Treatment Outcomes of Direct Oral Anticoagulants in Cerebral Venous Thrombosis: A Prospective Observational Study in Vietnam

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TREATMENT OUTCOMES OF DOACs IN PATIENTS WITH CEREBRAL VENOUS THROMBOSIS: A PROSPECTIVE OBSERVATIONAL STUDY IN VIETNAM

Short title	Treatment Outcomes of DOACs in CVT
Version	1.0
Date	Update: 05/21/2025
Project leader	Dr. Dinh Trung Hieu Hanoi Medical University, Bach Mai Hospital Email: dr.dinhhieu1092@gmail.com
Sponsor	Self-funded
Subsidising party	None (self-funded)

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS

CVT	Cerebral venous thrombosis
DOACs	Direct oral anticoagulants
VKA	Vitamin K antagonists
RCT	Randomized controlled trial
NIHSS	National Institutes of Health Stroke Scale
mRS	Modified Rankin Scale
MRV	Magnetic resonance venography
CTV	Computed tomography venography
DSA	Digital Subtraction Angiography
ICH	Intracranial hemorrhage
ISTH	International Society on Thrombosis and Haemostasis

SUMMARY

Rationale: Cerebral venous thrombosis (CVT) is a rare condition. Once the diagnosis is established, current guidelines consistently recommend the early initiation of anticoagulation therapy with heparin, even in the presence of intracerebral hemorrhage. Upon clinical and radiological stabilization, treatment is typically transitioned to oral anticoagulants, including either vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs). Since 2019, emerging evidence from randomized controlled trials such as RESPECT-CVT, CHOICE-CVT, and SECRET, along with large-scale international observational studies including ACTION-CVT and DOAC-CVT has demonstrated that DOACs can be safely used in the treatment of CVT. However, due to the rarity of the condition, most existing studies are limited by small sample sizes. Therefore, there is a growing need for additional studies across diverse geographic regions to expand the global evidence base on DOACs use in CVT. Such data will help enable more accurate assessment and analysis of treatment outcomes in patients with CVT receiving DOACs therapy.

Objective: To evaluate treatment outcomes of DOAC therapy in CVT patients.

Study Design: A prospective cohort study at Bach Mai Hospital, Vietnam, enrolling a minimum of 69 patients with CVT treated with DOACs.

Study Population: Adult patients (≥18 years old) with radiologically confirmed CVT, treated with therapeutic-dose heparin in the acute phase and subsequently with a direct oral anticoagulant. All will be recruited from Bach Mai Hospital, the national referral center for CVT in northern Vietnam.

Primary study endpoint: the primary endpoint is a composite of the number of patients who experience either major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH), or a venous thromboembolic event (VTE) - including recurrent CVT, deep vein thrombosis of any limb, pulmonary embolism, or splanchnic vein thrombosis — within up to 6 months of follow-up.

The secondary endpoint:

- Mortality Rate: all death from any cause during the 6-month follow-up.
- Functional outcome: proportion of patients with mRS 0–1 at 3 and 6 months.
- Number of participants with major bleeding events
- Number of participants with clinically relevant non-major bleeding (CRNMB) events
- Number of participants with symptomatic recurrent venous thromboembolism (VTE)
- Number of participants who discontinued anticoagulant therapy early
- Number of participants with arterial thrombotic events
- Number of participants with arterial thrombotic events
- Serial D-dimer measurements after CVT
- Venous recanalization
- Frequency of chronic headache after CVT

Nature and Extent of Risks, Burdens, and Benefits: This study is non-interventional in nature and does not introduce any additional procedures, risks, or burdens for participants. All information utilized will be obtained exclusively from standard clinical care and follow-up, without altering the course of treatment. No experimental interventions will be administered, and participation does not affect patients' access to care or outcomes.

ClinicalTrials.gov Identifier:

1. INTRODUCTION AND RATIONALE

CVT accounts for only 0.5-1% of all diagnosed and treated stroke cases worldwide[1]. Previous studies have demonstrated that patients with CVT typically exhibit distinct clinical characteristics compared to those with other types of stroke. Notably, disproportionately affects younger individuals, with the majority of cases occurring in patients under 50 years of age and approximately two-thirds involving women[2]. Clinically, CVT often presents with symptoms associated with elevated intracranial pressure or focal brain parenchymal lesions, which may or may not be associated with mass effect[3].

Current international guidelines uniformly recommend initiating treatment with low-molecular-weight heparin (LMWH) or unfractionated heparin during the acute phase. Once the clinical status and imaging findings have stabilized, oral anticoagulation is advised for a duration of 3-12 months, depending on the patient's individual risk profile.

In recent years, increasing attention has been directed toward the safety and efficacy of DOACs in the management of CVT. The first randomized controlled trial (RCT) evaluating DOAC use in CVT was the RESPECT-CVT trial[4], published in 2019, which assessed dabigatran. This was followed by CHOICE-CVT[5], was conducted in China. Both studies compared dabigatran with vitamin K antagonists (VKAs) and found no significant differences in safety and efficacy between the two groups. In 2023, the SECRET trial - an RCT comparing rivaroxaban with VKA - reported comparable outcomes[6]. However, due to the rarity of CVT, all of these RCTs were limited by relatively small sample sizes, underscoring the inherent difficulty of conducting large-scale RCTs for rare conditions.

To complement these findings, large multicenter observational studies have been undertaken. Notably, the ACTION-CVT and DOAC-CVT studies have provided real-world evidence supporting the use of DOACs, demonstrating comparable safety and effectiveness to VKAs[7,8]. DOACs also offer several practical advantages, including fixed dosing, fewer drug–food interactions, and no requirement for routine INR monitoring. Nevertheless, even these observational studies have not enrolled patient numbers in the thousands, thereby limiting the statistical power for robust subgroup analyses.

Recent international guidelines now permit the use of either VKAs or DOACs in the treatment of CVT, acknowledging the growing body of evidence indicating similar safety and efficacy profiles[9–11]. Research in this area remains ongoing worldwide.

In Vietnam, research on CVT treatment outcomes - particularly regarding the use of DOACs - is still limited. Moreover, due to the rarity of the condition and the complexity of evaluating multiple risk factors, patients with CVT are typically referred to major stroke centers for specialized management. Consequently, patient cohorts from such tertiary centers may provide insights that are representative of the national CVT population, rather than being confined to local or institutional patterns.

The primary objective of the present study, Treatment Outcomes of DOACs in CVT, is to evaluate the real-world safety and efficacy of DOACs in the management of CVT in Vietnam. The secondary objective is to assess clinical outcomes and identify factors associated with treatment response during follow-up.

2. OBJECTIVE

Primary Objective

To evaluate the effectiveness and safety of DOACs in patients with CVT over a 6-month follow-up period, using the composite outcome of major bleeding events or recurrent venous thromboembolism.

Secondary Objectives

Patients with CVT treated with DOACs will be assessed at 3 and 6 months to determine the following clinical outcomes:

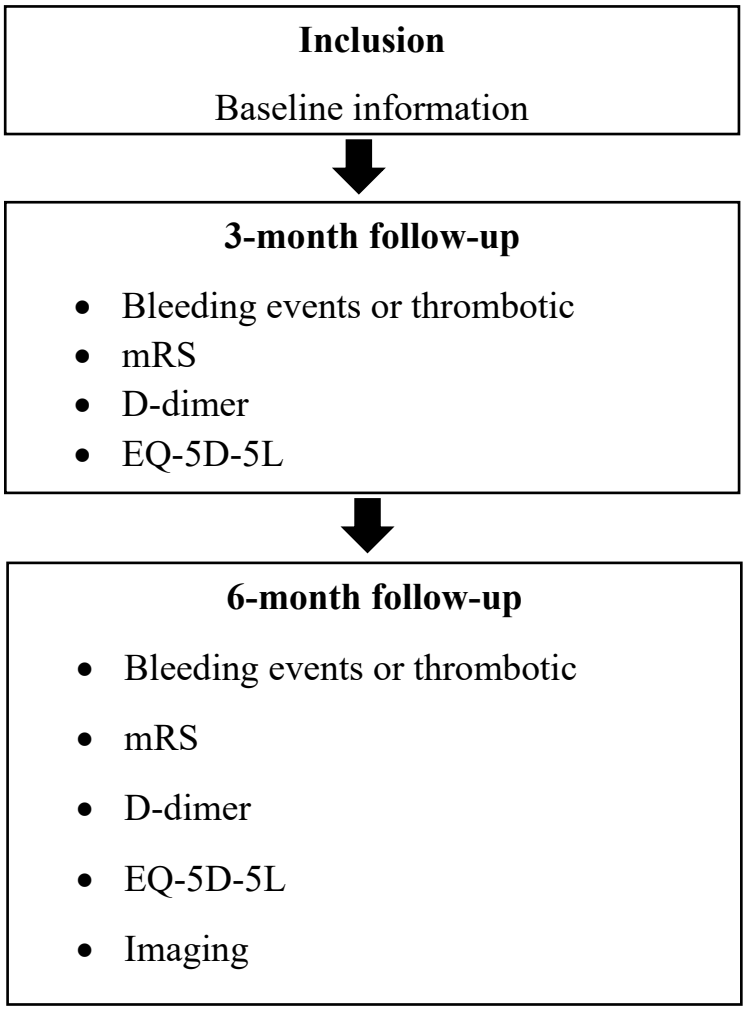
- Mortality Rate
- Functional outcome
- Number of participants with major bleeding events
- Number of participants with clinically relevant non-major bleeding (CRNMB) events
- Number of participants with symptomatic recurrent venous thromboembolism (VTE)

- Venous recanalization
- Number of participants who discontinued anticoagulant therapy early
- Number of participants with arterial thrombotic events
- Frequency of participants with chronic headache after CVT
- Health-related quality of life (EQ-5D-5L utility index score)
- Serial D-dimer measurements after CVT

3. STUDY DESIGN

Treatment Outcomes of DOACs in CVT is a prospective, single-center observational study. The study involves the collection of treatment data during both the acute hospitalization phase and subsequent outpatient follow-up. It was conducted at Bach Mai Hospital, a central and tertiary referral center for the management of cerebral venous thrombosis (CVT) in Vietnam.

A schematic diagram of the study design and follow-up is provided below



4. ELIGIBILITY CRITERIA

4.1. Population

All consecutive adult patients diagnosed with CVT at Bach Mai Hospital were considered eligible for inclusion. Patients could be enrolled during initial hospitalization or through the outpatient stroke clinic. Both newly diagnosed cases and those referred from other facilities for further management were included.

4.2. Inclusion criteria

- Signed informed consent (ICF) to participate in the study
- Age ≥ 18 years
- Confirmed diagnosis of cerebral venous thrombosis (CVT) based on clinical presentation and neuroimaging, including one or more of the following:

  MRI and MRV, AND/OR
  CT and CTV, AND/OR
  MRI or CT combined with DSA
- Initiation of DOACs within 5 to 15 days after starting treatment with heparin

4.3. Exclusion criteria

- CVT accompanied by antiphospholipid syndrome with all three positive laboratory criteria: lupus anticoagulant, anticardiolipin antibodies, and anti–β2-glycoprotein antibodies
- CVT in pregnant patients requiring continuous anticoagulation throughout pregnancy
- CVT with coexisting bleeding disorders, including immune thrombocytopenia with platelet count <100,000/mL, hemophilia A or B, von Willebrand disease, or a history of prolonged bleeding after surgery or invasive procedures
- CVT in patients with mechanical heart valves, atrial fibrillation, and moderate to severe mitral stenosis
- CVT in patients with a glomerular filtration rate (GFR) <15 mL/min
- CVT with severe hepatic impairment

- Patients already receiving anticoagulation therapy for another underlying condition at the time of CVT diagnosis

5. METHODS

5.1. Study endpoint

5.1.1. Primary study endpoint

The primary endpoint of the study is a composite outcome assessed over a 6-month follow-up period, comprising: (1) the occurrence of VTE, including recurrent CVT, deep vein thrombosis of any limb, pulmonary embolism, or thrombosis involving the splanchnic, jugular, caval, renal, or catheter-related veins; and (2) major bleeding events, defined according to the criteria established by the International Society on Thrombosis and Haemostasis (ISTH) (see Appendix B).

5.1.2. Secondary study endpoint

Assessed at 3 and 6 months (± 1 month):

- Functional outcome: defined as a score of 0–1 on the Modified Rankin Scale (mRS). The mRS ranges from 0 (no symptoms) to 6 (death). Lower scores reflect better functional recovery.
- Number of participants with major bleeding events: defined according to the criteria established by the International Society on Thrombosis and Haemostasis (ISTH)[12] (see Appendix B)
- Number of participants with clinically relevant non-major bleeding (CRNMB) events: defined according to the criteria established by the International Society on Thrombosis and Haemostasis (ISTH)[13] (see Appendix B)
- Number of participants with symptomatic recurrent VTE
- Health-related quality of life, measured by the EQ-5D-5L instrument and the Vietnamese population value set validated by Mai et al[14].
- Serial D-dimer measurements after CVT: plasma D-dimer levels will be measured at 3 and 6 months using a standardized quantitative assay. Values will be reported in ng/mL and interpreted in the context of post-CVT coagulation activity

Assessed at 6 months (± 1 month):

- Mortality Rate
- Number of participants who discontinued anticoagulant therapy early
- Number of participants with arterial thrombotic events
- Venous recanalization
- Frequency of chronic headache following CVT

5.2. Study procedures

Baseline clinical and radiological data, including patient demographics, risk factors, imaging findings, anticoagulant treatment details, and in-hospital events during the acute phase of CVT, will be collected for all enrolled patients.

Participants will be followed up at 3 and 6 months after diagnosis. Data collected at these time points will include:

- Type and duration of oral anticoagulant therapy
- Clinical events, including recurrent thrombotic or bleeding events
- Degree of disability will be assessed using mRS
- Venous recanalization will be assessed at 6 months using brain MRI with venography or CT venography. Recanalization will be categorized as complete, partial, or none, based on the classification proposed by Aguiar de Sousa et al[15]
- Health-related quality of life, evaluated using the EQ-5D-5L instrument. This tool evaluates five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels of severity. A utility index score will be calculated using the Vietnamese EQ-5D-5L value set, ranging from −0.511 to 1.000, where:1.000 indicates perfect health, 0.000 corresponds to death, scores below 0 indicate health states considered worse than death by the general Vietnamese population.
- Presence of chronic headache, defined as a headache occurring on ≥15 days per month and persisting for more than 3 months following the acute CVT event, consistent with the International Classification of Headache Disorders, 3rd edition

(ICHD-3)[16]. Headache-related disability, assessed using the Headache Impact Test (HIT-6)[17]

All data will be collected as part of routine clinical care during outpatient visits or structured telephone interviews and recorded using standardized case report forms.

5.3. Sample size

Due to the rarity of the disease and the single-center design of the Treatment Outcomes of DOACs in CVT study, a minimum of 69 patients are expected to be enrolled over a 2-year period starting in June 2025. Patient recruitment is anticipated to be completed by June 2027, with final 6-month follow-up assessments expected to conclude by December 2027.

6. STATISTICAL ANALYSES

All statistical analyses will be conducted using R software (version 4.4.1). Statistical significance will be set at a two-sided p-value < 0.05.

Descriptive statistics will be used to summarize baseline characteristics. Continuous variables will be reported as means ± standard deviations (SD) or medians with interquartile ranges (IQR), depending on distribution. Categorical variables will be expressed as counts and percentages.

The primary endpoint: a composite of major bleeding (per ISTH criteria) or symptomatic recurrent venous thromboembolism (VTE), including cerebral venous thrombosis, deep vein thrombosis, pulmonary embolism, or splanchnic vein thrombosis—will be analyzed as a time-to-event outcome. Kaplan–Meier survival curves will be constructed, and group comparisons will be performed using the log-rank test. Cumulative event rates at 6 months will be reported with 95% confidence intervals.

For secondary endpoints, the following analyses will be conducted:

- Functional outcome (mRS 0-1 vs 2-6 at 3 and 6 months) will be analyzed using logistic regression to identify predictors of favorable recovery.

- Venous recanalization status at 6 months will be described as complete, partial, or absent, based on follow-up imaging, and summarized as proportions.
- Rates of major bleeding, any bleeding, symptomatic recurrent VTE, and arterial thrombotic events will be summarized descriptively and reported with 95% confidence intervals.
- Health-related quality of life (EQ-5D-5L), chronic post-CVT headache (HIT-6), at 3 and 6 months will be compared using paired t-tests or Wilcoxon signed-rank tests, as appropriate.
- Changes in D-dimer levels from baseline to follow-up will be analyzed using paired tests and visualized longitudinally.

Missing data will be handled using complete case analysis. If the missing rate exceeds 10% for any variable, sensitivity analyses will be performed.

7. ETHICAL CONSIDERATIONS

This study is a doctoral research project conducted as part of the PhD training program at Hanoi Medical University. The study was officially approved by the university on March 3, 2025, under Decision No. 580/QĐ-ĐHYHN.

Ethical approval was granted by the Ethics Committee of Bach Mai Hospital on July 4, 2025, under Decision No. 45/BM-HĐĐĐ. The study will be conducted in accordance with the principles of the Declaration of Helsinki (2013) and Good Clinical Practice (GCP) guidelines. The research will take place at Bach Mai Hospital, a national tertiary referral center for cerebrovascular diseases in Vietnam.

All eligible participants will be required to provide written informed consent before enrollment. Patients will be informed of the study's purpose, procedures, potential risks and benefits, their rights to confidentiality, and the option to withdraw from the study at any point without affecting their ongoing care.

This is a prospective, observational study. All interventions and follow-up procedures are part of standard clinical management for patients with cerebral venous thrombosis (CVT).

No experimental drugs or procedures will be introduced. Treatment decisions—including the use of direct oral anticoagulants—are made entirely by the attending physicians based on current guidelines and clinical judgment.

To protect privacy, personal data will be de-identified and stored on secure hospital servers with restricted access. Only aggregated, anonymized data will be used for publication or dissemination.

Any protocol deviations or serious adverse events observed during the study will be documented and reported to the Institutional Review Board (IRB) in accordance with national and institutional regulations.

8. LIMITATIONS

This study has several limitations. First, it is a single-center investigation conducted at Bach Mai Hospital, a national tertiary referral center. While this may raise concerns regarding generalizability, the hospital receives the majority of CVT cases from a wide geographic area in northern Vietnam, including referrals from provincial and district-level hospitals. Therefore, the study population is expected to be broadly representative of the CVT patient population in real-world clinical practice within the region.

Second, given the rarity of CVT and the fixed 2-year enrollment window, the sample size is expected to be limited. This may reduce the statistical power to perform robust subgroup analyses or develop complex multivariable models. However, the study is designed to maximize data completeness through close follow-up and adherence to protocol-defined procedures.

Third, although the study currently includes both DOAC and VKA group, the planned analysis will primarily focus on the DOAC subgroup. This approach reflects the growing interest in the real-world effectiveness and safety of DOACs in CVT management. Including VKA patients in the recruitment phase may still provide useful contextual information for future comparative analyses.

Finally, some outcome data, such as follow-up imaging for venous recanalization or standardized cognitive assessments, may be unavailable for a small number of patients due to loss to follow-up or logistical constraints. Nonetheless, the study team is committed to minimizing missing data through proactive patient engagement and structured follow-up planning.

9. Funding and Conflicts of Interest

This study is investigator-initiated and self-funded. All study-related activities, including patient recruitment, data collection, follow-up, and statistical analysis, are carried out using the resources of the research team at the Bach Mai Hospital. No external funding or sponsorship has been obtained from pharmaceutical companies, academic institutions, or governmental agencies.

The investigators declare no conflicts of interest. There are no financial, institutional, or personal relationships that could be perceived to influence the design, conduct, interpretation, or publication of this study.

10. Administrative Aspects, Monitoring, and Publication

10.1. Study Administration

The study is conducted under the supervision of Bach Mai Hospital. A designated principal investigator is responsible for overall coordination, compliance with the protocol, and ensuring data quality. Study procedures are implemented in accordance with the approved protocol, Good Clinical Practice (GCP), and local regulatory requirements.

10.2. Data Management and Monitoring

Study data will be collected and stored in a secure, password-protected electronic database. Data entry will be performed by trained personnel and subject to regular quality

control checks. The study team will periodically monitor data for completeness, consistency, and adherence to the study protocol. No formal external monitoring or auditing is planned, given the observational and non-interventional nature of the study.

10.3. Confidentiality

Patient confidentiality will be strictly maintained. All data will be de-identified and coded using unique study identifiers. Access to identifiable patient information will be restricted to authorized personnel only.

10.4. Protocol Amendments

Any significant changes to the study protocol will be documented, submitted for ethical approval, and communicated to all relevant parties, including the study registry if applicable.

10.5. Publication Policy

The results of the study will be disseminated through scientific publications and conference presentations. Authorship will follow the criteria established by the International Committee of Medical Journal Editors (ICMJE). The research team is committed to transparency and will ensure that study findings are made publicly accessible regardless of outcome.

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APPENDIX A.

Standard Operating Procedure for the Scoring of Cerebral Venous Recanalization

Objective

Imaging Modalities Accepted

- Magnetic resonance venography (MRV)
- Computed tomography venography (CTV)
- Digital subtraction angiography (DSA), if available

Grade	Definition
0	No recanalization: Persistent occlusion with no visible flow.
1	Partial recanalization: Incomplete restoration of venous flow.
2	Complete recanalization: Full restoration of flow with no residual occlusion.

APPENDIX B.

ISTH Definitions of Major and Clinically Relevant Non-Major Bleeding

Major Bleeding

Defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria[12] as any of the following:

- Fatal bleeding
- Symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal)
- Bleeding causing a fall in hemoglobin of ≥2 g/dL
- Bleeding leading to transfusion of ≥2 units of whole blood or red cells

Clinically Relevant Non-Major Bleeding

As per ISTH SSC definition[13]: Bleeding that does not meet the criteria for major bleeding AND is associated with one or more of the following:

- Requires medical intervention by a healthcare professional
- Leads to unscheduled contact with a physician (visit or telephone)
- Results in temporary cessation of anticoagulation therapy
- Causes discomfort or impairment of activities of daily living