
| AGE (mean, min-max) | 25.3 (15–45) | 26 (15–36) | 27 (15–45) | |
| GENDER | | | | |
| Male | 08 (18%) | 03 (14%) | 05 (21%) | |
| Female | 37 (82%) | 18 (86%) | 19 (79%) | |
| RISK FACTOR | | | | |
| OCP | 08 (18%) | 03 (14%) | 05 (21%) | .613 |
| Anemia | 13 (29%) | 06 (29%) | 07 (29%) | |
| Dehydration | 06 (13%) | 04 (19%) | 02 (08%) | |
| Pregnancy/Puerpureum | 22 (49%) | 10 (48%) | 12 (50%) | |
| Unknown Factor | 07 (16%) | 03 (14%) | 04 (17%) | |
| Thrombophilia | 04 (09%) | 01 (05%) | 03 (13%) | |
| CLINICAL PRESENTATION | | | | |
| Headache | 40 (89%) | 18 (86%) | 22 (92%) | .531 |
| Vomiting | 36 (80%) | 17 (81%) | 19 (79%) | .883 |
| Seizure | 23 (51%) | 11 (52%) | 12 (50%) | .875 |
| Aphasia | 18 (40%) | 08 (38%) | 10 (42%) | .809 |
| Visual Symptom | 05 (11%) | 02 (10%) | 03 (13%) | .754 |
| Altered Sensorium | 28 (62%) | 13 (62%) | 15 (63%) | .968 |
| Paresis or Motor Dysfunction | 29 (64%) | 14 (67%) | 15 (63%) | .773 |
| Papilledema | 23 (51%) | 11 (52%) | 12 (50%) | .875 |
| AFFECTED VESSEL | | | | |
| Superior Sagital Sinus | 25 (56%) | 12 (57%) | 13 (54%) | .843 |
| Transverse Sinus | 17 (38%) | 08 (38%) | 09 (38%) | .968 |
| Sigmoid Sinus | 13 (29%) | 06 (29%) | 07 (29%) | .965 |
| Straight Sinus | 17 (38%) | 08 (38%) | 09 (38%) | .968 |
| Cortical Vein | 18 (40%) | 08 (38%) | 10 (42%) | .809 |
| BRAIN LESION | | | | |
| Edema | 33 (73%) | 16 (76%) | 17 (71%) | .688 |
| Hemorrhage | 29 (64%) | 14 (67%) | 15 (63%) | .773 |
| Venous infarct | 33 (73%) | 16 (76%) | 17 (71%) | .688 |
| Sign of Intracranial HTN | 28 (62%) | 13 (62%) | 15 (63%) | .968 |
| NIHSS | | | | |
| NIHSS on admission (mean, min-max) >3 | 09 (05–22) | 11 (05–15) | 08 (06–22) | .927 |
| NIHSS on discharge (mean, min-max) (0-1) | 03 (01–04) | 02 (01–08) | 03 (01–04) | .259 |
| HEPARIN | | | | |
| UFH | 03 (07%) | 00 | 03 (13%) | .097 |
| LMWH | 40 (89%) | 21 (100%) | 19 (79%) | |
| Start of OAC (days) mean (min-max) | 05 (05–12) | 05 (05–12) | 05 (05–12) | .573 |
| Duration (months) mean (min-max) | 03 (03–12) | 03 (03–12) | 03 (03–12) | .058 |

OCP: Oral Contraceptive Pills; HTN: Hypertension; NIHSS: National Institute of Health Stroke Scale; UFH: Un-Fractioned Heparin; LMWH: Low Molecular Weight Heparin.

according to the radiologists' findings was calculated. Percentage of clinical outcome was measured by NIHSS. We also calculated the recurrence of thrombosis, complication, and the number of deceased. A calculated $p$-value of a variable by Chi-square and independent $T$-test were used to determine the significant difference between the two treatment groups. $p$-Value $<.05$ was considered as statistically significant.

## Results

Out of 70 patients enrolled in total, 15 were excluded because of the above-mentioned exclusion criteria (i.e. 5 patients were suffering from kidney failure and their creatinine clearance values were less than 30 ml/h; four patients had heart failure and were on dual antiplatelet therapy; and six patients had anti-HCV related chronic liver disease and thrombocytopenia); six patients of NOAC group denied to participate and left cohort; and four patients of VKA group lost the follow-up. Out of 45 participants, 21 were treated with rivaroxaban (NOAC group), while 24 were treated with warfarin (VKA group). Median age was 26 years in the NOAC group and 25.3 years in the VKA group ($p = .705$). Female cases counted for 18 (86%) and 19 (79%) in NOAC and VKA groups, respectively. Risk factors, clinical presentation, affected vessels and brain lesions for both groups are depicted in Table 1. Results from both groups were comparable and statistically no significant differences were observed ($p$-value more than .05). Table 2 shows the outcomes in terms of cerebral venous recanalization (primary outcome), NIHSS score (secondary or clinical outcome), recurrence of thrombosis and complications. Overall recanalization was achieved by 71% ($n = 15$) & 80% ($n = 18$) of the cases from NOAC group at 3 & 6-month follow-ups, respectively; and by 71% ($n = 17$) & 83% ($n = 20$) of the cases from VKA group at 3 & 6-month follow ups, respectively. At 12-month follow-up, overall recanalization was achieved by all (100%) cases from both groups, and no recurrence of thrombo-embolism was observed. NIHSS score 0 (excellent clinical outcome) was recorded in 95% ($n = 20$) of patients from NOAC group at 3, 6 and 12-month follow-ups. On the other hand, 88% ($n = 21$) cases from the VKA group at 3-month follow-up, and 96% ($n = 23$) later at 6 & 12 month follow-ups showed excellent clinical outcome (NIHSS score 0). Before the start of oral anticoagulants treatment, 14 (67%) patients from NOAC group and 15 (63%) from VKA group had intracranial hemorrhage.

**Table 2.** Recanalization rate, periprocedural complications and clinical outcomes.

| VARIABLES | All Patients $N = 45$ | Rivaroxaban $N = 21$ | Warfarin $N = 24$ | *p*-Value |
|---|---|---|---|---|
| RECANALIZATION: | | | | |
| At 3 months | | | | |
| Overall | 32 (71%) | 15 (71%) | 17 (71%) | .377 |
| Partial | 11 (24%) | 03 (14%) | 08 (33%) | |
| Complete | 21 (47%) | 12 (57%) | 09 (38%) | |
| At 6 months | | | | |
| Overall | 38 (84%) | 18 (86%) | 20 (83%) | .598 |
| Partial | 10 (22%) | 04 (19%) | 06 (25%) | |
| Complete | 28 (62%) | 14 (67%) | 14 (58%) | |
| At 12 months | | | | |
| Overall | 45 (100%) | 21 (100%) | 24 (100%) | .754 |
| Partial | 05 (11%) | 02 (10%) | 03 (13%) | |
| Complete | 40 (89%) | 19 (90%) | 21 (87%) | |
| CLINICAL OUTCOMES: | | | | |
| At 3 months | | | | |
| NIHSS score 0 (Excellent outcome) | 41 (91%) | 20 (95%) | 21 (88%) | .368 |
| NIHSS score 1–4 | 04 (9%) | 01 (5%) | 03 (12%) | |
| At 6 & 12 months | | | | |
| NIHSS score 0 (Excellent outcome) | 43 (96%) | 20 (95%) | 23 (96%) | .924 |
| NIHSS score 1–4 | 02 (4%) | 01 (5%) | 01 (4%) | |
| BLEEDING COMPLICATIONS | | | | |
| All bleeding events | 08 (18%) | 02 (10%) | 06 (25%) | .161 |
| Clinically non relevant minor bleeding | 06 (13%) | 02 (10%) | 04 (17%) | |
| Clinically relevant non major bleeding | 02 (4%) | 00 | 02 (8%) | |
| Major bleeding | 00 | 00 | 00 | |

NOAC: New Oral Anticoagulant; NIHSS: National Institute of Health Stroke Scale.

Fortunately, no worsening of hemorrhage or new formation of intracerebral hematoma was seen throughout the follow up period in NOAC patients treated with rivaroxaban. Adverse effects like abdominal discomfort, thrombocytopenia, urticaria, elevated liver enzyme and alopecia were not seen during the 1 year follow-up. Only two (10%) patients showed minor clinically non-relevant non–major bleeding (i.e. bleeding from nose) and no major and/or clinically relevant non–major bleeding was seen in NOAC group. Contrarily, two patients from the VKA group developed clinically relevant non–major bleeding (genitourinary bleeding), and four others observed minor clinically non relevant non–-major bleeding (i.e. two patients blooded from nose and two from gums). Overall, 8 (18%) cases from both groups showed bleeding events (regardless of its severity) i.e. 2 (10%) from NOAC group and 6 (25%) from VKA group (Table 2).

## Discussion

In this trial, we have evaluated the effectiveness and safety of rivaroxaban in CVT patients comparing with warfarin. Our observations in terms of demoghraphic profile, risk factors, neurological lesions, clinical presentation and affected vessels are aren't radically different from the available studies, and are in line with the most important cohort of patients with CVT[24]. Inter-group dissimilarities are not significant in terms of radiological, clinical outcome and clinically relevant major or minor bleeding. After parenteral UFH or LMWH treatment initially for 5–12 days, overall recanalization (partial + complete) was achieved by 18 (86%) patients from NOAC group and by 20 (83%) patients from VKA group at 6-month follow-up; and in all (100%) patients from both the groups at 12-month follow-up. Excellent clinical outcome (NIHSS score 0) was recorded in 20 (95%) and 23 (96%) patients from NOAC and VKA groups, respectively at 6-month follow-up. Only 2 (10%) patients from NOAC group observed minor clinically non-relevant non–major bleeding that was resolved after 6-month treatment. No major and clinically relevant non–major bleeding events occurred among NOAC patients.

Geisbusch et al. have published data of 16 cerebral venous and sinus thrombosis patients, comparing the recanalization status, complications and clinical outcomes of rivaroxaban with warfarin[19]. Overall outcome was excellent in 93.8%, and all patients showed at least partial recanalization. No statistical significant differences were found between the groups, except the use of heparin before start of oral anticoagulation ($p = .03$). One patient in the warfarin and two patients in the rivaroxaban group had minor bleeding ($p = .55$) within the median (range) follow-up of 8 months.

Anticoli et al. have presented data of 6 CVT patients treated with rivaroxaban, showing an excellent outcome in 100% of patients and complete or partial recanalization in 83% at three months follow-up. At 12 months, they observed an excellent outcome in 100% of patients and complete (33%) or partial recanalization (67%) in all cases. There were no bleeding complications (major, clinically relevant non-major, or minor) or recurrent thrombotic events during follow-up visits[20]. In our trial, 2 (10%) patients from NOAC group developed clinically non-relevant minor bleeding that was however, self-resolved and no major intervention was given, except rivaroxaban dose reduction.

Recently, Shankar et al. reported a case study of 21 patients treated directly with rivaroxaban without bridging therapy of heparin[25]. An excellent clinical outcome was observed in 95% of the patients, at an evaluation conducted after 3 months of the treatment, with a complete and partial recanalization in 60% and 40% of the participants,

respectively. Their results were pretty similar to our current data. They recorded no bleeding events during the trial.

Mutgi et al. published an editorial of two patients suggesting that after 3 months of treatment with rivaroxaban, both patients showed partial to complete recanalization. No bleeding or recurrence of thrombosis was observed during the follow-up period. Their observations were also promoting the effective role of rivaroxaban in CVT although the sample size was very small[18]. We found no worsening or recurrence of thrombosis during our trial. These findings suggested that anticaoagulation therapy either with rivaroxaban or warfarin for a period of 6 months or more was related to: a few clinically relevant non major bleeding events; no worsening of baseline hemorrhagic lesions or new intracranial hemorrhage; and less recurrence of thromboembolism in patients with CVT. These observations together with evidence of few bleeding events demonstrates that rivaroxaban is a not inferior to warfarin in combating CVT. Previously documented studies on VTE recurrence in patients with CVT couldn't arbitrate the major bleeding events[26,27].

Role of other newer oral anticoagulants like "dabigatran" in CVT was documented by Jose et al.,[28] comparing the efficacy and safety of dabigatran with warfarin, to treat recurrent venous thromboembolisms in CVT patients. They reported that anticoagulated with either dabigatran or warfarin, CVT patients had low risk of recurrent VTE, suggesting that both dabigatran and warfarin may be safe and effective for preventing recurrent VTE in patients with CVT. In another trial Rusin et al., compared oral anticoagulants i.e. dabigatran, rivaroxaban and apixaban in 18, 10 and 8 CVT patients, respectively[29]. At 3 and 6-month follow-ups, a complete or partial recanalisation was observed in 34 cases (94.4%). Three patients (8.3%) experienced major bleeding: two from rivaroxaban group and one from dabigatran group. A favorable clinical outcome was observed in 24 (66.7%) patients, with no fatality. CVT recurrence was reported in two patients (5.6%) while two others developed venous thrombosis. Recurrence was seen in those patients who had permanent risk factor of inherited thromphilia after anticoagulant withdrawal. Recanalization and clinical outcome were comparable to our present data, major bleeding in 8.3% cases however, was a serious concern. Mendonça et al. have studied the role of dabigatrin in CVT, mentioning it potentially as an altenative option for the treatment of CVT. They reported an excellent clinical outcome and recanalization in more than 80% patients with no bleeding complications[30].

## Conclusion

Clinical outcome and recanalization rate of the patients treated with rivaroxaban have established the efficacy of this drug with less adverse effects. Therapeutic outcomes are acceptable and non-inferior to warfarin. Hence rivaroxaban may be considered a safe option for the treatment of CVT with satisfactory results in terms of clinical improvement as compared to conventional medication. However, we propose large prospective randomized controlled studies to evaluate and validate the appropriateness and safety of rivaroxaban anticoagulant for the treatment of CVT.

## Transparency

### Declaration of funding

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication.

### Declaration of financial/other relationships

MM, MIHK, MY, KAA, NH and SH declare that they have no conflict of interest.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

### Author contributions

MM and MIHK conceived, designed and wrote the manuscript. MY performed the data collection and statistical analysis. KAA approved the final content of the manuscript. NH and SH technically reviewed and revised the manuscript.

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### Compliance with ethics guidelines

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 2000 (5). Informed consent was obtained from all patients for being included in the study.

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## References

[1] Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2):162–170.
[2] Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med. 2005;352(17):1791–1798.
[3] Nasr DM, Brinjikji W, Cloft HJ, et al. Mortality in cerebral venous thrombosis: results from the national inpatient sample database. Cerebrovasc Dis. 2013;35(1):40–44.
[4] Silvis SM, Lindgren E, Hiltunen S, et al. Postpartum period is a risk factor for cerebral venous thrombosis. Stroke. 2019;50(2):501–503.
[5] Ferro JM, Bousser MG, Canhao P, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis – endorsed by the European Academy of Neurology. Eur J Neurol. 2017;24(10):1203–1213.
[6] Einhaupl K, Stam J, Bousser MG, et al. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. Eur J Neurol. 2010;17(10):1229–1235.
[7] Saposnik G, Barinagarrementeria F, Brown RD, Jr., et al. Diagnosis and management of cerebral venous thrombosis: a statement for

healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(4):1158–1192.
[8] McEvoy G, Snow EK, American Society of Health-System Pharmacists. AHFS drug information 2018. Bethesda (MD): American Society of Health System Pharmacists; 2018. English.
[9] Schardein JL, Macina OT. Human developmental toxicants: aspects of toxicology and chemistry. Boca Raton (FL): CRC Press; 2006.
[10] Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, natural substances, and foods. J Clin Pharmacol. 2005;45(2):127–132.
[11] Zhang K, Young C, Berger J. Administrative claims analysis of the relationship between warfarin use and risk of hemorrhage including drug-drug and drug-disease interactions. J Manag Care Pharm. 2006;12(8):640–648.
[12] Kimmel SE. Warfarin therapy: in need of improvement after all these years. Expert Opin Pharmacother. 2008;9(5):677–686.
[13] Kubitza D, Becka M, Wensing G, et al. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939-an oral, direct Factor Xa inhibitor-after multiple dosing in healthy male subjects. Eur J Clin Pharmacol. 2005;61(12):873–880.
[14] Kubitza D, Becka M, Roth A, et al. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. Curr Med Res Opin. 2008;24(10):2757–2765.
[15] Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499–2510.
[16] Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358(26):2776–2786.
[17] Deshpande CG, Kogut S, Laforge R, et al. Impact of medication adherence on risk of ischemic stroke, major bleeding and deep vein thrombosis in atrial fibrillation patients using novel oral anticoagulants. Curr Med Res Opin. 2018;34(7):1285–1292.
[18] Mutgi SA, Grose NA, Behrouz R. Rivaroxaban for the treatment of cerebral venous thrombosis. Int J Stroke. 2015;10 Suppl A100(Suppl A100):167–168.
[19] Geisbusch C, Richter D, Herweh C, et al. Novel factor xa inhibitor for the treatment of cerebral venous and sinus thrombosis: first experience in 7 patients. Stroke. 2014;45(8):2469–2471.
[20] Anticoli S, Pezzella FR, Scifoni G, et al. Treatment of cerebral venous thrombosis with rivaroxaban. J Biomed Sci. 2016;5:3.
[21] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–891.
[22] Darmawan G, Hamijoyo L, Oehadian A, et al. Cerebral venous sinus thrombosis in systemic lupus erythematosus. Acta Med Indones. 2018;50(4):343–345.
[23] Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692–694.
[24] Ferro JM, Canhao P, Stam J, et al. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35(3):664–670.
[25] Shankar Iyer R, Tcr R, Akhtar S, et al. Is it safe to treat cerebral venous thrombosis with oral rivaroxaban without heparin? A preliminary study from 20 patients. Clin Neurol Neurosurg. 2018;175:108–111.
[26] Martinelli I, Bucciarelli P, Passamonti SM, et al. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. Circulation. 2010;121(25):2740–2746.
[27] Miranda B, Ferro JM, Canhao P, et al. Venous thromboembolic events after cerebral vein thrombosis. Stroke. 2010;41(9):1901–1906.
[28] Ferro JM, Coutinho JM, Dentali F, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. JAMA Neurol. 2019;76(12):1457.
[29] Rusin G, Wypasek E, Papuga-Szela E, et al. Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience. Neurol Neurochir Pol. 2019;53(5):384–387.
[30] Mendonca MD, Barbosa R, Cruz-e-Silva V, et al. Oral direct thrombin inhibitor as an alternative in the management of cerebral venous thrombosis: a series of 15 patients. Int J Stroke. 2015;10(7):1115–1118.