Venous Thromboembolic Events After Cerebral Vein Thrombosis

Bruno Miranda, MD; José M. Ferro, MD, PhD; Patrícia Canhão, MD, PhD; Jan Stam, MD, PhD; Marie-Germaine Bousser, MD; Fernando Barinagarrementeria, MD; Umberto Scoditti, MD; the ISCVT Investigators

Background and Purpose—After cerebral vein and dural sinus thrombosis (CVT), there is an increased risk of further venous thromboembolic events (VTEs). Time to a second cerebral or systemic venous thrombotic event and risk factors for recurrence have not been investigated in large prospective studies.

Methods—We used the International Study on Cerebral Vein and Dural Sinus Thrombosis, which included 624 patients with CVT followed up for a median of 13.9 months. Outcome measures included all symptomatic VTEs and CVT recurrence. Potential predictors of recurrence, including demographic characteristics, imaging features, thrombophilic abnormalities, other risk factors for CVT, and anticoagulation, were analyzed by Cox survival analysis.

Results—Of the 624 included patients, 36 (5.8%) had at least 1 venous thromboembolic event. The rate of VTEs after the initial CVT was 4.1 per 100 person-years. Of all VTEs, 63.2% (n=24) occurred within the first year. Fourteen patients (2.2%) had an episode of recurrent CVT and the rate of recurrence was 1.5 per 100 person-years. Nine (64.3%) of these CVT recurrences occurred within the first year. Male gender (hazard ratios=2.6; 95% CI, 1.4 to 5.1; P=0.004) and polycythemia/thrombocythemia (hazard ratios=4.4; 95% CI, 1.6 to 12.7; P=0.005) were the only factors associated with a significant higher risk of VTEs in multivariate survival analysis.

Conclusions—The risk of recurrence of CVT is low but is moderate for other VTEs. Recurrence of venous thrombosis after CVT is more frequent among men and in patients with polycythemia/thrombocythemia. (Stroke. 2010;41:1901-1906.)

Key Words: anticoagulants ■ cerebral venous thrombosis ■ recurrence ■ venous thromboembolism

Cerebral vein and dural sinus thrombosis (CVT) most often affects young people and has an average rate of death or dependency of 15%.1–3 A potential long-term complication of CVT is the occurrence of new venous thromboembolic events (VTEs), including recurrent CVT.

After an episode of CVT, the risk of a second cerebral or systemic venous thrombotic event and the risk factors for recurrence are poorly known. Accurate data are needed to identify patients with a high risk of recurrence and to guide antithrombotic treatment after the acute phase of CVT.

Current guidelines suggest oral anticoagulation therapy for 3 to 12 months after a first episode of CVT depending on event-related features and thrombophilic characteristics.4 These recommendations are extrapolated from studies on extracerebral venous thrombosis, which may be inaccurate, because the risk of thrombotic events after CVT appears to be lower.5

Previous studies report an overall recurrence rate after CVT of 2% to 3% for another CVT and approximately 5% for any venous thrombotic event.3,5–8 In a retrospective study, the presence of thrombophilic risk factors did not predict recurrent venous thrombosis after a CVT, and the risk of thrombotic recurrence was also not influenced by anticoagulant therapy.8 However, in a recent pediatric cohort, G20210A prothrombin mutation and nonadministration of anticoagulation before relapse were associated with recurrent venous thrombosis.9

We used longitudinal data from the cohort of patients with CVT of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) to investigate recurrent thrombotic events after a first episode of CVT. We analyzed the association with clinical imaging information, risk factors for CVT as well as with the duration of anticoagulant therapy.

Materials and Methods

Study Population
This study includes all participants of the ISCVT cohort, a prospective multinational, multicenter, observational study that included 624
consecutive patients (aged >15 years) with symptomatic CVT from 89 hospitals in 21 countries.3

Methods

The diagnosis of CVT was confirmed by conventional angiography, CT venography, MRI combined with MR venography, surgery, or autopsy according to established diagnostic criteria.10 Demographic and clinical data, date of confirmation of the diagnosis by imaging (considered as Day 0), and the location and number of occluded sinuses and veins were recorded. The etiologic workup for CVT was done by the local investigators with the help of an attachment to the inclusion form. A systematic search for thrombophilia was performed in 75% of the participating centers. Thrombophilia screening included protein S, protein C, antithrombin III, G20210A mutation, factor V Leiden, methylenetetrahydrofolate reductase (MTHFR) mutation, lupus anticoagulant, and anticardiolipin antibodies.

We categorized patients into 4 groups according to the identified risk factors for CVT: (1) those who only had transient risk factors (pregnancy or puerperium, infection, mechanical precipitants, oral contraceptives and other drugs with a prothrombotic effect, recent surgery, or dehydration); (2) those with only permanent risk factors (genetic or acquired thrombophilia, all malignancies, polycythemia/thrombocythemia, severe anemia, vasculitis or other inflammatory prothrombotic systemic disorder); (3) patients with both transient and permanent risk factors; and (4) patients without identifiable risk factors (cryptogenic CVT).

Patients were followed up at 6 months, 12 months, and yearly thereafter, the majority by direct interview and observation by the local investigators. Information about recurrent symptomatic CVT (new neurological symptoms with new cerebral venous occlusion on repeated CT venography or MRI) and other symptomatic VTEs (confirmed by appropriate studies decided by the individual clinician) was registered for this study. We analyzed all new VTEs after Day 0, which occurred either during hospitalization for the initial CVT or during follow-up after discharge.

The choice and duration of acute and postdischarge treatments were left to the decision of the treating physician, but all treatments and start-stop dates were recorded. Anticoagulation included intravenous or subcutaneous heparin in the acute phase and oral warfarin therapy (target international normalized ratio between 2.0 and 3.0).

Statistical Analysis

The outcomes analyzed were: (1) VTEs (recurrent CVT, lower limb deep vein thrombosis, pulmonary embolism, upper limb vein thrombosis, abdominal or pelvic venous thrombosis); and (2) CVT recurrence.

The Kaplan–Meier method11 was used to calculate the cumulative incidence of the outcomes. In patients with >1 outcome event during the follow-up period, only the first event after the initial CVT was included for the survival curve analysis. The recurrence rate for each outcome measure was calculated as the number of events over the total number of person-years. The period of observation was calculated from Day 0 (diagnosis of initial CVT) until the outcome of interest, death, or end of follow-up, whichever came first.

As potential predictors of venous thromboembolic recurrence, the following variables were selected a priori for the analysis: (1) demographic factors: age (analyzed as continuous variable and also dichotomized according to the median age of the cohort), elderly patient (≥65 years), and gender; (2) imaging features: location and number of occluded sinuses or veins (dichotomized as ≥2 and >2 sinuses or veins involved); (3) thrombophilic risk factors: genetic or acquired thrombophilia, presence of specific genetic abnormalities (protein S, protein C, antithrombin III deficiencies, G20210A mutation, factor V Leiden, and MTHFR mutation), the presence of >1 genetic risk factor, severe thrombophilia (presence of Protein S, protein C, antithrombin III deficiencies, >1 genetic abnormality or antiphospholipid syndrome), or acquired thrombophilia (antiphospholipid syndrome, nephrotic syndrome, hyperhomocysteinemia); and (4) the 4 etiologic groups described in the “Methods” section, women ≤50 years of age on oral contraceptives, women with CVT during pregnancy or postpartum period, and some etiologies known to be associated with increased risk of venous thromboembolism such as malignancy and polycythemia/thrombocythemia.

We used univariate Cox proportional hazards models to calculate hazard ratios (HRs) and 95% CIs for risk factors and to evaluate the impact of anticoagulation therapy on recurrence. We applied multivariate survival analysis to identify independent risk factors associated with the outcome VTEs. There were too few recurrences of CVT to allow multivariate survival analysis. In the final statistical model, we included variables that contributed significantly (P≤0.05) to the outcome in the univariate analysis as well as variables that, even if not significant in the univariate analysis, we considered important for thrombotic recurrence on the basis of published data: age ≥65 years, male gender, malignancy, cryptogenic CVT, presence of thrombophilia, and duration of oral anticoagulant therapy (days). Cox regression was done by a backward stepwise selection of variables and a probability value of 0.05 was adopted as the limit for inclusion of a covariant. We did not correct for multiple comparisons. We used SPSS Statistics 17.0 for Windows (SPSS Inc, Chicago, Ill) for all analyses.

Results

Six hundred twenty-four patients were included in the present analysis. Information at the end of the study follow-up was available for 98.7% of the patients. The median period of observation was 13.9 months (range, 1 to 43.1 month). A total of 36 (5.8%) of the 624 patients had at least 1 venous thromboembolic event. A detailed distribution of all venous thromboembolic cases after initial CVT is presented in Table 1. Sixteen (42%) VTEs occurred in the first 6 months and 24 (63.2%) within the first year. Two patients had 2 recurrences diagnosed during the same acute hospital admission (1 had recurrent CVT and pulmonary embolism; the other had lower limb deep vein thrombosis and pulmonary embolism). The cumulative probability of venous thrombotic recurrence was
1.7% at 3 months, 2.6% at 6 months, 4.0% at 12 months, 6.5% at 2 years, and 12.8% at 3 years (Figure 1). The venous thromboembolic recurrence rate was 4.1 per 100 person-years.

Fourteen (2.2%) patients had an episode of recurrent CVT. One patient had a fatal recurrent CVT. The cumulative incidence of a recurrent CVT event after 3, 6, and 12 months was 0.2%, 0.9%, and 1.7%, respectively. The 2-year cumulative incidence was 2.3% and increased to 5.7% at 3 years (Figure 2). Five (35.7%) of the total CVT recurrences occurred in the first 6 months and 9 (64.3%) within the first year. The CVT recurrence rate was 1.5 per 100 person-years.

The results of the univariate analysis of the effects of the demographic, imaging features, thrombophilic risk factors, and other risk factors on the incidence of a recurrence are shown in Table 2. When age was analyzed as a continuous variable, no association was found for CVT recurrence (HRs=0.9; 95% CI, 0.9 to 1.0; P=0.071) or VTEs (HRs=1.0; 95% CI, 0.9 to 1.0; P=0.950). Male gender (HRs=6.2; 95% CI, 2.1 to 18.6; P=0.001) was an important risk factor for CVT recurrence. Male gender (HRs=2.7; 95% CI, 1.4 to 5.3; P=0.003) and polycythemia/thrombocythemia (HRs=4.9; 95% CI, 1.7 to 14.0; P=0.003) were associated with an increased risk of venous thrombotic recurrence. In a recent meta-analysis, the presence of MTHFR mutation was not significantly associated with a higher risk of CVT. Therefore, we performed an additional analysis on the role of genetic thrombophilia excluding the MTHFR
However, no significant association was found between this genetic thrombophilia excluding MTHFR mutation and recurrent CVT (HRs = 0.6; 95% CI, 0.1 to 3.1; \(P = 0.572\)) or VTEs (HRs = 1.3; 95% CI, 0.6 to 2.8; \(P = 0.533\)).

In the acute phase, 520 (83.3%) patients received anticoagulation therapy in therapeutic dosages with intravenous heparin or subcutaneous low-molecular-weight heparin. Oral anticoagulation after acute heparin therapy was prescribed to 476 (76.3%) patients. Information about the end date of oral anticoagulant therapy was not available for 5 patients. In those who continued anticoagulation, the median duration of treatment was 7.5 months. Details about anticoagulation treatment in patients with and without recurrence are presented in Table 3. At the time of recurrence, 21 (58.3%) with VTEs and 9 (64.3%) with a CVT recurrence were on anticoagulant therapy. Oral anticoagulation after the acute phase was not associated with a significant lower risk of VTEs (HRs = 1.4; 95% CI, 0.6 to 3.4; \(P = 0.459\)) or CVT recurrence (HRs = 1.0; 95% CI, 0.3 to 3.7; \(P = 0.981\)). In patients on oral anticoagulation, the duration of anticoagulant

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Overall Group (n=624)</th>
<th>Recurrent CVT (Patients=14)</th>
<th>VTEs (Patients=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td>HRs (95% CI)†</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Age &gt;37</td>
<td>312 (50.0)</td>
<td>4 (1.3)</td>
<td>0.4 (0.1–1.3)</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>51 (8.2)</td>
<td>0 (0)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Male gender</td>
<td>159 (25.5)</td>
<td>9 (5.7)</td>
<td>6.2 (2.1–18.6)§</td>
</tr>
<tr>
<td>Imaging features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior sagittal sinus</td>
<td>387 (62.1)</td>
<td>11 (2.8)</td>
<td>2.3 (0.6–8.3)</td>
</tr>
<tr>
<td>Left lateral sinus</td>
<td>279 (44.8)</td>
<td>8 (2.9)</td>
<td>1.7 (0.6–4.8)</td>
</tr>
<tr>
<td>Right lateral sinus</td>
<td>257 (41.3)</td>
<td>8 (3.1)</td>
<td>1.8 (0.6–5.3)</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>112 (18.0)</td>
<td>0 (0)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Cortical veins</td>
<td>107 (17.2)</td>
<td>1 (0.9)</td>
<td>0.4 (0.1–3.1)</td>
</tr>
<tr>
<td>Jugular veins</td>
<td>74 (11.9)</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Deep venous system</td>
<td>68 (10.9)</td>
<td>1 (1.5)</td>
<td>0.7 (0.1–5.4)</td>
</tr>
<tr>
<td>&gt;2 sinuses or veins</td>
<td>179 (28.7)</td>
<td>4 (2.2)</td>
<td>1.0 (0.3–3.2)</td>
</tr>
<tr>
<td>Thrombophilic RF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any thrombophilia</td>
<td>214 (34.3)</td>
<td>3 (1.4)</td>
<td>0.4 (0.1–1.6)</td>
</tr>
<tr>
<td>Genetic thrombophilia</td>
<td>140 (22.4)</td>
<td>2 (1.4)</td>
<td>0.5 (0.1–2.3)</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>33 (7.5)</td>
<td>1 (3.0)</td>
<td>1.3 (0.2–10.2)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>21 (4.8)</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>4 (0.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>33 (7.5)</td>
<td>1 (3.0)</td>
<td>1.8 (0.2–14.4)</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>37 (8.4)</td>
<td>0 (0)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>MTHFR mutation</td>
<td>43 (9.9)</td>
<td>0 (0)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>&gt;1 genetic RF</td>
<td>36 (7.7)</td>
<td>1 (2.8)</td>
<td>1.3 (0.2–10.1)</td>
</tr>
<tr>
<td>Severe thrombophilia</td>
<td>102 (16.3)</td>
<td>1 (1.0)</td>
<td>0.3 (0.1–2.3)</td>
</tr>
<tr>
<td>Acquired thrombophilia</td>
<td>98 (15.7)</td>
<td>1 (1.0)</td>
<td>0.3 (0.0–2.5)</td>
</tr>
<tr>
<td>Etiological group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient RF only</td>
<td>216 (34.6)</td>
<td>5 (2.3)</td>
<td>1.1 (0.4–3.4)</td>
</tr>
<tr>
<td>Pregnancy/puerperium*</td>
<td>77 (20.2)</td>
<td>0 (0)</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Oral contraceptives*</td>
<td>207 (54.3)</td>
<td>3 (1.4)</td>
<td>2.4 (0.2–22.7)</td>
</tr>
<tr>
<td>Permanent RF only</td>
<td>138 (22.1)</td>
<td>3 (2.2)</td>
<td>1.0 (0.3–3.4)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>46 (7.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Polycythemia/thrombocythemia</td>
<td>18 (2.9)</td>
<td>1 (5.6)</td>
<td>3.1 (0.4–24.1)</td>
</tr>
<tr>
<td>Transient + permanent RF</td>
<td>192 (30.8)</td>
<td>3 (1.6)</td>
<td>0.5 (0.1–1.9)</td>
</tr>
<tr>
<td>Cryptogenic CVT</td>
<td>78 (12.5)</td>
<td>3 (3.8)</td>
<td>2.1 (0.6–7.5)</td>
</tr>
</tbody>
</table>

*Analyses among 381 women ≤50 years of age.
†HRs represent the comparison between patients with and without CVT recurrence.
‡HRs represent the comparison between patients with and without VTEs.
§//\(P = 0.05\). The percentages for each specific genetic abnormality were calculated using the no. of performed tests as the denominator.
RF indicates risk factor.
therapy was also not significantly associated with venous thromboembolic recurrences (HRs = 1.0; 95% CI, 0.99 to 1.00; P = 0.963).

In the final Cox regression analysis model, male gender (HRs = 2.6; 95% CI, 1.4 to 5.1; P = 0.004) and polycythemia/thrombocythemia (HRs = 4.4; 95% CI, 1.6 to 12.7; P = 0.005) were the only significant independent risk factors associated with a higher risk of VTEs.

### Discussion

The main new findings of this study are the description of the risk of a recurrent cerebral or a new systemic venous thrombotic event after CVT and the identification of male gender and polycythemia/thrombocythemia as independent predictors of venous thromboembolism after CVT. The large number of included subjects from a variety of countries and centers, the prospective design, and the good quality of follow-up data are the main strengths of this study. Limitations include the fact that local investigators decided the investigations for symptomatic extracerebral thrombotic recurrences and thrombophilia screening was not performed in 25% of the centers. The median follow-up in ISCVT was 13.9 months. Considering that most patients with a CVT are relatively young and have a life expectancy of several decades, a study with a longer follow-up might detect more recurrent events and additional predictors. Furthermore, VTEs were not centrally adjudicated. These 2 factors could, therefore, underestimate the number of outcome events.

Information about risk factors for thrombotic recurrence after CVT is limited. One previous retrospective study did not identify any clinical predictor for recurrence. When we compare our results with studies on extracerebral venous thrombosis, male gender was also associated with a higher risk of venous thrombotic recurrence, whereas the influence of aging is controversial. It is important to note that a significant proportion of women had the initial CVT while on oral contraceptives and during pregnancy or the postpartum period. These factors are established transient risk factors for venous thrombosis and could explain the lower rate of further thrombotic events among women. However, we could not find a significant difference in thrombotic recurrence between women with and without these gender-specific risk factors, which favors the existence of other gender-specific risk factors. The association between polycythemia or thrombocythemia and venous thrombotic events is well established and now confirmed for CVT.

Current European guidelines on the treatment of CVT after the acute phase propose different durations of oral anticoagulation therapy in the presence of transient risk factors, genetic thrombophilia, or idiopathic CVT. In the ISCVT cohort, the different etiologic groups and the presence of genetic or acquired thrombophilia were not associated with a higher risk of thrombotic recurrence. Nonetheless, it is difficult to interpret these findings because the modest number of patients with specific genetic prothrombotic conditions and the low event rate make this study underpowered to investigate the role of specific prothrombotic conditions in the recurrence of venous events. In a pediatric CVT cohort, prothrombin G20210A mutation predicted recurrent venous thromboembolism. The same study also reported persistent venous occlusion as an independent predictor of venous thrombotic recurrence. Studies in adult patients with CVT found that venous recanalization occurs mostly within 4 months after CVT irrespective of anticoagulation. Furthermore, no significant differences in relapses or outcome were found in those with incomplete or no recanalization. In our study, baseline imaging features such as location and thrombus load were not associated with thrombotic recurrence.

Six months after a CVT, the likelihood of VTEs was 2.6% and the risk increased to 6.5% after 2 years. In the ISCVT cohort, we found an overall rate of VTEs after CVT of 4.1 per 100 person-years. Regarding CVT recurrence, the cumulative probability increased in a similar way from 0.9% at 6 months to 2.3% at 2 years. The rate per 100 person-years of CVT recurrence found was 1.5. In a systematic review, Dentali and colleagues calculated an overall rate of 2.8% for CVT recurrence and 3.7% for extracerebral venous thrombotic events, but the results and duration of follow-up varied widely between studies. More recently, a retrospective study reported a CVT recurrence rate of 2.2 per 100 person-years and a rate of 5.0 per 100 person-years for recurrent venous thromboembolism. In the same study, the majority of the recurrences occurred within the first year. We also found that 63.2% of VTEs and 64.3% of CVT recurrences occurred within the first year. Nevertheless, there was a steady increase in the risk of outcome events and the Kaplan–Meier curves showed a rather linear relation to time. The relatively short period of observation and the smaller number of patients in follow-up at later time points might explain the high event rates found within the first year. The venous thrombotic recurrence rate in our study was similar to the rate found in smaller prospective studies but CVT recurrence was less frequent than 2 retrospective analyses. Venous thrombosis after CVT seems to be less frequent than the recurrence rate reported after deep vein thrombosis or pulmonary embolism. One possible reason is the absence in CVT of the hydrostatic factor that can promote thrombosis in patients with predisposing conditions.
We could not find an association between anticoagulation or duration of anticoagulation and prevention of thrombotic recurrence. A significant number of patients (58.3%) had thrombotic recurrence while on anticoagulation and the proportion was even higher (64.3%) among patients with recurrent CVT. These findings could be explained by differences in sample size and prognostic characteristics between individuals who continued anticoagulation and those who did not continue anticoagulant therapy. Furthermore, the level of anticoagulation with international normalized ratio monitoring was not evaluated and could influence the results. Gok-Bierska and colleagues also reported no benefit in survival or recurrence for those receiving oral anticoagulants, but a higher risk of recurrent events was found in children not taking anticoagulation. We need to be cautious when interpreting these results because all these observational studies did not have the appropriate design for the assessment of the efficacy and appropriate duration of anticoagulant therapy after the acute phase of cerebral venous thrombosis. Our findings suggest that CVT may be a different clinical entity from CVST. These findings could be explained by differences in sample size and prognostic characteristics between individuals who continued anticoagulation and those who did not continue anticoagulant therapy. Furthermore, the level of anticoagulation with international normalized ratio monitoring was not evaluated and could influence the results.

Acknowledgments
We thank all investigators who contributed to the ISCVT study. Their names and institutions are listed in a previous publication.

Source of Funding
The ISCVT Study was supported by PRAXIS grant C/SAU/10248/1998 from the Fundação para a Ciência e Tecnologia.

Disclosures
None.

References
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Stroke. 2010;41:1901-1906; originally published online July 15, 2010;
doi: 10.1161/STROKEAHA.110.581223
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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