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Original Article

Timing and Predictors of Recanalization After Anticoagulation in Cerebral Venous Thrombosis

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Background and Purpose Vessel recanalization after cerebral venous thrombosis (CVT) is associated with favorable outcomes and lower mortality. Several studies examined the timing and predictors of recanalization after CVT with mixed results. We aimed to investigate predictors and timing of recanalization after CVT.

Methods We used data from the multicenter, international AntiCoagulaTION in the Treatment of Cerebral Venous Thrombosis (ACTION-CVT) study of consecutive patients with CVT from January 2015 to December 2020. Our analysis included patients that had undergone repeat venous neuroimaging more than 30 days after initiation of anticoagulation treatment. Prespecified variables were included in univariate and multivariable analyses to identify independent predictors of failure to recanalize.

Results Among the 551 patients (mean age, 44.4±16.2 years, 66.2% women) that met inclusion criteria, 486 (88.2%) had complete or partial, and 65 (11.8%) had no recanalization. The median time to first follow-up imaging study was 110 days (interquartile range, 60–187). In multivariable analysis, older age (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.03–1.07), male sex (OR, 0.44; 95% CI, 0.24–0.80), and lack of parenchymal changes on baseline imaging (OR, 0.53; 95% CI, 0.29–0.96) were associated with no recanalization. The majority of improvement in recanalization (71.1%) occurred before 3 months from initial diagnosis. A high percentage of complete recanalization (59.0%) took place within the first 3 months after CVT diagnosis.

Conclusion Older age, male sex, and lack of parenchymal changes were associated with no recanalization after CVT. The majority recanalization occurred early in the disease course suggesting limited further recanalization with anticoagulation beyond 3 months. Large prospective studies are needed to confirm our findings.

Keywords Stroke; Sinus thrombosis, intracranial; Cerebral veins; Vascular disease

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Introduction

Cerebral venous thrombosis (CVT) is a rare but potentially devastating cause of neurologic disease. CVT accounts for 1% of all strokes, leads to poor outcome or death in about 15% of patients, and preferentially impacts a younger population.[1,2] Nearly 85% of CVT cases have at least one identifiable risk factor, including pregnancy, oral contraceptive pill (OCP) use, inherited and acquired thrombophilia, dehydration, trauma, malignancy, or infection.[1] Standard therapy consists of anticoagulation, typically with parenteral anticoagulation followed by an oral anticoagulant such as vitamin K antagonists or a direct oral anticoagulant.[3-5] In addition to preventing clot propagation and recurrent venous thrombosis, anticoagulant treatment improves the likelihood of vessel recanalization, which is associated with favorable outcomes and lower mortality after CVT.[6]

Several studies have evaluated predictors of recanalization after CVT. However, results have been conflicting, likely due to the small sample size and heterogeneity of the patient population and treatments used.[7-11] Additionally, studies investigating the rate and temporal profile of recanalization in patients with CVT produced variable results.[7,10] Recently, a multicenter study suggested that recanalization can start after a few days of treatment and is associated with decreased likelihood of expansion of associated brain lesions.[12] Another analysis of the RE-SPECT CVT (A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis) trial showed nearly 85% full or partial recanalization rates after 6 months of treatment.[5]

Given the link between recanalization and clinical outcomes, we sought to identify clinical and imaging predictors of recanalization and examine improvement in recanalization in patients with CVT receiving oral anticoagulation treatment.

Methods

Study design

We conducted a secondary analysis of the AntiCoagulaTION in the Treatment of Cerebral Venous Thrombosis (ACTION-CVT) cohort. ACTION-CVT is a multicenter, international (USA, Italy, Switzerland, and New Zealand) retrospective observational cohort of consecutive patients with symptomatic CVT confirmed on imaging who were admitted over a 6-year period (January 1, 2015 to December 31, 2020).[13] Patients included in the cohort were adults 18 years and older who were treated with oral anticoagulation for their CVT. The original cohort excluded patients who were not treated with oral anticoagulation as well as patients in whom a specific anticoagulation strategy (direct oral anticoagulant or vitamin K antagonist) would typically be used or preferred over another, such as in the setting of previously diagnosed antiphospholipid antibody syndrome, active cancer, and pregnancy.[14-16] For this analysis, we only included patients with repeat imaging (either computed tomography venography, magnetic resonance venography, magnetic resonance imaging brain, or cerebral angiography) a minimum of 30 days after anticoagulation treatment initiation. Our analysis excluded patients that had recanalization prior to initiation of anticoagulation treatment or received endovascular treatment for their CVT in an attempt to isolate recanalization from medical treatment alone. Institutional Review Board (IRB) approval from lifespan IRB (#1606888-5) was obtained to perform the study, and the requirement for written informed consent was waived. De-identified data are available upon reasonable request to the corresponding author.

Study variables

The following baseline demographic and clinical factors were abstracted from the electronic medical record: age, sex, race and ethnicity, body mass index (BMI), risk factors for CVT (history of prior venous thromboembolism [VTE], recent head trauma, recent lumbar puncture, recent mastoiditis/sinusitis, tobacco use, OCP use, being within 12 weeks postpartum, and family history of VTE), relevant clinical history (days from symptom onset to treatment initiation, clinical symptoms at presentation), imaging variables (brain imaging findings such as venous infarct, cerebral edema, intracerebral hemorrhage, and CVT vessel involvement), laboratory findings (abnormal genetic thrombophilia test results), and oral anticoagulant type (warfarin vs. direct oral anticoagulant). CVT involvement was divided into superficial, cortical, deep, or both superficial and deep vein involvement. For abnormal thrombophilia tests, we only considered presence of genetic mutations such as Factor V Leiden and/or prothrombin gene G20210A mutation, since testing for other thrombophilias (such as antiphospholipid syndrome or protein C, protein S, and antithrombin deficiency) can be inaccurate in the acute setting.[17]

Outcomes

Recanalization status was determined using serial, clinically indicated imaging, and was based on the official radiology report of any relevant repeat imaging study. Based on the original ACTION-CVT study, no recanalization is defined by no change or worsening in opacification or flow in the affected cerebral sinus or vein from baseline imaging, partial recanalization is improved opacification or flow in the affected cerebral sinus or vein but with residual thrombus present on follow-up imaging, and complete recanalization is full recanalization of the thrombosed vein or sinus without any residual thrombus.[13] Our outcomes were no

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recanalization seen on the last venous imaging and improvement in recanalization over time.

Statistical analysis

Baseline demographic and clinical characteristics are reported using standard descriptive statistics. First, we performed univariate analysis (chi-squared test, t-test, Wilcoxon rank-sum test) to identify predictors of no recanalization using prespecified variables: age, female sex, BMI ≥30, active smoking, superficial and deep vein involvement, OCP use, occurrence within 12 weeks postpartum, recent mastoiditis, recent head trauma, recent lumbar puncture, personal history of VTE, family history of VTE, presence of abnormal genetic thrombophilia test result, days from symptom onset to treatment initiation, and presence of parenchymal changes (venous infarct, cerebral edema, or intracerebral hemorrhage). Missing data were not imputed. Variables significant to $P<0.10$ in the univariate logistic regression analysis were included in the multivariable logistic regression model. We performed three sensitivity analyses. First, we examined predictors of no recanalization using imaging obtained within 6 months ±30 days from admission. Recanalization status was carried over only for recanalized patients if no subsequent imaging was available. We chose this time interval based on current CVT guidelines that recommend repeat imaging within 3 to 6 months of initial diagnosis.[2] Second, we excluded patients that had "partial recanalization" throughout the study time and examined predictors of "no recanalization" compared to "complete recanalization." The rationale for this sensitivity analysis is to account for possible differences in definitions for complete and partial recanalization between the included institutions. Third, we performed a *post hoc* analysis where we included patients that only had repeat imaging performed within 30 days of anticoagulation initiation (n=60) in order to account for early recanalization.

For our second objective, we assessed improvement in recanalization (partial to complete recanalization, or no recanalization to partial or complete recanalization). We chose to review imaging done at clinically-relevant time intervals where repeat imaging is recommended by CVT guidelines: <75 days, 3 months ±15 days, 6 months ±30 days, and 12 months ±30 days from admission.[2] The first follow-up scan was assessed for improvement and complete recanalization compared to the baseline admission scan; all follow-up scans were compared with their preceding scan. The rate of complete recanalization represents the cases of partial or no recanalization on prior image that were found to have complete recanalization at the follow-up time point. Since we do not know exactly when complete recanalization occurred, we considered the time to complete recanalization as the time between initial diagnosis and first follow-up imaging study showing complete recanalization. In patients with recurrent CVT on imaging, the image prior to recurrence was assessed for recanalization status. Data were analyzed using Stata (version 15.1; StataCorp, College Station, TX, USA) and a $P<0.05$ was considered statistically significant.

Results

Of 1,025 patients, 551 patients (mean age, 44.4±16.2 years, 66.2% women) met inclusion criteria for our analysis (Figure 1). Patients included in the analysis were younger, more likely to be women, have a family history of VTE, use OCPs, and longer duration of symptom onset to anticoagulation initiation compared to patients that were excluded (Supplementary Table 1). The majority of included patients were non-Hispanic (90.0%) and White (74.9%). Among those that identified as women, 42.5% were on an OCP and 4.6% were in the 12-week postpartum period when they had the CVT. Factor V Leiden and/or prothrombin gene G20210A mutation were detected in 10.7% patients. A minority of patients (11.3%) had both superficial and deep vein involvement.

The median number of follow-up imaging studies was 2 (interquartile range [IQR], 1–2). The median follow-up was 411 days (IQR, 202–759), and median time to first follow-up imaging study was 110 days (IQR, 60–187). During follow-up time, 219 (39.7%) had complete, 267 (48.5%) had partial, and 65 (11.8%) had no recanalization. The majority of patients had the same imaging modality performed during their initial diagnosis and follow-up (73.3%).

Predictors of no recanalization: univariate analysis

Baseline characteristics of patients with any recanalization (com-

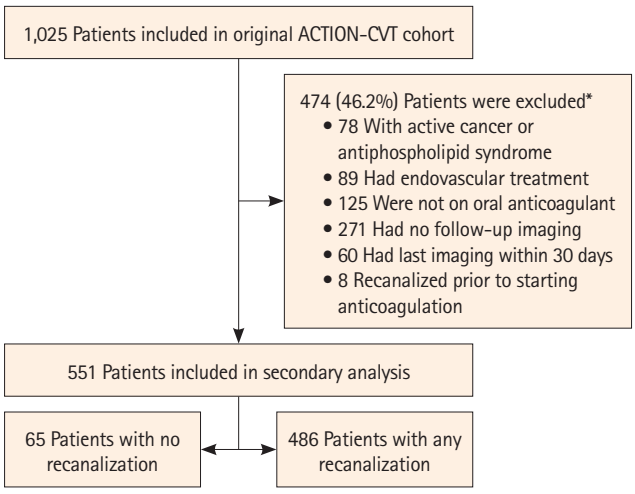

Figure 1. Flow diagram depicting patient inclusion in secondary analysis. ACTION-CVT, AntiCoagulaTION in the Treatment of Cerebral Venous Thrombosis. *Numbers do not sum to group total as some patients were excluded for more than one reason.

plete or partial) and no recanalization are included in Table 1. Patients with no recanalization were older (56.4±15.6 years vs. 42.8±15.6 years), less likely to be women (44.6% vs. 69.1%), had lower rates of OCP use (7.7% vs. 31.5%), and were less likely to have both superficial and deep vein involvement (3.1% vs. 12.4%). In univariate analysis, older age was associated with greater odds of no recanalization (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.04–1.07; *P*<0.001) (Table 2). Female sex (OR, 0.36; 95% CI, 0.21–0.61; *P*<0.001), superficial and deep vein involvement (OR, 0.23; 95% CI 0.05–0.94; *P*=0.04), presence of parenchymal changes (OR, 0.46; 95% CI, 0.27–0.78; *P*<0.01), presence of provoking factors (OR, 0.49; 95% CI, 0.28–0.85; *P*=0.01), and OCP use (OR, 0.18; 95% CI, 0.07–0.46; *P*<0.001) were all associated with recanalization (Table 2). In a *post hoc* analysis, we found no difference in clinical functional outcomes (modified Rankin Scale 0–2) at 90 days between patients with and without recanalization at 90 days (94.8% vs. 94.7%; *P*>0.999).

Predictors of no recanalization: multivariable analysis

In multivariable analysis, factors associated with no recanalization were older age (OR, 1.05; 95 % CI 1.03–1.07; *P*<0.001), male sex (OR, 0.44; 95% CI, 0.24–0.80; *P*=0.01), and lack of parenchymal changes (OR, 0.53; 95% CI, 0.29–0.96; *P*=0.04) (Table 3). There was a trend towards an inverse association between both superficial and deep vein involvement and no recanalization (OR, 0.23; 95% CI, 0.05–1.02; *P*=0.05).

Sensitivity analyses

Our results remained largely unchanged in our three sensitivity analyses. When examining predictors of no recanalization on imaging obtained 6 months after diagnosis, we found a similar association between no recanalization and older age (OR, 1.05; 95% CI, 1.03–1.07; *P*<0.001) and male sex (OR, 0.42; 05% CI, 0.22–0.82; *P*=0.01) (Supplementary Tables 2 and 3). In this sensitivity analysis, involvement of both superficial and deep vein involvement was inversely associated with no recanalization (OR, 0.11; 95% CI, 0.01–0.85; *P*=0.03). Our second sensitivity analysis, where we excluded patients with "partial recanalization" throughout the study duration, also confirmed that older age, male sex, and lack of parenchymal changes were predictors of no recanalization (Supplementary Table 4). Our third sensitivity analysis, where we included patients with repeat imaging irrespective of the timing (including patients with repeat imaging only in the first 30 days), also confirmed that older age, male sex, and lack of parenchymal changes were predictors of no recanalization (Supplementary Table 5).

Table 1. Baseline characteristics of included patients (n=551)

Characteristic	No recanalization (n=65)	Complete or partial recanalization (n=486)	*P*
Patient characteristics			
Age (yr)	56.4±16.1	42.8±15.6	<0.001
Female sex	29 (44.6)	336 (69.1)	<0.001
Race			
White	51 (78.5)	360 (74.4)	0.48
Black	8 (12.3)	58 (12.0)	0.94
Asian	2 (3.1)	22 (4.5)	>0.99
Ethnicity			
Non-Hispanic	60 (92.3)	434 (89.7)	0.66
Hispanic	5 (7.7)	50 (10.3)	0.66
Body mass index ≥30	25 (38.5)	204 (42.0)	0.59
Personal history of VTE or PE	10 (15.4)	44 (9.1)	0.11
Family history of VTE	5 (7.7)	67 (13.9)	0.24
Presence of provoking factors	21 (32.3)	240 (49.4)	0.01
Recent head trauma	6 (9.2)	42 (8.6)	0.01
Recent mastoiditis or sinusitis	9 (13.8)	41 (8.4)	0.87
Recent lumbar puncture	2 (3.1)	20 (4.1)	>0.99
12 weeks postpartum	1 (1.5)	16 (3.3)	0.71
Oral contraceptive pill use	5 (7.7)	150 (31.5)	<0.001
Active smoking	7 (10.8)	44 (9.1)	0.67
Clinical presentation			
Headache	48 (73.8)	397 (81.7)	0.13
Encephalopathy	11 (16.9)	66 (13.6)	0.47
Papilledema	7 (11.1)	57 (12.4)	0.76
Focal deficit	17 (31.5)	138 (33.3)	0.80
Seizure	9 (13.8)	112 (23.0)	0.09
Coma	0 (0.0)	8 (1.6)	0.61
FVL and/or PTG*	4/40 (10.0)	41/380 (10.8)	>0.99
Imaging findings			
CVT involvement			
Either superficial, deep, or cortical vein	63 (96.9)	425 (87.6)	0.02
Superficial and deep vein involvement	2 (3.1)	60 (12.4)	0.02
Venous infarct	12 (18.5)	125 (25.7)	0.20
Cerebral edema	12 (18.5)	139 (28.6)	0.09
Intracranial hemorrhage	13 (20.0)	184 (37.9)	0.01
Hospital course			
Symptom onset to anticoagulation initiation (day)	5.5 (2–29)	5 (2–14)	0.38
Oral anticoagulant medication†			
Warfarin	43 (66.2)	331 (68.1)	0.75
Compliance with INR checks	37/42 (88.1)	298/324 (92.0)	0.38
Apixaban	22 (33.8)	157 (32.3)	0.80

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Table 1. Continued

Characteristic	No recanalization (n=65)	Complete or partial recanalization (n=486)	*P*
Rivaroxaban	6 (9.2)	48 (9.9)	0.87
Dabigatran	2 (3.1)	34 (7.0)	0.29
Duration of oral anticoagulation (day)	195 (106–350)	178 (94–241)	0.08
Duration of treatment to imaging (day)‡	227 (149–389)	186 (112–310)	0.05

Data are presented as mean±standard deviation, number (%), or median (interquartile range). The totals of some categorical variables may not match the group populations due to missing data.
VTE, venous thromboembolism; PE, pulmonary embolism; FVL, Factor V Leiden; PTG, prothrombin gene G20210A mutation; CVT, cerebral venous thrombosis; INR, international normalized ratio.
*% represent the number of patients with a positive result (numerator) over the number of patients who underwent the specific test (denominator); †Numbers do not sum to group totals because patients that received both warfarin and a direct oral anticoagulant at different time points were included under both medications; ‡First image that shows signs of recanalization; in cases of no recanalization, we used the date when the most recent image was obtained.

Timing of recanalization

The majority of improvement (71.1%) in recanalization (from no recanalization to partial or complete, and from partial to complete recanalization) occurred within less than 3 months after diagnosis. The percentage of improvement further decreased to 33.3%, 25.7%, and 20.0% by 3, 6, and 12 months after diagnosis (Table 4). Among all the patients with complete recanalization, the majority of cases (59.0%) occurred at 3 months after diagnosis; another 15.4% and 16.7% had complete recanalization at close to 6 and 12 months, respectively. Scans showing complete recanalization were performed at a median of 170 days following index scan (IQR, 93–232 days).

Discussion

In a large, multicenter, international, retrospective, observational study of patients with CVT, we found that older age, male sex, and lack of parenchymal changes were associated with no recanalization after CVT. The majority of improvement in recanalization and complete recanalization occurred within the first 3 months.

Our findings add to the growing literature on predictors and rates of recanalization after CVT.[6] Two studies found that younger age (using <50 and <37 years as cut-off) was associated with a greater rate of recanalization[7,10] while others found no association between age and recanalization.[8,9] Apart from lower rates of recanalization, older age is an independent predictor of higher rates of death and disability after CVT, perhaps due to the differences in clinical presentation and associated risk factors such as hypercoagulability of malignancy.[18] Similarly, the data on sex and recanalization is inconsistent, with some studies finding that women were more likely to have complete recanalization,[9,10] while others found no difference.[7,8,11] Our study is line with a systematic review and meta-analysis showing that younger age and female sex were the most consistent predictors of recanalization.[6] Our study builds on these findings by using a larger and heterogenous cohort of patients, thereby increasing the power

Table 2. Univariate analysis of no recanalization of vein(s) on repeat imaging

Variable	No recanalization	
	Odds ratio (95% CI)	*P*
Age, years	1.05 (1.04–1.07)	<0.001
Female sex	0.36 (0.21–0.61)	<0.001
Body mass index ≥30	0.86 (0.51–1.47)	0.59
Active smoking	1.20 (0.52–2.80)	0.67
Superficial and deep vein involvement	0.23 (0.05–0.94)	0.04
Presence of provoking factors	0.49 (0.28–0.85)	0.01
Recent head trauma	1.08 (0.44–2.64)	0.87
Recent mastoiditis or sinusitis	1.74 (0.81–3.78)	0.16
Recent lumbar puncture	0.75 (0.17–3.24)	0.69
12 weeks postpartum	0.45 (0.06–3.48)	0.45
Oral contraceptive pill use	0.18 (0.07–0.46)	<0.001
History of VTE or PE	1.83 (0.87–3.83)	0.11
Family history of VTE	0.52 (0.20–1.34)	0.17
Abnormal genetic thrombophilia test*	0.90 (0.42–1.91)	0.77
Symptom onset to treatment initiation, >5 days	1.06 (0.62–1.78)	0.84
Presence of parenchymal changes†	0.46 (0.27–0.78)	<0.01

CI, confidence interval; VTE, venous thromboembolism; PE, pulmonary embolism; CT, computed tomography; MRI, magnetic resonance imaging.
*Includes presence of Factor V Leiden and prothrombin gene G20210A mutation; †Venous infarct, cerebral edema, or intracerebral hemorrhage as seen on non-contrast CT Head or MRI brain.

Table 3. Multivariable predictors of no recanalization of vein(s) on repeat imaging

Variable	No recanalization	
	Odds ratio (95% CI)	*P*
Age, years	1.05 (1.03–1.07)	<0.001
Female sex	0.44 (0.24–0.80)	0.01
Presence of provoking factors	0.91 (0.50–1.67)	0.76
Oral contraceptive pill use	0.58 (0.20–1.67)	0.32
Superficial and deep vein involvement	0.23 (0.05–1.02)	0.05
Presence of parenchymal changes*	0.53 (0.29–0.96)	0.04

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.
*Venous infarct, cerebral edema, or intracerebral hemorrhage as seen on non-contrast CT Head or MRI brain.

Table 4. Percentage of patients with any improvement in recanalization and complete recanalization over time

Time from diagnosis	Improvement* in recanalization (%) (95% CI)	Complete recanalization† (%) (95% CI)
0–74 days	71.1 (63.7–77.5)	35.2 (25.9–45.9)
3 months ± 15 days	33.3 (17.0–55.0)	23.8 (9.7–47.6)
6 months ± 30 days	25.7 (16.9–37.0)	15.4 (8.4–26.5)
12 months ± 30 days	20.0 (8.2–41.2)	16.7 (6.1–38.3)

CI, confidence interval.
*Improvement is defined as no recanalization to partial or complete recanalization, and partial to complete recanalization. Analysis included patients with follow up imaging after initial hospitalization; †Represents patients that previously had partial or no recanalization and now developed complete recanalization during the time point.

of detecting a statistically meaningful association.

Our study found a possible association between recanalization and parenchymal changes and superficial and deep vein involvement. Parenchymal changes such as venous infarct, cerebral edema, or intracranial hemorrhage typically cause neurological deficits and seizures, both of which may result in earlier presentation to the emergency room and a lower likelihood of misdiagnosing a CVT.[19] Parenchymal changes may also be a marker for an acutely developing rather than a chronic clot, which may be more responsive to anticoagulation therapy. Although we were unable to confirm this association in our secondary analysis, we suspect this may have been due to a lack of power rather than a lack of association. The presence of both superficial and deep vein involvement showed a trend towards an association with recanalization in our primary analysis, and an association was present in the secondary analysis restricted to recanalization status 6 months after diagnosis. Possible explanations include an underlying thrombophilia causing a more generalized clot that is responsive to anticoagulation, or a more severe disease from an extensive clot leading to earlier presentation and treatment.

Several studies have examined recanalization rates after CVT.[6] In a meta-analysis of 8 studies with 382 patients, approximately 80% of cases demonstrated recanalization (complete or partial) 9 months after diagnosis.[6] In addition, the RE-SPECT CVT trial showed that 85% of patients achieved recanalization at 6 months.[5] However, many of these studies were retrospective, or with small sample size, or with imaging not obtained at routine time intervals, thereby limiting the ability to estimate rates of recanalization. Furthermore, a recent important yet small study showed that very early partial recanalization occurred in 68% of CVT cases and was associated with increased odds of regression and reduced odds of progression of non-hemorrhagic brain lesions.[12] Our study builds on prior findings by showing the greatest improvement in recanalization and complete recanalization occurs within the first 3 months and thus continuation of anticoagulation beyond this time frame may not be beneficial in achieving further recanalization.

The strengths of our study lie in its use of a large cohort of patients from academic and non-academic hospitals from various countries, increasing the generalizability of our results. Our findings must be considered in light of several limitations. First, the retrospective and observational design of the study limits our ability to assess for recanalization at scheduled intervals (for example, every 3 months), given that the time between imaging was left at the discretion of the treating physician. Additionally, around 45% of patients in the original ACTION-CVT cohort did not have recanalization data and were not included in our analysis. Therefore, our findings are only relevant to patients who survived and had at least one repeat imaging study performed. Similarly, given that our study was a secondary analysis, we were reliant on provoking factors that were documented in the initial ACTION-CVT cohort. We therefore lacked information on additional provoking factors for CVT, such as presence of inflammatory disorders. Second, patients with history of known antiphospholipid syndrome, pregnancy, and active malignancy were excluded from the original cohort. This may introduce a selection bias and limit our ability to determine whether these CVT risk factors may be associated with recanalization. Third, the retrospective nature of our study does not allow us to control for differences in imaging modality and their diverse accuracies during initial admission and follow-up. However, the majority of patients had the same imaging modality performed throughout their disease course. Fourth, we lacked central adjudication of our images. To reduce bias in the absence of centralized scoring of images, the primary outcome was determined by official radiology reads rather than site investigators. However, no scale was used to quantify recanalization, and accuracy and interobserver agreement of the recanalization status is unknown. Fifth, in patients with multiple vein involvement, we also do not have data on recanalization of each vein, which limits our knowledge on whether there is a difference in recanalization rates between superficial and deep veins. We also lack information on reversible parenchymal lesions, which has previously been found to be associated with early recanalization.[12] Sixth, our second objective, the timing of recanalization, is limited by the expectation that patients who are not recanalized by a certain time point are the ones that are going to continue getting rescanned. This bias may affect the percentage of patients with improvement and complete recanalization, especially as time elapses from the index event. Similarly, repeat imaging was not systematically performed, which can introduce a selection and indication bias. Seventh, we lack information on the direct oral anticoagulant

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doses and percentage of time that international normalized ratio was within therapeutic range, both of which could influence recanalization.

Conclusions

In a large, multicenter cohort of patients with CVT, we found that older age, male sex, and lack of parenchymal changes were associated with no recanalization. The majority of improvement in recanalization in CVT occurs within the first 3 months, suggesting that anticoagulation therapy beyond the first 3 months may have limited value in achieving further recanalization. Our study also suggests a low utility in assessing for further recanalization after the first 6 months; however, given our limitations, further studies are needed to validate our findings. Future studies should aim to determine whether certain antithrombotic regimens may be more effective in patients with predictors of no recanalization. Prospective studies with imaging performed at several defined time intervals (potentially 2 weeks, 3 months, 6 months, and 1 year) are needed to overcome the limitations of our study and prior studies and address the issue of timing of recanalization in CVT patients.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.00213.

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Conflicts of interest

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Author contribution

Conceptualization: SSO, LS, SY, AC, SC, NSP. Study design: SSO, LS, SY, AC, SC, NSP. Methodology: SSO, LS, SY, AC, SC, NSP. Data collection: all authors. Investigation: LS, SY. Statistical analysis: LS, SY. Writing—original draft: SSO, AC. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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Supplementary Table 1. Baseline characteristics of included and excluded patients

Characteristic	Included patients (n=551)	Excluded patients (n=474)
Patient characteristics		
Age (yr)	44.4±16.2	47.5±17.6
Female sex	365 (66.2)	278 (58.6)
Race		
White	411 (74.9)	299 (63.8)
Black	66 (12.0)	94 (20.0)
Asian	24 (4.4)	16 (3.4)
Ethnicity		
Non-Hispanic	494 (90.0)	418 (89.9)
Hispanic	55 (10.0)	47 (10.1)
Body mass index ≥30	229 (41.6)	195 (41.1)
CVT risk factors		
Personal history of VTE or PE	54 (9.8)	67 (14.1)
Family history of VTE	72 (13.1)	29 (6.2)
Recent head trauma	48 (8.7)	41 (8.7)
Recent mastoiditis or sinusitis	50 (9.1)	39 (8.2)
Recent lumbar puncture	22 (4.0)	24 (5.1)
12 weeks postpartum	17 (3.1)	21 (4.5)
Oral contraceptive pill use	155 (28.7)	80 (17.2)
Active smoking	51 (9.3)	95 (20.2)
Symptoms onset to diagnosis (day)	5 (1–11)	3 (1–7)
Clinical presentation		
Headache	445 (80.8)	317 (67.2)
Encephalopathy	77 (14.0)	132 (27.9)
Papilledema	64 (12.3)	36 (8.2)
Focal deficit	155 (33.0)	121 (36.3)
Seizure	121 (22.0)	122 (25.8)
Coma	8 (1.5)	21 (4.4)
FVL and/or PTG*	45/420 (10.7)	30/279 (10.8)
Imaging findings		
CVT involvement		
Either superficial, deep, or cortical vein	488 (88.7)	425 (85.6)
Superficial and deep vein involvement	62 (11.3)	68 (14.4)
Venous infarct	137 (24.9)	136 (28.7)
Cerebral edema	151 (27.4)	167 (35.2)
Intracranial hemorrhage	197 (35.8)	193 (40.7)
Hospital course		
Symptom onset to anticoagulation initiation (day)	5 (2–14)	4 (2–9)
Oral anticoagulant medication†		
Warfarin	374 (67.9)	224 (47.3)
Dabigatran	179 (32.5)	119 (25.1)
Rivaroxaban	54 (9.8)	34 (7.2)
Apixaban	36 (6.5)	24 (5.1)

Data are presented as mean±standard deviation, number (%), or median (interquartile range). The totals of some categorical variables may not match the group populations due to missing data.
CVT, cerebral venous thrombosis; VTE, venous thromboembolism; PE, pulmonary embolism; FVL, Factor V Leiden; PTG, prothrombin gene G20210A mutation.
*% represent the number of patients with a positive result (numerator) over the number of patients that underwent the specific test (denominator); †Numbers do not sum to group totals because patients that received both warfarin and a direct oral anticoagulant at different time points were included under both medications.

Supplementary Table 2. Baseline characteristics of patients included in sensitivity analysis examining predictors of no recanalization on imaging obtained 6 months after diagnosis (n=447)

Characteristic	No recanalization (n=57)	Complete or partial recanalization (n=390)
Patient characteristics		
Age (yr)	55.6±5.5	42.3±15.5
Female sex	25 (43.9)	272 (69.7)
Race		
White	45 (78.9)	291 (75.0)
Black	7 (12.3)	47 (12.1)
Asian	2 (3.5)	17 (4.4)
Ethnicity		
Non-Hispanic	52 (91.2)	348 (89.7)
Hispanic	5 (8.8)	40 (10.3)
Body mass index ≥30	21 (36.8)	163 (41.8)
CVT risk factors		
Personal history of VTE or PE	6 (10.5)	32 (8.2)
Family history of VTE	4 (7.0)	53 (13.7)
Recent head trauma	4 (7.0)	35 (9.0)
Recent mastoiditis or sinusitis	8 (14.0)	30 (7.7)
Recent lumbar puncture	2 (3.5)	19 (4.9)
12 weeks postpartum	0 (0.0)	14 (3.6)
Oral contraceptive pill use	7 (12.3)	131 (34.2)
Active smoking	4 (7.0)	34 (8.8)
Clinical presentation		
Headache	43 (75.4)	323 (82.8)
Encephalopathy	9 (15.8)	52 (13.3)
Papilledema	6 (10.9)	49 (13.5)
Focal deficit	13 (27.1)	114 (34.0)
Seizure	12 (21.1)	89 (22.8)
Coma	0 (0.0)	5 (1.3)
FVL and/or PTG*	4 (10.5)	32 (10.6)
Imaging findings		
CVT involvement		
Either superficial, deep, or cortical vein	56 (98.2)	336 (86.2)
Superficial and deep vein involvement	1 (1.8)	54 (13.8)
Venous infarct	12 (21.1)	92 (23.6)
Cerebral edema	10 (17.5)	106 (27.2)
Intracranial hemorrhage	14 (24.6)	140 (35.9)
Hospital course		
Symptom onset to anticoagulation initiation (day)	5 (2–29)	5 (2–14)
Oral anticoagulant medication†		
Warfarin	39 (68.4)	264 (67.7)
Dabigatran	20 (35.1)	123 (31.5)
Rivaroxaban	5 (8.8)	35 (9.0)
Apixaban	2 (3.5)	30 (7.7)
Duration of oral anticoagulation (day)	209 (181–210)	149 (90–190)
Duration of treatment to imaging (day)‡	209 (200–210)	157 (93–196)

Data are presented as mean±standard deviation, number (%), or median (interquartile range). The totals of some categorical variables may not match the group populations due to missing data.
CVT, cerebral venous thrombosis; VTE, venous thromboembolism; PE, pulmonary embolism; FVL, Factor V Leiden; PTG, prothrombin gene G20210A mutation.
*% represent the number of patients with a positive result (numerator) over the number of patients who had available data or underwent the specific test (denominator); †Numbers do not sum to group totals because patients that received both warfarin and a direct oral anticoagulant at different time points were included under both medications; ‡First image that shows signs of recanalization; in cases of no recanalization, we used the date when the most recent image was obtained.

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Supplementary Table 3. Univariate and multivariable analysis of no recanalization of vein(s) on repeat imaging

Variable	Univariate analysis	
	Odds ratio (95% CI)	*P*
Age, years	1.05 (1.03–1.07)	<0.001
Female sex	0.34 (0.19–0.60)	<0.001
Body mass index ≥30	0.81 (0.46–1.44)	0.48
Active smoking	0.78 (0.27–2.39)	0.66
Superficial and deep vein involvement	0.11 (0.02–0.82)	0.03
Provoking factors		
Recent head trauma	0.77 (0.26–2.24)	0.63
Recent mastoiditis or sinusitis	1.96 (0.85–4.52)	0.11
Recent lumbar puncture	0.71 (0.16–3.13)	0.65
12 weeks postpartum	0.33 (0.00–2.03)	0.28
Birth control use	0.27 (0.12–0.61)	<0.01
History of VTE or PE	1.32 (0.53–3.30)	0.56
Family history of VTE	0.48 (0.17–1.37)	0.17
Abnormal genetic thrombophilia test*	0.91 (0.41–2.05)	0.82
Symptom onset to treatment initiation, >5 days	0.98 (0.56–1.71)	0.93
Presence of parenchymal changes†	0.54 (0.30–0.95)	0.03
	Multivariable analysis	
	Odds ratio (95% CI)	*P*
Age, years	1.05 (1.03–1.07)	<0.001
Female sex	0.42 (0.22–0.82)	0.01
Superficial and deep vein involvement	0.11 (0.01–0.85)	0.03
Birth control use	0.94 (0.35–2.51)	0.90
Presence of parenchymal changes†	0.56 (0.39–1.04)	0.07

CI, confidence interval; VTE, venous thromboembolism; PE, pulmonary embolism; CT, computed tomography; MRI, magnetic resonance imaging.
*Includes presence of Factor V Leiden, and prothrombin gene G20210A mutation; †Venous infarct, cerebral edema, or intracerebral hemorrhage as seen on non-contrast CT Head or MRI brain.

Supplemental Table 4. Multivariable analysis of predictors of no recanalization compared to complete recanalization

Variable	Odds ratio (95% CI)	*P*
Age, years	1.05 (1.03–1.07)	<0.001
Female sex	0.44 (0.24–0.80)	0.01
Superficial and deep vein involvement	0.34 (0.06–1.93)	0.22
Birth control use	0.59 (0.19–1.80)	0.35
Presence of parenchymal changes*	0.45 (0.23–0.90)	0.02

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.
*Venous infarct, cerebral edema, or intracerebral hemorrhage as seen on non-contrast CT Head or MRI brain.

Supplementary Table 5. Univariate and multivariable analysis of no recanalization, including patients with repeat imaging within 30 days of anticoagulation initiation

Variable	Univariate analysis	
	Odds ratio (95% CI)	*P*
Age, years	1.05 (1.04–1.07)	<0.001
Female sex	0.36 (0.21–0.61)	<0.001
Body mass index ≥30	0.86 (0.51–1.47)	0.59
Active smoking	1.20 (0.52–2.80)	0.67
Superficial and deep vein involvement	0.44 (0.17–1.13)	0.09
Provoking factors		
Recent head trauma	1.08 (0.44–2.64)	0.87
Recent mastoiditis or sinusitis	1.74 (0.81–3.78)	0.16
Recent lumbar puncture	0.74 (0.17–3.24)	0.69
12 weeks postpartum	0.45 (0.06–3.48)	0.45
Birth control use	0.18 (0.07–0.46)	<0.001
History of VTE or PE	1.83 (0.87–3.83)	0.11
Family history of VTE	0.52 (0.20–1.34)	0.17
Abnormal genetic thrombophilia test*	0.92 (0.31–2.71)	0.88
Symptom onset to treatment initiation, >5 days	1.06 (0.63–1.78)	0.84
Presence of parenchymal changes†	0.46 (0.27–0.78)	0.004
	Multivariable analysis	
	Odds ratio (95% CI)	*P*
Age, years	1.04 (1.02–1.05)	<0.001
Female sex	0.59 (0.35–0.997)	0.049
Birth control pills	0.77 (0.36–1.67)	0.512
Presence of parenchymal imaging findings†	0.60 (0.37–0.97)	0.036

CI, confidence interval; VTE, venous thromboembolism; PE, pulmonary embolism; CT, computed tomography; MRI, magnetic resonance imaging.
*Includes presence of Factor V Leiden, and prothrombin gene G20210A mutation; †Venous infarct, cerebral edema, or intracerebral hemorrhage as seen on non-contrast CT Head or MRI brain.

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