DOAC-CVT

Direct Oral Anticoagulants for the treatment of Cerebral Venous Thrombosis

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DIRECT ORAL ANTICOAGULANTS FOR THE TREATMENT OF CEREBRAL VENOUS THROMBOSIS: AN INTERNATIONAL PHASE IV STUDY

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PROTOCOL SIGNATURE SHEET

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Head of Department: Prof. dr. B. Uitdehaag		
Principal Investigator: Dr. J. Coutinho		

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LIST OF ABBREVIATIONS

CVT	Cerebral venous thrombosis
VKA	Vitamin K antagonists
DOAC	Direct oral anticoagulants
VTE	Venous thromboembolism
NIHSS	National Institutes of Health Stroke Scale
MRV	Magnetic resonance venography
ICH	Intracranial hemorrhage
CNS	Central nervous system
mRS	Modified Rankin Scale
ISTH	International Society on Thrombosis and Haemostasis
IRB	Institutional Review Board
GDPR	General Data Protection Regulation
eGFR	Estimated glomerular filtration rate

SUMMARY

Rationale: Patients with cerebral venous thrombosis (CVT) are currently treated with anticoagulants during 3-12 months after diagnosis, to prevent worsening of the CVT and recurrent thrombosis, and to promote venous recanalization. Until recently, patients were generally treated with vitamin K antagonists (VKA). Direct oral anticoagulants (DOACs) are more practical in use than VKA and carry a lower risk of intracranial hemorrhage (ICH) in other conditions. One of the burning clinical questions is whether CVT patients can be safely treated with DOACs instead of VKA. In 2019, the first randomized trial on the safety and efficacy of DOACs in CVT was published (RESPECT-CVT). This exploratory study included 120 patients and the results suggest that DOACs can be safely used to treat CVT. Following RESPECT-CVT, use of DOACs to treat CVT is expected to rise, but given the limited sample size and strict selection criteria of RESPECT-CVT, additional data regarding the efficacy and safety of DOACs in CVT are required, especially from routine clinical care.

Objective: To assess the safety and efficacy of DOACs for the treatment of CVT in a real-world setting.

Study design: DOAC-CVT will be an international, prospective, comparative cohort study. We aim to recruit 500 patients and anticipating a 3:2 ratio in DOAC:VKA use, we expect that in total 300 patients treated with a DOAC will be included.

Study population: Patients are eligible if they are >18 years old, have a radiologically confirmed CVT, and have started oral anticoagulant treatment (DOAC or VKA) within 30 days of CVT diagnosis.

Primary study endpoint: The primary endpoint is a composite of major bleeding (according to the criteria of the International Society on Thrombosis and Haemostasis) AND symptomatic recurrent venous thrombosis after 6 months of follow-up.

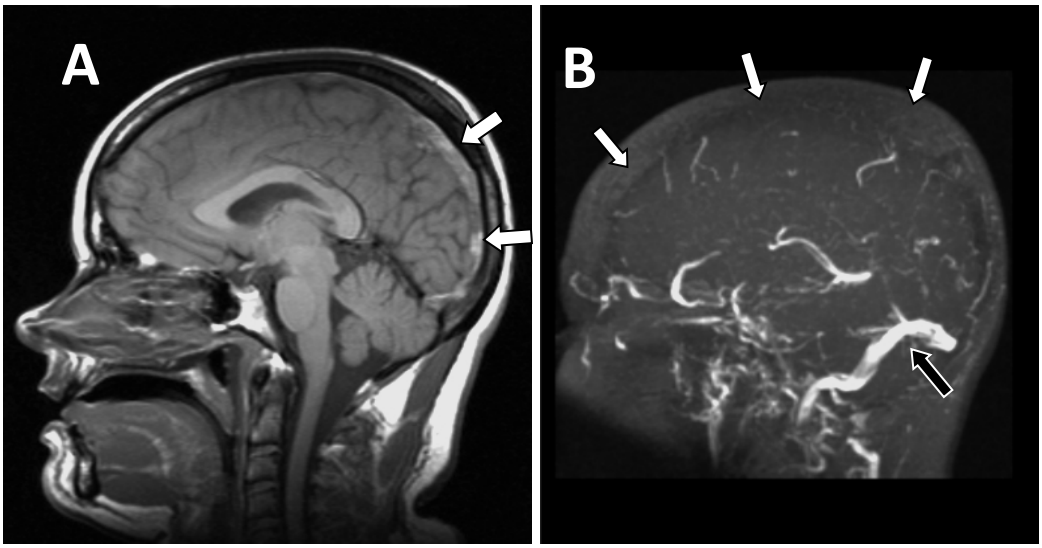
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This is an observational study which poses no risk or burden to the participant. Only data that are collected as part of routine clinical care will be used.

ClinicalTrials.gov Identifier: NCT04660747

1. INTRODUCTION AND RATIONALE

Cerebral venous thrombosis (CVT) is an uncommon thrombotic disorder that mainly affects young adults and children (Figure 1).[1] CVT often leads to severe neurological deficits, epileptic seizures, and decreased consciousness, and has a mortality rate of 5-15%.[2,3] A unique aspect of CVT is that the increased cerebral venous pressure leads to an intracerebral hemorrhage (ICH) in about 40% of patients.[2] Despite this high risk of major bleeding, anticoagulation is widely considered the main treatment for CVT, based on evidence from two small randomized trials.[4] Current guidelines recommend initial treatment with (low-molecular weight) heparin for 1-2 weeks, followed by vitamin K antagonists (VKA) for 3-12 months.[5,6]

Figure 1. T1-weighted MRI (A) and MR-venography (B) of a patient with superior sagittal sinus thrombosis.



A: Mid-sagittal T1 weighted MRI showing hyperintensity in the superior sagittal sinus, indicating fresh thrombus within the venous sinus (white arrows).
B: Sagittal MR-venogram of the same patient. There is absence of flow within the superior sagittal sinus, confirming there is a thrombosis in this vein (white arrows). There is normal opacification of the lateral sinus (black arrow).

One of the current burning clinical questions is whether CVT patients can be safely and effectively treated with direct oral anticoagulants (DOACs) instead of VKA. Apart from the practical advantages (stable dosing, no monitoring required), the substantially lower risk of ICH with DOACs compared to VKA in both venous thromboembolism and atrial fibrillation has sparked worldwide interest among neurologists.[7,8]

In 2019, the results of the first randomized trial on DOACs in CVT (RESPECT-CVT) were published.[9] The study was not powered for either superiority or non-inferiority, since it was clear from the start that such a large sample size would not be achievable in a disease as

rare as CVT. Nevertheless, the data of RESPECT-CVT indicate that dabigatran has a similar efficacy and safety as INR-adjusted warfarin for the treatment of CVT. A few small[10,11] and non-peer-reviewed[12] cohort studies have been published indicating results in the same direction.[13] Following the results of RESPECT-CVT, the use of DOACs to treat CVT is expected to rise. However, given the limited sample size of RESPECT-CVT (n=120) and the strict inclusion and exclusion criteria, additional data regarding the safety and efficacy of DOACs in CVT are much needed, especially data from routine clinical care.
The main aim of the DOAC-CVT study (Direct oral anticoagulants for the treatment of cerebral venous thrombosis: an international phase IV study) will be to validate the efficacy and safety data of RESPECT-CVT in a real-world setting.

2. OBJECTIVES

Primary Objective

To assess the safety and efficacy of DOACs vs. VKAs in patients with CVT, in terms of the 6-month risk of symptomatic recurrent venous thromboembolic event (VTE) or major bleeding.

Secondary Objectives

In patients with CVT treated with DOACs vs. VKAs, to assess the 3, 6- and 12-month*:

- All-cause mortality
- Symptomatic recurrent VTE rate
- Major bleeding rate
- Clinically relevant non-major bleeding rate
- Arterial thrombotic event rate
- Modified Rankin Scale score
- Oral anticoagulant cross-over rate with reasons for cross-over
- Cerebral venous recanalization rate at 6 months**

* 12-month follow-up: if performed as part of routine care

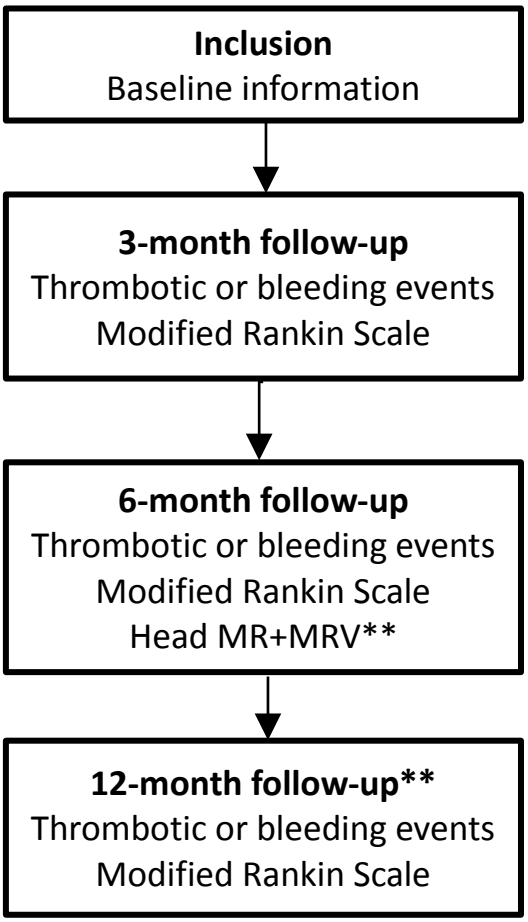
** Only in centers that perform 6-month follow-up imaging as part of routine clinical care

3. STUDY DESIGN

DOAC-CVT will be an international, prospective, phase IV, comparative observational cohort study. The study will use data that are collected as part of routine clinical care. It will be carried out during the course of 3 years at up to 50 hospitals worldwide with expertise in the treatment of CVT. Since this is an observational study, the choice of anticoagulant type and duration of treatment are left at the discretion of the treating physicians and patients.

A blinded adjudication committee will evaluate the occurrence of the following endpoints: symptomatic recurrent VTE, major bleeding, clinically relevant non-major bleeding, arterial thrombotic events, and death (classified as cardiovascular, non-cardiovascular, or undetermined cause). Adjudication will be based on a standardized report form describing relevant clinical information and diagnostic test results, including slices of relevant imaging and local imaging reports.

Figure 2. Flowchart of baseline and follow-up time points and routine assessments at each time point*



* Follow-up visits may be by phone or video

** If done routinely at site

4. STUDY POPULATION

4.1 Population

Consecutive patients with CVT treated at the participating centres. Both patients who are admitted to the hospital and patients who are treated via outpatient clinic are eligible. A recruitment log will be kept by participating centers, which will also list non-included CVT patients with reasons of exclusion.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Written informed consent for the use of observational data
- Age >18 years at the time of CVT diagnosis
- Radiologically confirmed CVT diagnosis (CT-venography, MRI or catheter angiography)
- Oral anticoagulant treatment (DOAC or VKA) started within 30 days of CVT diagnosis (patient may initially be treated with heparin)

4.3 Exclusion criteria

As this is a phase IV study, the patient population should reflect routine clinical practice as much as possible. As such, the only exclusion criteria will be absolute contra-indications for the use of DOACs, i.e.:

- Pregnancy or lactation (post-partum women are eligible if they do not give breast-feeding)
- Mechanical heart valve
- Severe renal insufficiency (defined as an eGFR <15 ml/min)
- Severe liver disease resulting in clinically relevant coagulopathy

4.4 Sample size calculation

DOAC-CVT is designed as a pragmatic exploratory phase IV study. If we were to plan the study as a non-inferiority study, more than 2000 patients would be required, due the low event rate of the primary endpoint (less than 3% in RESPECT-CVT).[9] Given the rarity of CVT, such a sample size is not realistic. Instead we aim to recruit the maximum number of patients that is realistically achievable through our global collaborative network. During the

3-year period of patient inclusions, we aim to recruit at least 500 patients. Expecting a 3:2 ratio in DOAC:VKA use, approximately 300 patients treated with a DOAC are expected to be included in DOAC-CVT.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Primary study endpoint

The primary endpoint is the composite of symptomatic recurrent VTE (i.e. recurrent CVT, DVT of any limb, pulmonary embolism, splanchnic vein, jugular, caval, renal, or catheter-related thrombosis) AND major bleeding (according to the criteria of the International Society on Thrombosis and Haemostasis [ISTH][14]; see Appendix B) after 6 months of follow-up.

5.1.2 Secondary study endpoints

Assessed at 3, 6 and 12 months*:

- All-cause mortality
- Symptomatic recurrent VTE rate
- Major bleeding rate[14] (see Appendix B)
- Clinically relevant non-major bleeding rate[15] (see Appendix B)
- Arterial thrombotic event rate
- Modified Rankin Scale score
- Oral anticoagulant crossover rate with reasons for crossover

Assessed at 6 months**:

- Cerebral venous recanalization rate – only if assessed as part of routine care

* ± 1 month; 12-month follow-up only if performed as part of routine care
** ± 2 months; cerebral venous recanalization will be scored according to the previously published Aguiar de Sousa classification[16] (see Appendix A)

5.2 Study procedures

This study will only analyse data that are collected as part of routine clinical care. Three and six month follow-up visits are routine care in all participating sites. However, since not all hospitals perform a 12 month follow-up visit and not all hospitals perform a head MR with MR-venography or CT-venography at the 6-month follow-up visit as part of routine care, data on 12-month outcomes and on venous recanalization will be missing for some participating centers.

5.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

5.4 Premature termination of the study

The study will be prematurely terminated if the Steering Committee decides this observational study is no longer clinically relevant, e.g. because new insights have rendered the research question irrelevant. In case of premature study termination, the results of the study thus far will be published as an exploratory report.

6. STATISTICAL ANALYSES

Baseline characteristics will be presented for patients who are initially started on a DOAC and those who are initially started on VKA. Categorical data will be presented as counts and proportions, continuous data as means and standard deviations or medians and (interquartile) ranges, as appropriate. Missing outcome data will be imputed using multiple imputation.

6.1 Primary study endpoint

6.1.1 Main analysis of primary endpoint

Comparisons will be made according to the intention-to-treat principle (i.e. according to the first oral anticoagulant that was started). Based on the results of the RESPECT CVT trial,[9] we expect an approximate 1.7% event rate for the primary outcome in the DOAC group and a 3.3% event rate in the VKA group, i.e. around 12 events in the total sample.

We will use propensity score inverse probability treatment weighting to calculate an adjusted odds ratio for the primary outcome. Based on the direct acyclic graph (Figure 3), the following confounders will be used to compute the propensity score:

- Age at time of CVT diagnosis
- ICH at CVT diagnosis, or after diagnosis but before start of oral anticoagulant treatment
- Glasgow Coma Scale at CVT diagnosis
- CNS infection concurrent with the index CVT
- Known antiphospholipid syndrome, or presence of antiphospholipid antibodies at start of oral anticoagulant treatment
- Cancer (defined as currently under treatment or diagnosed within 6 months prior to start of oral anticoagulant treatment)
- Previous VTE
- Previous major bleeding prior to the index CVT (according to ISTH criteria)

We will analyze the balance of confounders among both treatment groups after propensity score inverse probability-weighting. Center of inclusion will be included as an additional covariate in the final model.

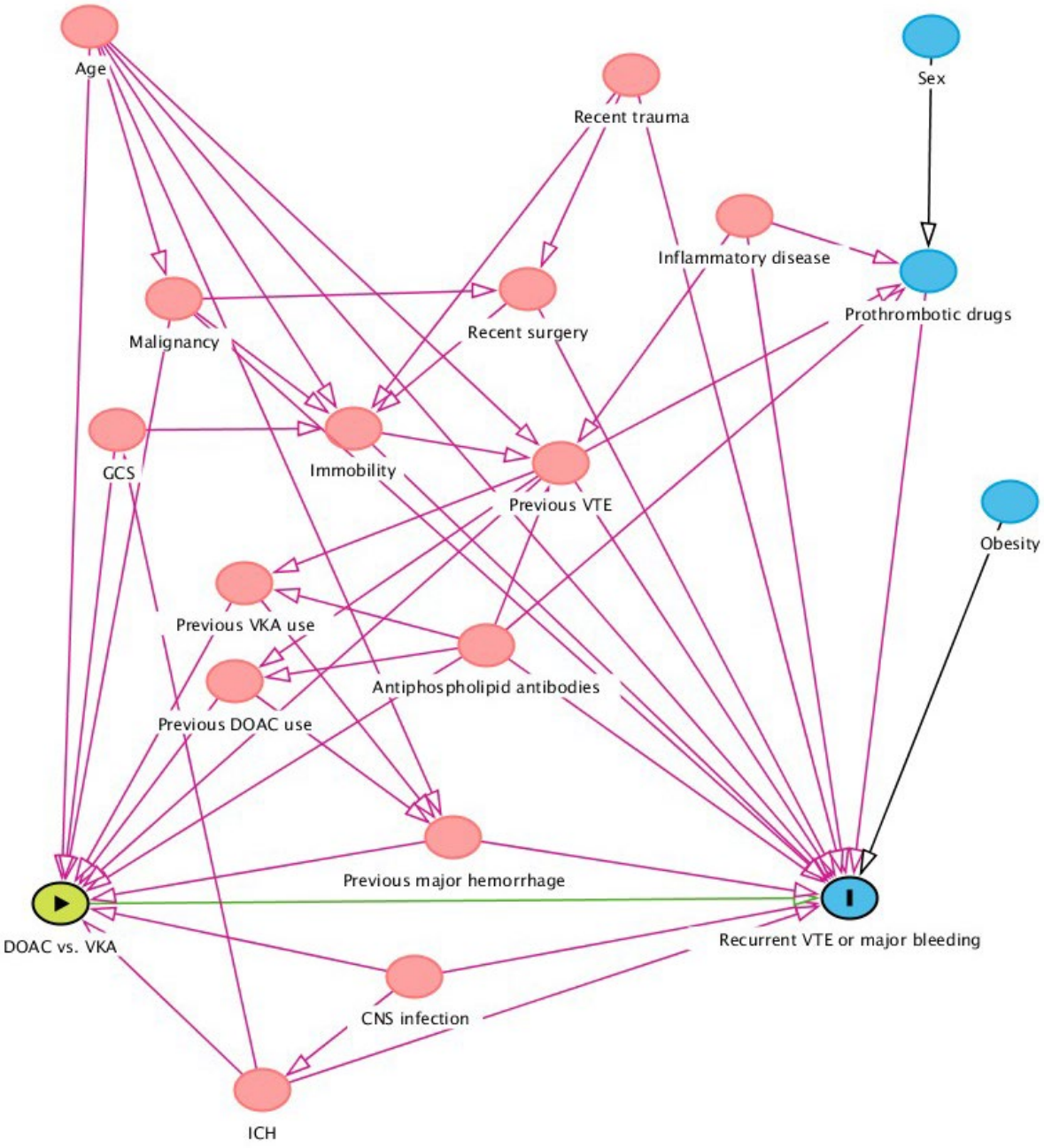


Figure 3. Directed Acyclic Graph depicting factors influencing anticoagulant treatment choice and risk of recurrent venous thrombotic event or major bleeding

6.1.2 Sensitivity analyses for the primary endpoint

In addition to the main analysis as described above, we will perform at least two sensitivity analyses for the primary endpoint.

Firstly, we will perform a survival analysis of the primary endpoint using the inverse probability-weighting from the main analysis. Patients will be censored at the time of anticoagulant-switch or at the last follow-up moment (after 3, 6 or 12 months).

Secondly, we will use two multi-state models to analyse the hazard rate of the primary outcome among those who did and did not undergo anticoagulant switch in each treatment group (see Figure 4 and 5).

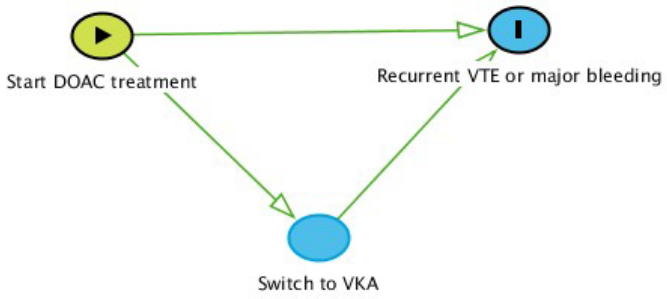


Figure 4. Structure of multistate model for the DOAC treatment arm

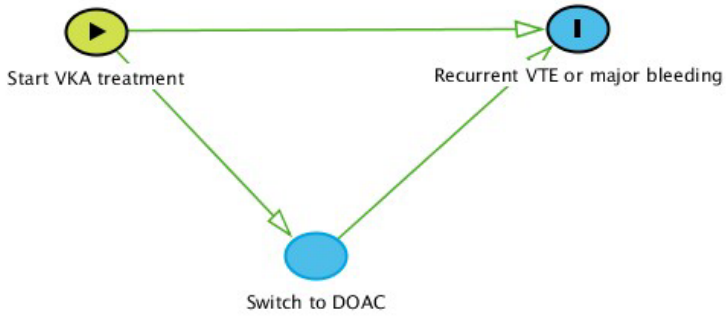


Figure 5. Structure of multistate model for the VKA treatment arm

6.1.3 Subgroup analysis of primary endpoint

In an exploratory subgroup analysis, we will report all primary and secondary outcomes stratified by type of DOAC (i.e. apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban). For this analysis no formal statistical comparisons will be performed.

6.2 Secondary study parameter(s)

All secondary outcomes at 6 months will be analysed with the same method as used for the main analysis. Confounders to be included in each propensity score calculation are detailed in Appendix C.

7. ETHICAL CONSIDERATIONS

7.1 Regulation statement

This study will be conducted in accordance with the principles of the Declaration of Helsinki, as amended by the World Medical Association General Assembly in October 2013, and with the guidelines for Good Clinical Practice.

7.2 Recruitment and consent

The study uses only data that are collected as part of routine care. The local investigator at each participating center will inform eligible subjects of the study. All patients or their proxy's will be asked for written informed consent to allow use of their data in a coded manner in accordance with the European Union General Data Protection Regulation (GDPR) and other applicable laws for that particular hospital.

7.3 Benefits and risks assessment

This study poses no risk and no burden to participants. Only existing patient care data will be used.

8. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

8.1 Handling, storage, and maintenance of data and documents

All patients will be assigned a unique study ID which contains no identifying information. Study data will be entered into the study database under this unique study ID by the local investigator. The study database will not contain directly identifying data such as name, address or date of birth. The subject identification code list linking the study ID with the source data remains at the local hospital and is stored by the local investigator separate from the study database. Only local investigators participating in the registry will have access to this list.
The study data will be kept for 15 years after enrollment of the last patient into the registry.

The Amsterdam UMC will function as the controller of the data for this study. Castor Electronic Data Capture system will be used to collect all data in a standardized manner (www.castoredc.com). Amsterdam UMC has a data processor agreement with Castor EDC. Each center should comply with local laws and institutional rules regarding data storage and data transfer, sign the Data Transfer Agreement, and send the local IRB approval to the Study Coordinator before enrollment can start. Additional Data Transfer Agreements for the execution of substudies will be prepared as necessary.

8.2 Study Oversight

The project leader has the final responsibility for the execution of the DOAC-CVT study. The Steering Committee will oversee the conduction of the study and provide support and guidance. The Steering Committee will meet twice a year, either in person or digitally. Additional Steering Committee meetings may be scheduled at the request of the Executive Committee. A national leader will be appointed by the Executive Committee for each country that participates in the study, and all national leaders are members of the Steering Committee. The Executive Committee supervises the day-to-day study execution for the Steering Committee. The day-to-day study execution will be coordinated by the study coordinator.

Executive Committee
Dr. Jonathan Coutinho (project leader) Amsterdam University Medical Center, Amsterdam, the Netherlands
Dr. Jukka Putaala Helsinki University Hospital, Helsinki, Finland
Prof. Jose Ferro Hospital de Santa Maria, Lisbon, Portugal
Prof. Turgut Tatlisumak Sahlgrenska University Hospital, Gothenburg, Sweden

Steering Committee
Dr. Jonathan Coutinho Amsterdam University Medical Center, Amsterdam, the Netherlands
Dr. Jukka Putaala Helsinki University Hospital, Helsinki, Finland
Prof. Jose Ferro Hospital de Santa Maria, Lisbon, Portugal
Prof. Turgut Tatlisumak Sahlgrenska University Hospital, Gothenburg, Sweden
Drs. Mayte Sanchez van Kammen Amsterdam University Medical Center, Amsterdam, the Netherlands
Dr. Diana Aguiar de Sousa Hospital de Santa Maria, Lisbon, Portugal
Dr. Katarina Jood Sahlgrenska University Hospital, Gothenburg, Sweden
All national leaders (see Appendix D)

Independent Adjudication Committee
Prof. Saskia Middeldorp, chair Amsterdam University Medical Center, Amsterdam, the Netherlands
Prof. Lia Neto Hospital de Santa Maria, Lisbon, Portugal
Prof. Marcel Arnold Bern University Hospital, Bern, Switzerland

8.3 Public disclosure and publication policy

This study will be registered at clinicaltrials.gov, and the protocol will be published prior to database closure. The results of the study will be published in a peer-reviewed journal. A first draft of the main study paper will be drafted by the Executive Committee together with a PhD student. All Steering Committee members will be co-authors on the main study paper. All other investigators will be listed on

the main study paper as members of the DOAC-CVT study group. In addition, participating centres may contribute one additional co-author after inclusion of 10 patients, and an additional co-author for each additional 20 patients included afterwards. All authors must fulfil the ICJME criteria for scientific authorship. After publication of the primary study results, each participating investigator may submit proposals for a substudy to the Executive Committee. After approval by the Executive Committee, the local investigator of that hospital may take the lead in the execution and authorship of that particular substudy.

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APPENDIX A.

Standard Operating Procedure for the Scoring of Cerebral Venous Recanalization

[SOP with example images to be added]

APPENDIX B.

ISTH definitions of major and clinically relevant non-major bleeding

Major bleeding[14]
Symptomatic presentation and
- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

Clinically relevant non-major bleeding[15]
Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
- Requiring medical intervention by a healthcare professional
- Leading to hospitalization or increased level of care
- Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

APPENDIX C.

All secondary outcomes at 6 months will be analysed with the same method as used in the main analysis. Confounders to be included in each propensity score calculation are listed below per outcome:

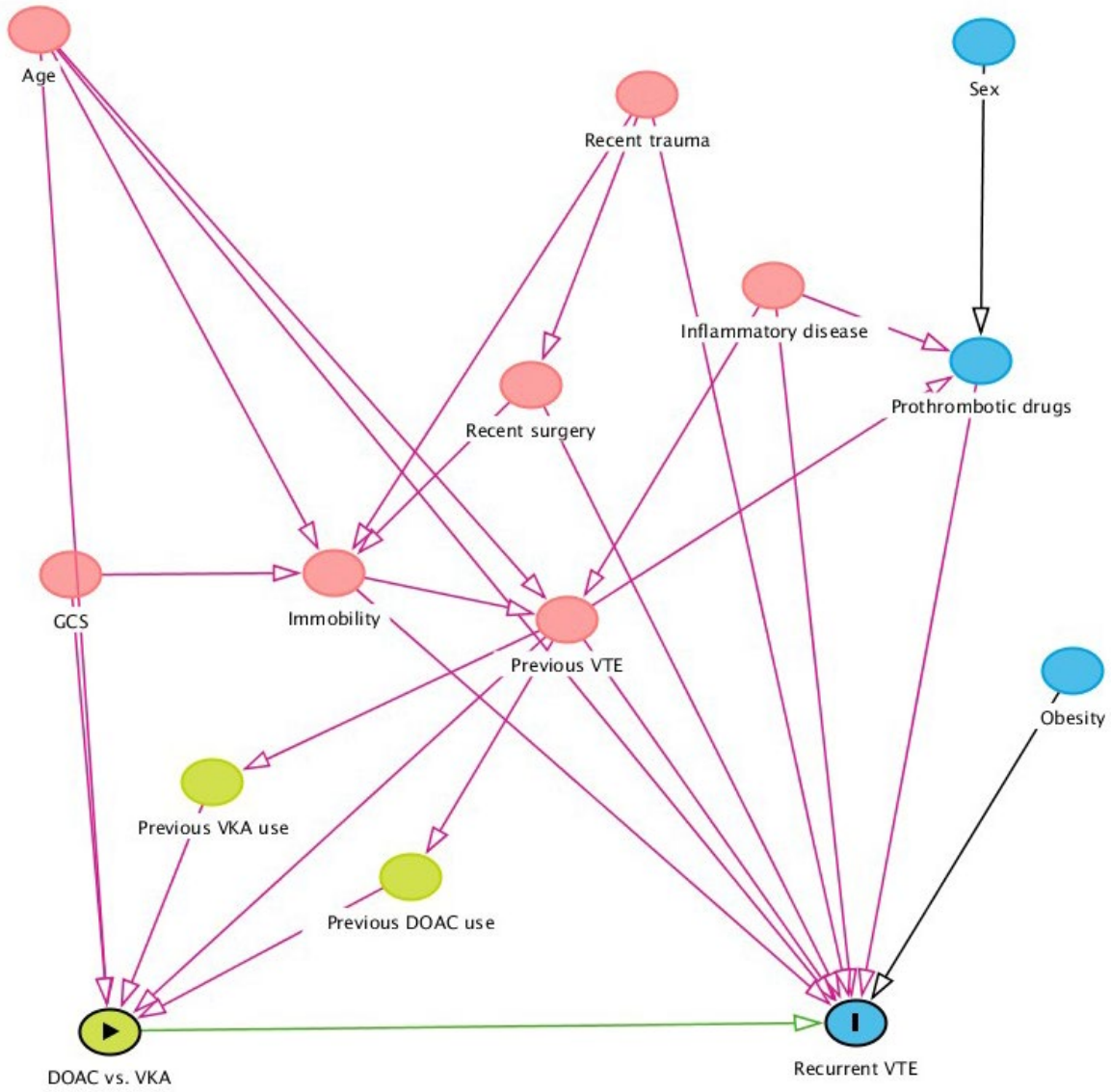

Figure 6. Directed Acyclic Graph depicting factors influencing anticoagulant treatment choice and risk of recurrent venous thrombotic event

Symptomatic recurrent VTE rate (Figure 6)

- Age at time of CVT diagnosis
- GCS at CVT diagnosis
- Previous VTE

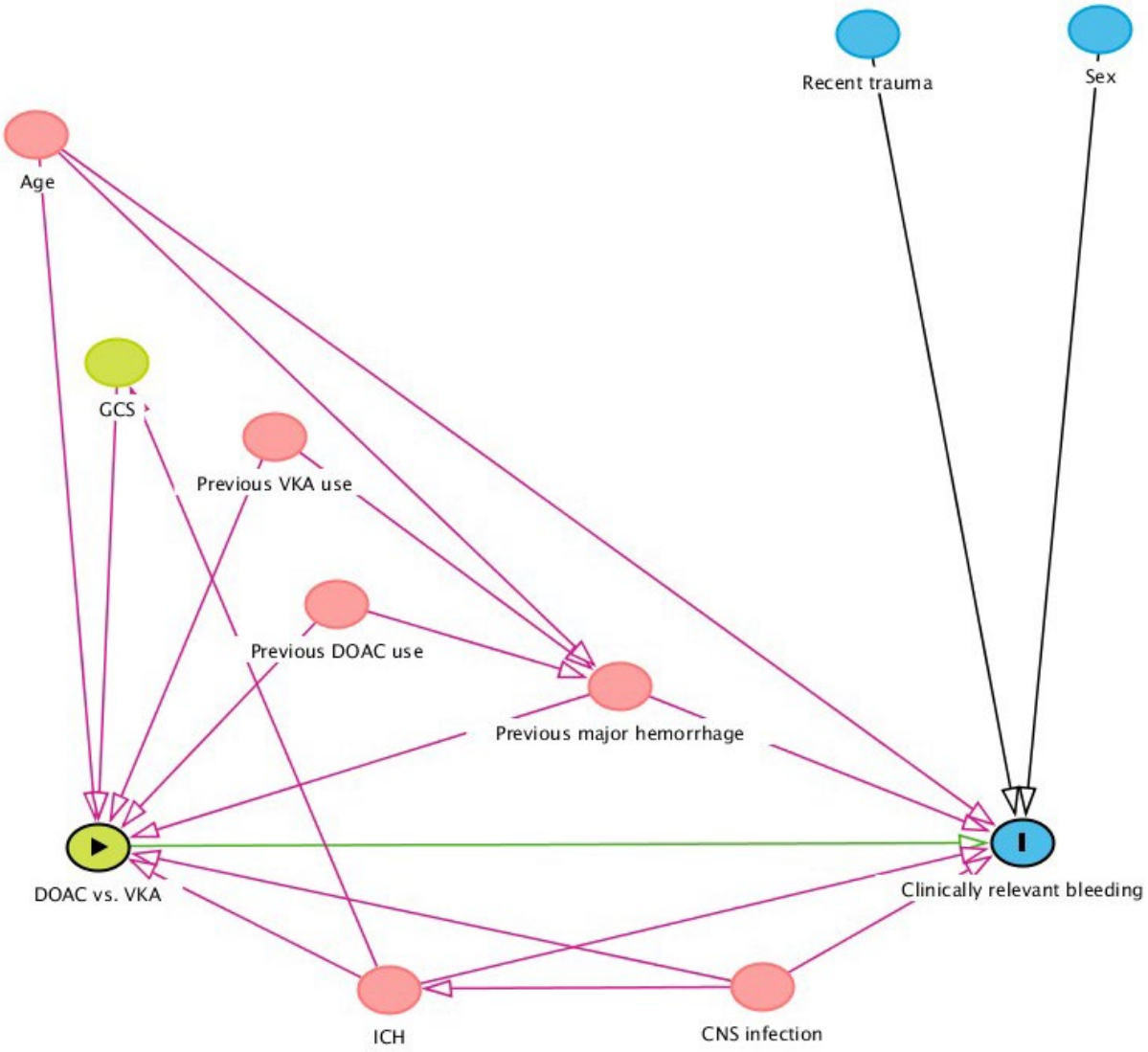

Figure 7. Directed Acyclic Graph depicting factors influencing anticoagulant treatment choice and risk of major or clinically relevant non-major bleeding

Major bleeding rate[14] (Figure 7)

- Age at CVT diagnosis
- CNS infection concurrent with the index CVT
- ICH at CVT diagnosis, or after diagnosis but before start of oral anticoagulant treatment
- Previous major bleeding prior to the index CVT (according to ISTH criteria)[14]

Clinically relevant non-major bleeding rate[15] (Figure 7)

- Age at CVT diagnosis
- CNS infection concurrent with the index CVT

- ICH at CVT diagnosis, or after diagnosis but before start of oral anticoagulant treatment
- Previous major bleeding prior to the index CVT (according to ISTH criteria)[14]

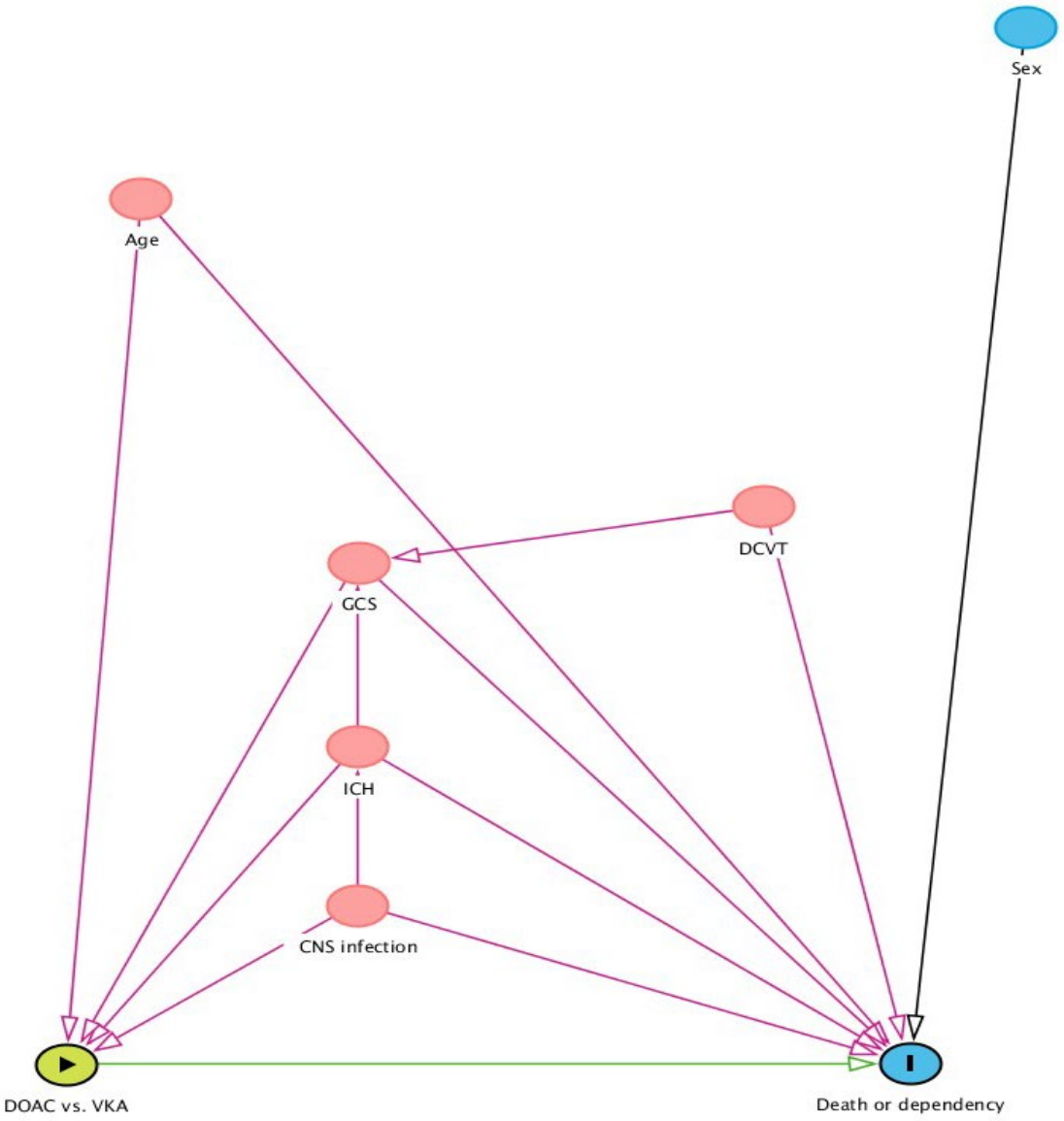

Figure 8. Directed Acyclic Graph depicting factors influencing anticoagulant treatment choice and risk of death or dependency[2]

All-cause mortality (Figure 8)

- Age at CVT diagnosis
- CNS infection concurrent with the index CVT
- GCS at CVT diagnosis
- ICH at CVT diagnosis, or after diagnosis but before start of oral anticoagulant treatment

Modified Rankin Scale score (Figure 8)

- Age at CVT diagnosis
- CNS infection concurrent with the index CVT
- GCS at CVT diagnosis
- ICH at CVT diagnosis, or after diagnosis but before start of oral anticoagulant treatment

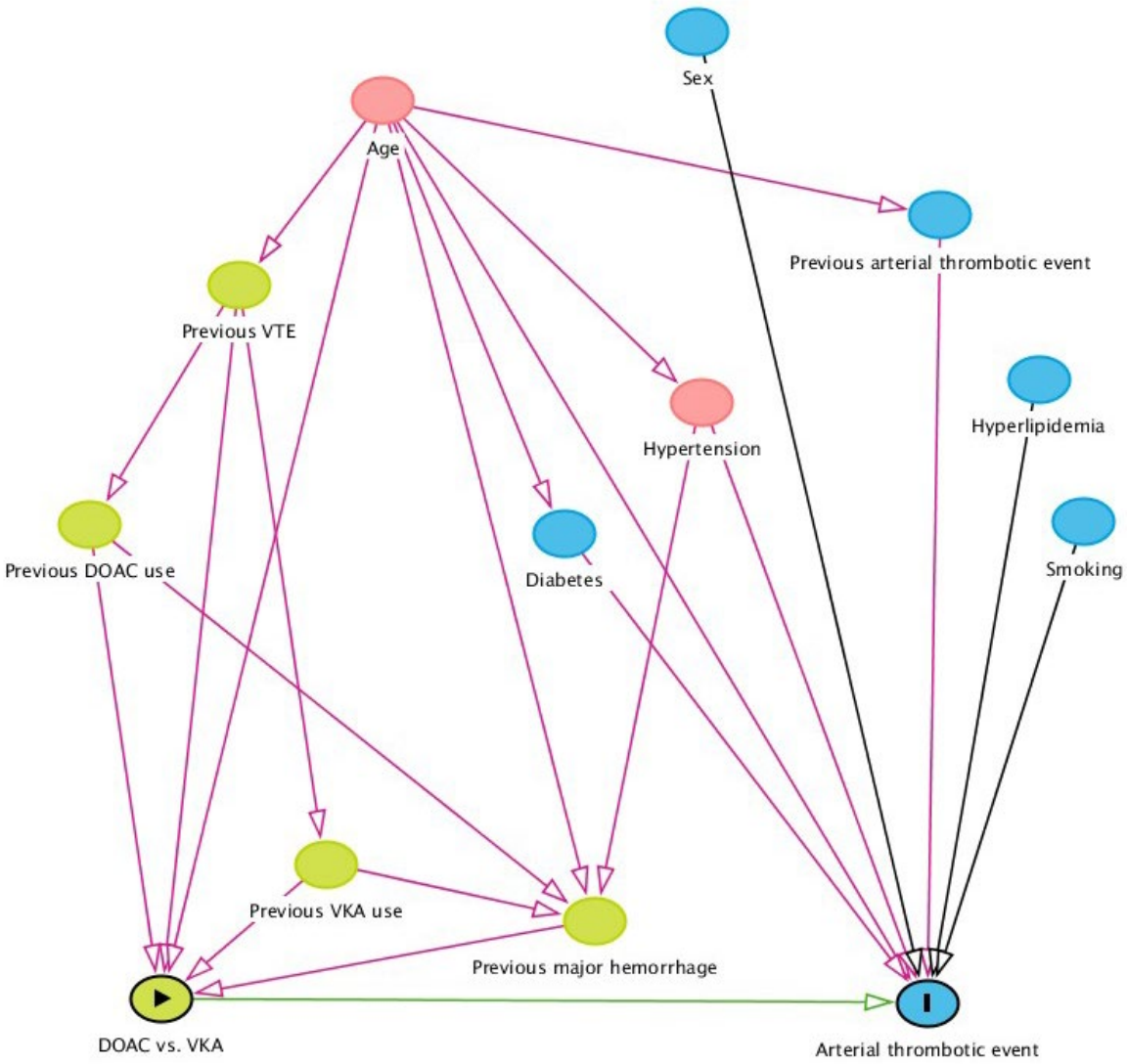

Figure 9. Directed Acyclic Graph depicting factors influencing anticoagulant treatment choice and risk of arterial thrombotic event

Arterial thrombotic events (Figure 9)

- Age at CVT diagnosis
- History of hypertension (as determined by treating physician)

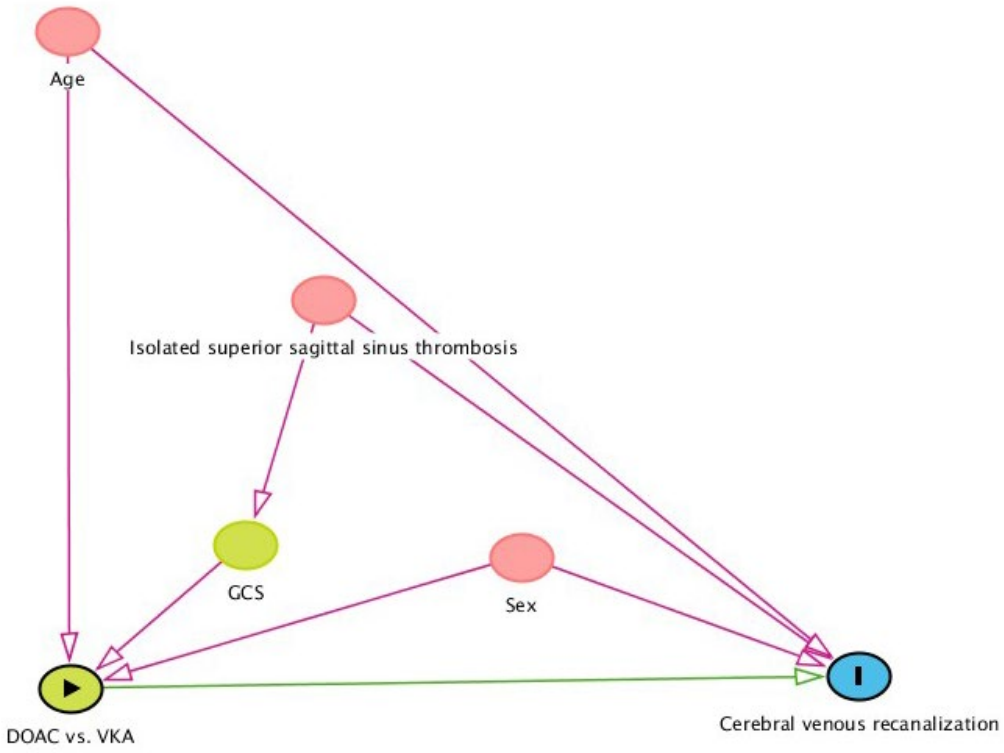

Figure 10. Directed Acyclic Graph depicting factors influencing anticoagulant treatment choice and cerebral venous recanalization[17]

Cerebral venous recanalization rate (Figure 10)

- Age at CVT diagnosis
- Sex
- Isolated superior sagittal sinus thrombosis at diagnosis

APPENDIX D.

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