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RESEARCH ARTICLE

Predictors of Recurrent Venous Thrombosis After Cerebral Venous Thrombosis

Analysis of the ACTION-CVT Study

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Abstract

Background and Objective

Cerebral venous thrombosis (CVT) is a rare cause of stroke carrying a nearly 4% risk of recurrence after 1 year. There are limited data on predictors of recurrent venous thrombosis in patients with CVT. In this study, we aim to identify those predictors.

Methods

This is a secondary analysis of the ACTION-CVT study which is a multicenter international study of consecutive patients hospitalized with a diagnosis of CVT over a 6-year period. Patients with cancer-associated CVT, CVT during pregnancy, or CVT in the setting of known anti-phospholipid antibody syndrome were excluded per the ACTION-CVT protocol. The study outcome was recurrent venous thrombosis defined as recurrent venous thromboembolism (VTE) or de novo CVT. We compared characteristics between patients with vs without recurrent venous thrombosis during follow-up and performed adjusted Cox regression analyses to determine important predictors of recurrent venous thrombosis.

Results

Nine hundred forty-seven patients were included with a mean age of 45.2 years, 63.9% were women, and 83.6% had at least 3 months of follow-up. During a median follow-up of 308 (interquartile range 120–700) days, there were 5.05 recurrent venous thromboses (37 VTE and

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Glossary

aHR = adjusted hazard ratio; **CVT** = cerebral venous thrombosis; **DOACs** = direct oral anticoagulants; **ISCVT** = International Study on Cerebral Vein and Dural Sinus Thrombosis; **RAPS** = rivaroxaban in antiphospholipid syndrome; **VTE** = venous thromboembolism.

24 de novo CVT) per 100 patient-years. Predictors of recurrent venous thrombosis were Black race (adjusted hazard ratio [aHR] 2.13, 95% CI 1.14–3.98, $p = 0.018$), history of VTE (aHR 3.40, 95% CI 1.80–6.42, $p < 0.001$), and the presence of one or more positive antiphospholipid antibodies (aHR 3.85, 95% CI 1.97–7.50, $p < 0.001$). Sensitivity analyses including events only occurring on oral anticoagulation yielded similar findings.

Discussion

Black race, history of VTE, and the presence of one or more antiphospholipid antibodies are associated with recurrent venous thrombosis among patients with CVT. Future studies are needed to validate our findings to better understand mechanisms and treatment strategies in patients with CVT.

Cerebral venous thrombosis (CVT) is an uncommon cause of stroke, usually affecting younger patients,[1] patients with thrombophilia, and women who are pregnant, postpartum, or receiving oral contraceptives.[2] The annual incidence is estimated to be nearly 10–20 cases per million.[3-6] In the absence of contraindications, parenteral followed by oral anticoagulation is the recommended treatment.[7]

In patients with venous thromboembolism (VTE), trials showed a recurrence of approximately 3%–5% per year on anticoagulation therapy.[8-10] There are limited data about the equivalent risk in patients with CVT, particularly in modern patient cohorts. For instance, the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) showed a recurrence rate of 4.0% at 1 year and 6.5% at 2 years,[11] but only 41.5% were on anticoagulation at the time of the recurrence.[12] Two other observational studies showed a risk of VTE recurrence after CVT between 2.4-3.5 events per 100 patient-years.[13,14] The RE-SPECT CVT trial compared dabigatran to warfarin and showed no recurrent VTE at 24 weeks in either group.[15] Therefore, studies evaluating predictors of recurrent venous thrombosis after CVT are limited by the low event rate and further confounded by inconsistent use of anticoagulation at the time of recurrence.[2,12,15]

Investigating predictors of recurrent events are important to help identify high-risk groups for further study and closer follow-up. In addition, a better understanding of the predictors of events occurring on anticoagulation is a prerequisite to improve treatment strategies.

Previous studies have found that racial and ethnic disparities affect outcomes in patients with stroke,[16-19] but very limited research had similar finding in CVT population.[20] This is particularly important in CVT because the feasibility of treatments such as direct oral anticoagulants (DOACs) and access to care for INR checks with warfarin are altered by socioeconomic factors. Because these are crucial to reduce the risk VTE recurrence after CVT, we included social determinants of health such as race and ethnicity among the potential predictors of recurrence.

In this study, we sought to identify risk factors for recurrent VTE in a modern CVT population from a large, multicenter, real-world observational study.

Methods

Institutional review board approval was obtained from each participating center to perform the study. Deidentified data are available on reasonable request to the corresponding author.

Patient Population

The "Anticoagulation in the Treatment of Cerebral Venous Thrombosis" (ACTION-CVT) study was a multicenter international retrospective cohort study that included consecutive patients with a confirmed diagnosis of acute CVT from January 1, 2015, to December 31, 2020.[21] Patients were identified using ICD-9 (325.0, 437.6, and 671.5) and ICD-10 codes (I67.6)[22,23] and were included irrespective of the service they were treated on. These diagnoses were confirmed by review of medical records and imaging studies.

Inclusion and Exclusion Criteria

The ACTION-CVT study aimed to compare direct oral anticoagulants to vitamin K antagonists and collected data on consecutive adult patients hospitalized with CVT confirmed on imaging. To reduce treatment by indication bias, ACTION-CVT excluded patients with CVT during pregnancy, known history of antiphospholipid antibody syndrome, and those with known active cancer.

Study Variables

We collected demographic variables (age, biological sex [Male and Female], self-reported race [Asian, Black, White, Other, Unknown] and ethnicity [Hispanic and Non-Hispanic]), clinical risk factors (body mass index closest to the time of diagnosis, history of VTE, active smoking, birth control use,

delivery within 12 weeks of diagnosis, and family history of venous thrombosis), presenting symptoms (headache, focal deficit, seizure, encephalopathy, or coma), laboratory variables (platelet count, hemoglobin level, one or more antiphospholipid antibodies present at the time of diagnosis but not meeting criteria for antiphospholipid antibody syndrome[24] at the time of index CVT diagnosis, factor V Leiden, and/or prothrombin gene mutation), and variables collected during follow-up (duration of treatment, duration of follow-up, and available follow-up INR checks in patients on warfarin) were obtained. Elevated hemoglobin was defined as hemoglobin >16.5 g/dL in men or >16.0 g/dL in women, and elevated platelet was defined as platelet count ≥450 × 109/L. Details of variables are further described in the ACTION-CVT study.[21]

Study Outcome

The study outcome was recurrent venous thrombosis (VTE or de novo CVT) during follow-up. Recurrent VTE was defined as new deep venous thrombosis (which involves any deep vein including upper or lower extremities or pelvis or pulmonary embolism during follow-up occurring more than 1 week after CVT diagnosis. The diagnostic methodology for DVT and PE was not collected in our study, but generally, DVT and PE are clinically suspected, and DVT is diagnosed with Doppler ultrasound or pelvic MRV, and PE is diagnosed with CT angiogram of the chest. The de novo CVT was defined as new CVT at a distant location from the original CVT or CVT recurrence at the same location in patients with complete recanalization of the initial CVT. Extension of the original CVT was not included in the recurrent venous thrombosis outcome. All outcomes were adjudicated by the individual sites with plausibility checks conducted by the central site and queries sent to confirm outcomes of interest as appropriate.

Analytical Plan

Data verification was conducted by queries to ensure data integrity and consistency. Missing data were not imputed. For univariate analyses, patients were divided into 2 groups based on whether they had recurrent venous thrombosis. Between-group comparisons were performed by t test, χ^2 test, Fisher exact test, or Wilcoxon rank-sum test as appropriate. We then built Cox regression models that included variables associated with recurrent venous thrombosis in univariate analyses ($p < 0.05$) to identify important predictors of recurrent venous thrombosis. Patients were censored at the time of recurrent venous thrombosis, death, or last follow-up. Sensitivity analysis was performed with exclusion of events occurring off oral anticoagulation. Kaplan-Meier survival estimates of recurrent venous thrombosis were plotted regarding identified risk factors. Proportionality was assessed using Schoenfeld residuals. Data were analyzed using Stata (version 15.1), and a $p < 0.05$ was considered statistically significant.

Results

Of 1,025 patients in ACTION-CVT, 67 were excluded because of active cancer and 11 were excluded because of a known diagnosis of antiphospholipid antibody syndrome. Thus, 947 patients were included with a mean age of included subjects was 45.2 years, and 63.9% (605) were women. During a median follow-up of 308 (interquartile range 120–700) days, there were 5.05 recurrent venous thromboses (37 VTE and 24 de novo CVT) per 100 patient-years. Among patients with de novo CVT, only 2 had same site recurrence after complete recanalization of the initial CVT.

At least 3-month follow-up was available in 83.6% (792/947) of patients. Compared with patients with <90 days of follow-up, patients with ≥90 days of follow-up data were less likely to be active smokers (12.2% vs 19.4%, $p = 0.017$). Other characteristics were not significantly different between the 2 groups and are summarized in eTable 1 (links.lww.com/WNL/C331).

Univariate Analyses

In univariate analyses, Black race (28.3% vs 14.7%, $p = 0.005$), history of VTE (24.6% vs 10.0%, $p < 0.001$), encephalopathy or coma on presentation (36.1% vs 20.5%, $p = 0.004$), lower platelet count (230.6 ± 97.1 vs 268.7 ± 101.8, $p = 0.006$), and ≥1 positive antiphospholipid antibodies (24.0% vs 8.4%, $p < 0.001$) were associated with recurrent venous thrombosis. Other characteristics did not significantly differ between the 2 groups (Table 1).

Factors Associated With Recurrent VTE in Cox Regression Analysis

In adjusted Cox regression analyses including variables achieving a statistically significant association ($p < 0.05$) with recurrent venous thrombosis on univariate analyses, predictors of recurrent venous thrombosis were Black race (adjusted HR 2.13, 95% CI 1.14–3.98, $p = 0.018$), history of VTE (adjusted HR 3.40, 95% CI 1.80–6.42, $p < 0.001$), and ≥1 positive antiphospholipid antibodies (adjusted HR 3.85, 95% CI 1.97–7.50, $p < 0.001$) (Figure). Other variables did not achieve statistical significance.

Sensitivity and Exploratory Analyses

Sensitivity analyses excluding events that occurred off oral anticoagulation yielded similar findings to the main analysis. In univariate analyses, factors associated with recurrent venous thrombosis were Black race (29.0% vs 14.1%, $p = 0.034$), history of VTE (28.1% vs 10.2%, $p = 0.005$), and ≥1 positive antiphospholipid antibodies (27.6% vs 9.0%, $p = 0.004$) (Table 2). In adjusted Cox regression analyses, predictors of recurrent venous thrombosis were Black race (adjusted HR 2.59, 95% CI 1.17–5.75, $p = 0.019$), history of VTE (adjusted HR 4.59, 95% CI 2.02–10.43, $p < 0.001$), and ≥1 positive antiphospholipid antibodies (adjusted HR 4.26, 95% CI 1.83–9.91, $p = 0.001$). Moreover, Black race, history of VTE, and ≥1 positive antiphospholipid antibodies continued to be predictors of recurrent venous thrombosis in sensitivity analyses including CVT extension as outcome (n = 19) and when not counting same site de novo CVT as outcome.

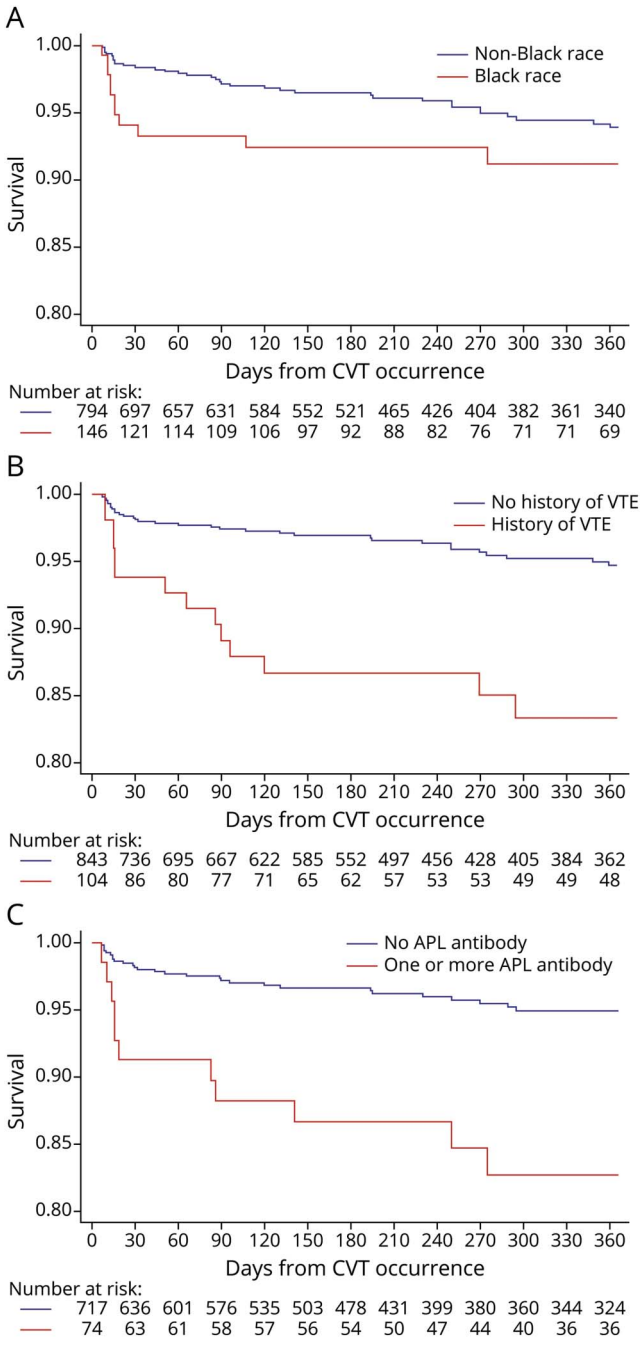
Furthermore, an additional analysis was performed comparing CVT triggers and availability of appropriate INR checks

Table 1 Differences in Baseline Characteristics and Follow-up Duration Across Patients With or Without Venous Thrombosis Recurrence

	Recurrent venous thrombosis (n = 61)	No recurrent venous thrombosis (n = 886)	*p* value
Age (mean ± SD)	45.69 ± 17.8	45.14 ± 16.63	0.802
Sex (% women)	36/61 (59.0%)	569/886 (64.2%)	0.413
Race			
Asian[a]	1/60 (1.7%)	38/880 (4.3%)	0.507
Black	17/60 (28.3%)	129/880 (14.7%)	0.005
White	38/60 (63.3%)	617/880 (70.1%)	0.269
Other[a]	4/60 (6.7%)	96/880 (10.9%)	0.390
Ethnicity (% Hispanic)[a]	6/60 (10.0%)	89/879 (10.1%)	1.000
Body mass index (mean ± SD)	30.36 ± 7.84	29.42 ± 7.64	0.364
History of VTE	15/61 (24.6%)	89/886 (10.0%)	0.000
Family history of VTE[a]	7/61 (11.5%)	91/879 (10.4%)	0.828
12 weeks postpartum[a]	0/60 (0.0%)	37/878 (4.2%)	0.163
Birth control use	11/60 (18.3%)	217/869 (25.0%)	0.248
Active smoking[a]	3/61 (4.9%)	123/880 (14.0%)	0.050
Clinical presentation			
Headache	44/60 (73.3%)	676/885 (76.4%)	0.591
Focal deficit	26/61 (42.6%)	340/885 (38.4%)	0.514
Seizure	14/61 (23.0%)	210/885 (23.7%)	0.890
Encephalopathy or coma	22/61 (36.1%)	182/886 (20.5%)	0.004
Elevated hemoglobin[a]	1/59 (1.7%)	53/868 (6.1%)	0.247
Elevated platelet[a]	1/59 (1.7%)	43/869 (4.9%)	0.355
Platelet count (mean SD)	230.59 ± 97.13	268.65 ± 101.84	0.006
One or more positive APL antibody	12/50 (24.0%)	62/741 (8.4%)	0.000
Factor V and/or prothrombin mutation[a]	7/39 (17.9%)	67/635 (10.6%)	0.181
Imaging findings	35/61 (57.4%)	500/882 (56.7%)	0.916
Venous infarct	13/61 (21.3%)	249/882 (28.2%)	0.243
Cerebral edema	22/61 (36.1%)	270/882 (30.6%)	0.373
Intracranial hemorrhage	28/60 (46.7%)	342/882 (38.8%)	0.226
Duration of treatment to imaging	181 (47–370)	178 (92–297)	0.592
Available follow-up INR checks for warfarin-treated patients[a]	34/41 (82.9%)	454/504 (90.1%)	0.179

Abbreviation: INR = international normalized ratio; VTE = venous thromboembolism.
[a] Fisher exact test was performed.

Figure Kaplan-Meier Survival Analysis for Recurrent Venous Thrombosis Predictors: Black Race (A), History of Venous Thrombosis (VTE) (B), and the Presence of at Least 1 Antiphospholipid (APL) Antibody (C).



Non-Black Race is defined as a self-reported race of Asian, White, other, or unknown.

across different race groups. In this analysis, Black race was associated with a lower rate of expected follow-up with INR checks when treated with warfarin (84.2% [64/76] vs 90.6% [423/467], $p = 0.091$). In addition, Black race was associated with decreased prevalence of factor V and/or prothrombin mutation (3/102 [2.9%] vs 71/567 [12.5%], $p = 0.003$). The

Table 2 Differences in Baseline Characteristics and Follow-up Duration Across Patients With or Without Venous Thrombosis Recurrence While Taking Oral Anticoagulant

	Recurrent venous thrombosis (n = 32)	No recurrent venous thrombosis (n = 813)	*p* value
Age (mean ± SD)	42.25 ± 17.98	44.93 ± 16.21	0.362
Sex (% women)	20/32 (62.5%)	527/813 (64.8%)	0.787
Race			
Asian[a]	1/31 (3.2%)	33/807 (4.1%)	1.000
Black[a]	9/31 (29.0%)	114/807 (14.1%)	0.034
White	19/31 (61.3%)	581/807 (72.0%)	0.195
Other[a]	2/31 (6.5%)	79/807 (9.8%)	0.760
Ethnicity (% Hispanic)[a]	3/32 (9.4%)	79/805 (9.8%)	1.000
Body mass index (mean ± SD)	31.44 ± 7.74	29.28 ± 7.52	0.111
History of VTE[a]	9/32 (28.1%)	83/813 (10.2%)	0.005
Family history of VTE[a]	4/32 (12.5%)	91/809 (11.2%)	0.776
12 weeks postpartum[a]	1/32 (3.1%)	27/804 (3.4%)	1.000
Birth control use[a]	9/32 (28.1%)	209/795 (26.3%)	0.838
Active smoking[a]	2/32 (6.3%)	109/809 (13.5%)	0.298
Clinical presentation			
Headache[a]	25/31 (80.6%)	639/812 (78.7%)	1.000
Focal deficit	11/32 (34.4%)	311/812 (38.3%)	0.654
Seizure[a]	7/32 (21.9%)	192/812 (23.6%)	1.000
Encephalopathy or coma[a]	9/32 (28.1%)	157/813 (19.3%)	0.254
Elevated hemoglobin[a]	1/31 (3.2%)	47/796 (5.9%)	1.000
Elevated platelet[a]	1/31 (3.2%)	37/796 (4.6%)	1.000
Platelet count (mean SD)	249.1 ± 107.55	268.93 ± 100.39	0.282
One or more positive APL antibody[a]	8/29 (27.6%)	62/692 (9.0%)	0.004
Factor V and/or prothrombin mutation[a]	2/22 (9.1%)	69/602 (11.5%)	1.000
Imaging findings	15/32 (46.9%)	446/809 (55.1%)	0.357
Venous infarct[a]	6/32 (18.8%)	226/809 (27.9%)	0.316
Cerebral edema[a]	8/32 (25.0%)	244/809 (30.2%)	0.694
Intracranial hemorrhage	11/32 (34.4%)	303/808 (37.5%)	0.720
Available follow-up INR checks for warfarin-treated patients	21/26 (80.8%)	467/519 (90.0%)	0.666

Abbreviations: INR = international normalized ratio; VTE = venous thromboembolism.
[a] Fisher exact test was performed.

prevalence of other CVT-provoking factors was not significantly different between Black vs non-Black race: being within 12 weeks postpartum (4.9% [7/143] vs 3.8% [30/788], $p = 0.490$), recent mastoiditis or sinusitis (8.2% [12/146] vs 8.6% [68/794], $p = 0.891$), and recent head trauma (4.8% [7/146] vs 9.1% [72/793], $p = 0.104$). Furthermore, the association between Black race and recurrent venous thrombosis persisted, and the effect size was unchanged after adjustment for factor V and/or prothrombin mutation (adjusted HR 2.34, 95% CI 1.13–4.84, $p = 0.022$).

Discussion

This large, multicenter, international, retrospective, observational study found that among patients diagnosed with CVT, Black race, history of VTE, and the presence of one or more positive antiphospholipid antibodies were associated with an increased risk of CVT recurrence. These factors were associated with recurrent venous thrombosis in various analyses and models: (1) only including recurrent venous thrombosis events that occurred while on anticoagulation, (2) considering CVT extension as recurrent venous thrombosis outcome, and (3) excluding same site CVT recurrence after complete recanalization from the recurrent venous thrombosis outcome.

These findings contrast with observations from previous studies. For instance, the ISCVT study showed that male sex and polycythemia/thrombocythemia were the only independent predictors of VTE after CVT.[11] Other multicenter studies found an association between venous thrombosis recurrence and history of VTE.[13] A prospective study of 187 patients in France identified previous VTE, presence of cancer or hematologic malignancies, and unknown CVT causes as independent risk factors for CVT recurrence.[2] Our study differs from other studies by using contemporary real-world data with different treatment strategies. For instance, in our study, nearly 43% of patients were treated with direct oral anticoagulants. Furthermore, prior large CVT cohorts such as ISCVT were conducted in different patient cohorts which may have led to differences in findings.[11]

The association between Black race and recurrent venous thrombosis is noteworthy. Consistent with previous studies,[25,26] our study found that Black race was associated with decreased prevalence of Factor V Leiden and/or prothrombin mutation. However, the association and effect size between Black race and recurrent venous thrombosis remained unchanged even after adjusting for Factor V Leiden and/or prothrombin mutation, suggesting that this difference is not driving the increased risk of recurrent venous thrombosis seen with Black race. The above findings suggest that the association between Black race and recurrent venous thrombosis is likely not the result of biological differences between different races but rather the result of socioeconomic inequities, structural racism, and disparities in access to health care. These disparities have been shown to exist in

several aspects of stroke care,[27] and this study shows that they may also exist in patients with CVT. For instance, in our study, Black race was associated with nonsignificantly lower rates of available follow-up INR checks when treated with warfarin, likely a reflection of access to care disparity and decreased availability of health care resources to Black race. Thus, tremendous efforts on multiple levels are needed to address these disparities.[28] Although our analysis demonstrates that the social construct of race is associated with differences in venous thrombosis recurrent, we cannot disambiguate the contribution of any specific social and/or structural factors driving racial differences in venous thrombosis recurrence.

The associations between a history of VTE and the presence of one or more antiphospholipid antibodies and recurrent venous thrombosis are likely because of several reasons. Both factors point to an intrinsic hypercoagulability, either because of a genetic predisposition (in patients with a history of VTE) or acquired (antiphospholipid antibodies), which may increase the likelihood of recurrence, even in anticoagulated patients. Current oral anticoagulants are imperfect. Warfarin, for instance, is limited by fluctuations of anticoagulation levels with a time to therapeutic range ranging between 55%-65% in clinical trials and real-world data.[8-10,29] Furthermore, although DOACs may be effective for CVT treatment in general,[15] they have not been extensively studied in patients who have intrinsic hypercoagulability. In fact, in patients with antiphospholipid antibody syndrome, the rivaroxaban in antiphospholipid syndrome (RAPS) trial showed that rivaroxaban is not noninferior to warfarin and the *Trial* of Rivaroxaban in Antiphospholipid Syndrome trial found rivaroxaban to be harmful in triple positive cases.[30,31] Thus, in acute patients with CVT with positive antiphospholipid antibodies on initial evaluation, it may be reasonable to use warfarin pending confirmation of diagnosis on repeat antibody testing 12 weeks later.[32-34] In addition, patients with prior VTE may require a more comprehensive diagnostic evaluation, including genetic testing and malignancy screening particularly if the prior VTE was recent. This is important because in addition to treatment of the underlying cancer, low molecular weight heparin or DOAC are preferred options in patients with VTE in the setting of active cancer.[35-37] Other measures to reduce clotting tendency such as adequate oral hydration and avoidance of medications with increased thrombosis risk such a hormonal contraception should also be considered. Furthermore, close follow-up of patients with herein identified that risk factors may improve medication adherence and adequate anticoagulation levels.

Our study has several limitations inherent to its retrospective and observational design. First, approximately 16% of patients were lost to follow-up within 90 days. Nevertheless, we performed survival analyses, and patients were included and censored at the time of lost to follow-up. Furthermore, important variables and recurrent venous thrombosis predictors in our study and previous studies were similar between patients with vs without 90 days follow-up. Second, similar to previous studies, we observed an overall low recurrence rate of venous thrombosis,[2,13,15] which may have left our analysis underpowered to identify possible other predictors. Third, we did not have data on several factors including self-reported sex, certain diagnosis such as polycythemia vera and essential thrombosis, and the time in therapeutic range for patients treated with warfarin or medication adherence rates. These factors require further investigation in future studies. That said, polycythemia vera and essential thrombosis, which have been shown to predict VTE recurrence in one study,[11] are very rare causes of CVT, and in our study, however, neither increased platelet count nor increased hemoglobin was associated with increased risk of recurrent venous thrombosis. Fourth, because not all patients had all antiphospholipid antibodies checked and testing was performed in the acute setting, it is possible that patients may have been labeled as falsely negative and others may have been falsely positive. This would however bias the results toward accepting the null hypothesis and is unlikely to affect the results of our study. Fifth, our data set does not capture the number of positive antibodies which may be important given that in triple positive antiphospholipid antibodies, warfarin may be superior to DOACs.[30,31] Sixth, some patients may have been classified as CVT extension when their CVT may have been a de novo CVT if they had complete recanalization that was not captured on an imaging study after occurrence and before extension. These cases are extremely rare because it would be highly improbable that a patient with a known CVT at a certain location and extension at the same site on follow-up imaging to have had complete recanalization between the 2 scans. Finally, ACTION-CVT excluded patients with CVT in the setting of pregnancy, antiphospholipid antibody syndrome, and active cancer to reduce the risk of treatment by indication bias. Thus, our findings may not be generalizable to the CVT population in general, particularly some of these conditions confer a high risk of recurrent VTE. Therefore, future studies including patients with such conditions are needed to confirm our findings.

Black race, history of VTE, and the presence of one or more antiphospholipid antibodies are associated with recurrent venous thrombosis and breakthrough recurrent venous thrombosis among patients with CVT on anticoagulation therapy. Future studies are needed to validate our findings to better understand mechanisms and treatment strategies in patients with CVT and anticoagulation failure.

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