Abstract

**Purpose of Review** Cerebral venous thrombosis (CVT) is a rare cause of stroke that most commonly affects younger women. Here, we review new literature relevant to the management and prognosis of individuals with CVT and ongoing areas of uncertainty.

**Recent Findings** Direct-acting oral anticoagulants (DOACs) are being increasingly integrated into routine care but are not yet recommended by guidelines. Recent randomized clinical trials and available case series offer reassuring safety data. Routine use of endovascular therapy is not associated with improved outcomes. The relationship between recanalization and prognosis is uncertain.

**Summary** The evidence base for management of CVT continues to improve. Ongoing areas of uncertainty include duration of therapy and whether certain subgroups of patients may benefit from neurointervention or personalized approaches to antithrombotic strategy. The state of knowledge will continue to benefit from large collaborative international efforts, and integration of patient partnerships to identify research priorities.

**Keywords** Cerebral venous thrombosis · Anticoagulation · DOAC · Recanalization · Prognosis · Endovascular therapy

Introduction

Cerebral venous thrombosis (CVT) accounts for approximately 0.5–1% of all strokes [1]. In contrast to other venous thromboses of “unusual sites,” which altogether comprise approximately 10% of all venous thromboembolism, CVT predominantly affects young patients and women of reproductive age [2]. Approximately 80% of cases affect individuals under the age of 50, and 75% of cases affect women [1]. Although the majority of survivors will achieve functional independence, 10–15% will have a more serious outcome resulting in death or dependence [3, 4]. Even higher-functioning survivors experience under-recognized disability from cognitive impairment, mood, fatigue and pain, which significantly impact quality of life [5, 6].

Due to the rarity of CVT, large randomized trials are not available to guide management. Standard-of-care treatments are consensus-based, derived mainly from observational studies or underpowered clinical trials [7, 8]. In the last few years, however, several new studies have advanced our understanding of treatment strategies and complications of CVT. Multiple ongoing trials will further clarify areas of lasting clinical equipoise in the near future.

There are a number of excellent contemporary reviews summarizing the current landscape of knowledge with respect to epidemiology, risk factors, clinical manifestations, diagnosis, prognosis and management of CVT [9•, 10, 11]. Here, we provide a focused update of new data that will help to inform contemporary management and identify areas of ongoing uncertainty.
Epidemiology

While the incidence of more common forms of venous thromboembolic disease (VTE), such as deep venous thrombosis of the leg and pulmonary embolism (DVT/PE), is about 1–2 per 1000 person-years [12], previous estimates of incident CVT are approximately 1 per 100,000 person-years [13, 14]. Likely due in part to improved ascertainment with increased use of routine vascular neuroimaging with CT angiography/venography, recent reports of incidence have been somewhat higher. Recent Australian and Norwegian studies using administrative data estimated rates of 1.6 and 1.75/100,000/year, respectively [14, 15]. A new Finnish study found an overall rate of 1.3/100,000/year, with incidence increasing annually by 5% between 2005 and 2014 [16]. Another new study using American inpatient data from New York and Florida found an incidence of 1.4–2/100,000 person-years between 2006 and 2016, also finding increasing annual incidence for both men and women [17•]. Similar to studies of DVT/PE, rates were higher in those with Black race-ethnicity than in those of Caucasian or Asian descent. To what degree these disparities reflect genetic as opposed to environmental factors in the context of social determinants of health is not known [17•]. A recent genome-wide association study in Europeans identified the first chromosomal region associated with genetic susceptibility to CVT in the 9q34.2 locus. Single-nucleotide polymorphisms in this region were in strong linkage disequilibrium with ABO blood type gene coding. Risk of CVT with blood group Types A, AB, or B was 2.85 (95% CI 2.32–3.52) times of that with type O [18••].

In contrast to DVT/PE, which becomes more common with age and affects roughly equal numbers of men and women [19], CVT more often affects younger women. Rates of CVT in women of childbearing age are approximately 3/100,000/year [13]. This is likely in part due to its association with pregnancy and the puerperium as well as hormonal contraception. CVT accounts for approximately one-third of pregnancy-associated stroke at an incidence of 9/100,000 pregnancies [20]. Oral contraceptives are a contributing factor in up to 70% of cases [21]. One case–control study identified a synergistic effect of obesity on the risk of CVT associated with oral contraception. However, 16% of the body mass index data was missing and substituted by interpolation, and further studies are needed to confirm this finding [22].

Other non-genetic and genetic risk factors for CVT have been recently summarized in a meta-analysis incorporating 20 non-genetic and 33 genetic studies [23•]. Significant acquired and genetic factors are summarized in Table 1.

During the past 18 months, there have been numerous reports of CVT associated with SARS-CoV-2 infection, both as a late complication of severe infection and as an isolated presenting symptom [24•, 25]. In contrast to estimated rates of COVID-19-associated deep vein thrombosis and pulmonary embolism, which appear to be upwards of 15–20% in hospitalized patients [26, 27], reported rates of CVT to date appear to be low overall. Estimated frequency in data from 34,000 hospitalized patients with COVID-19 in a recent meta-analysis of 28 reports was 0.08% (95% CI 0.01–0.05), with CVT accounting for 4% of cerebrovascular disorders in individuals with COVID-19 [24•]. The literature on COVID-19-associated CVT is constantly evolving, and its prevalence may be underestimated in the absence of routine vascular neuroimaging.

In March 2021, reports emerged regarding multiple cases across Europe of thromboses at unusual sites, predominantly CVT, with thrombocytopenia, very high d-dimer levels and reduced fibrinogen [28, 29]. Cases were reported following vaccination with the ChAdOx1 nCoV-19, generally within 4–28 days of the first dose and with a predominance towards younger adults and women [30–32]. Cases occurring with CVT as part of the presentation reported much higher case mortality rates (in excess of 30%) than in historical series of CVT (~5–10%) [33]. Other reports followed from other countries with similar cases after ChAdOx1 and Ad26. COV2.S, another adenovirus vector vaccine against SARS-CoV-2. An international collaborative effort identified a mechanism akin to spontaneous heparin-induced thrombocytopenia (HIT) as the pathophysiological mechanism [34]. High-titre serum antibodies to platelet factor 4 (PF4), known to be associated with HIT and not typically associated with CVT, were identified in association with the reaction [35–37, 38••]. The syndrome, termed both VITT (vaccine-induced thrombocytopenia) or TTS (thrombosis with thrombocytopenia syndrome), led to changes in vaccination strategies in multiple countries where use of the adenovirus vector SARS-CoV-2 vaccinations was subsequently limited to older

Table 1 Risk factors for CVT in adults [23•]

| Non-genetic                                      | Genetic                              |
|-------------------------------------------------|--------------------------------------|
| Provoking                                       | Factor V Leiden                      |
| Anaemia                                         | MTHFR (C677T)                        |
| APLAS and other autoimmune disease              | Prothrombin gene mutation            |
| Malignancy                                      | Protein C deficiency                 |
| Medications: oral contraceptive,                | Protein S deficiency                 |
| corticosteroids, L-asparaginase                  |                                      |
| Obesity                                         |                                      |
| Pregnancy/puerperium                            |                                      |
| Trauma                                          |                                      |
| Surgery                                         |                                      |
| Infection                                       |                                      |
| Alcohol                                         |                                      |
age groups or stopped entirely. Estimated rates of VITT/TTS varied, ranging from 1/25,000 to under 1/1,000,000 [28, 31, 39]. Recommended treatment approaches included avoiding heparins and avoiding platelet transfusions where possible, and using intravenous immunoglobulin with or without steroids or, in refractory cases, considering plasma exchange or monoclonal antibodies [40, 41••].

Clinical Presentation and Diagnosis

Recent reviews have described approaches to the clinical evaluation and diagnosis of CVT [9•, 10, 11, 42].

Initial clinical presentation can reflect symptoms accrued from raised intracranial pressure, location of thrombosis and thrombus burden. Common presentations include headache, seizures, focal symptoms and depressed level of consciousness. Most patients present subacutely within 48 h to 2 weeks of symptom onset; one-third to one half will present more acutely with stroke-like symptoms or thunderclap headache [43, 44]. Presenting symptoms in the two largest prospective series of CVT, the International Study of Cerebral Venous Thrombosis (ISCVT) [43] and the Turkish VENOST study [44], are summarized in Table 2.

A substudy of the ISCVT found that elderly patients were more likely to present with depressed level of consciousness and less likely to have isolated symptoms of intracranial hypertension [45]. One recent prospective international study of 1281 individuals found a 34% rate of acute symptomatic seizures, 6% of whom had status epilepticus. Neuroimaging findings associated with acute seizures included intracerebral haemorrhage, non-haemorrhagic lesions, cortical vein or sagittal sinus thrombosis and subarachnoid haemorrhage [46].

Table 2 Presenting findings of cerebral venous thrombosis

|                  | ISCVT (2004) | VENOST (2017) |
|------------------|-------------|--------------|
| N                | 624         | 1144         |
| Age (mean)       | 39           | 18–36 y (47%)|
| (median), range  | 37           | 37–50 (33%)  |
|                  | 16–86       | 51+(20%)     |
| % Female         | 75           | 68           |
| Headache         | 89%          | 87%          |
| Visual loss      | 13%          | 27%          |
| Cranial neuropathy/ diplopia | 14% (diplopia only) | 11% |
| Depressed level of consciousness/ encephalopathy | 22% | 18% |
| Seizure          | 40%          | 24%          |
| Focal deficits   | Motor 40%    | 18%          |
|                  | Sensory 5%   |               |
|                  | Other 3%     |               |

Treatment Strategy

The mainstay of acute treatment for CVT is anticoagulation. Goals of therapy predominantly focus on preventing thrombus propagation, restoring anterograde drainage, salvaging brain tissue from permanent damage and preventing recurrent thromboembolism [7]. Identifying and treating any underlying hypercoagulable state is paramount for long-term management. Supportive measures and management of complications include hydration, headache and seizure management and treatment of increased intracranial pressure.

Acute Treatment

Anticoagulation

Anticoagulation remains the first-line treatment of choice of CVT in the acute setting, even when there is concurrent intracranial haemorrhage (ICH). Although series estimate a 30–45% prevalence of intracranial bleeding at presentation [47–49], none to date have characterized haemorrhage type [50].

Existing reports suggest that a minority of patients will have new or worsening haemorrhage on follow-up scans, more commonly with those who have baseline ICH (9–21%) as opposed to those without (3–10%) [47, 49].

Both American and European guidelines recommend initiation of parenteral anticoagulation with unfractionated or low molecular-weight heparin prior to transitioning to oral anticoagulants [7, 8]. European guidelines provide a weak recommendation for low-molecular weight heparin (LMWH) over unfractionated heparin (UFH) based on a meta-analysis suggesting a non-significant trend towards improved functional outcomes and mortality with the former without a difference in rates of bleeding [8, 51].

Endovascular Therapy and Hemicraniectomy

Both American and European guidelines recommend use of endovascular therapy (EVT) only for individuals who continue to worsen clinically despite use of first-line anticoagulation [7, 8]. The TO-ACT trial examined use of neurointervention (with approach as per local standards) versus conservative management in patients with severe CVT (defined as presence of deep venous involvement, intracranial haemorrhage, mental status changes or Glasgow coma score (GCS) < 9). The trial was terminated early for futility after 67 participants of a target of 164 were randomized and found no difference in the rates of the primary endpoint of a modified Rankin Score (mRS) of 0–1 at 12 months (67% vs. 68%; RR 0.99, 95% CI 0.71–1.38). Three of 33 participants in the EVT group experienced periprocedural sinus
perforation [52••]. Use of EVT remains a case-by-case decision in current practice. Future work may help to identify individuals that may benefit from EVT as well as optimal technical approaches.

Decompressive hemicraniectomy similarly remains a case-by-case measure for those at risk of malignant mass effect from oedema and/or intracranial haemorrhage. A previous case series and systematic review of 69 individuals undergoing decompressive hemicraniectomy for CVT found overall rates of death or dependence of 40% at 12 months [53]. However, final results of the prospective DECOMPRESS-2 Trial, which were presented at the 2021 European Stroke Organization Conference but are not yet published, found higher rates of unfavourable outcomes, with 65% of 118 individuals achieving a mRS of 3–6 at 12 months. Over half of participants (58%) characterized as comatose prior to surgery, 23% with unilateral absent pupillary responses and 8% with bilaterally absent pupillary responses [54]. The optimal timing of restarting anticoagulation after hemicraniectomy is not established. A recent case series and review including 243 patients from 15 studies identified multiple approaches, though overall quality of the literature was low and reporting of early post-operative re-bleeding was heterogeneous [55]. The post-operative approach at our centre is to initiate next-day prophylactic dose of low molecular-weight heparin with daily escalation guided by repeat neuroimaging to reassess for intracranial bleeding.

**Post-acute Treatment**

**Use of DOACs in CVT**

Following acute treatment, most patients transition from parenteral therapy to oral anticoagulation. Current guidelines recommend using oral Vitamin K antagonists (VKA) with European guidelines recommending against routine use of direct-acting oral anticoagulants (DOACs) in CVT, particularly as initial therapy [7, 8]. Yet despite lacking formal endorsement in current guidelines, DOACs are being increasingly used in clinical practice as treatment for CVT, particularly following the acute phase of treatment [56, 57•]. DOACs have demonstrable safety and efficacy for treatment of DVT/PE [58–61]; for instance, there is a 50% relative risk reduction in rate of intracranial bleeding in comparison to both VKA and LMWH [62].

To date, two clinical trials examining use of DOACs for treatment of CVT have shown reassuring safety data. The exploratory RESPECT-CVT Trial randomized (1:1) 120 adults ages 18–80 with CVT to receive VKA (target INR 2–3) or dabigatran 150 mg twice daily between 5 and 15 days of diagnosis, following initial therapy with parental anticoagulation. Individuals with CVT associated with trauma, infection or malignancy were excluded. There was no difference between groups in the primary safety outcome of major bleeding or any VTE recurrence at 6 months, with one gastrointestinal haemorrhage in the dabigatran group and two intracranial haemorrhages in the VKA group. Majority of participants (91%) had a mRS of 0–1 at 6 months; furthermore, 60% in the dabigatran group and 67% in the warfarin group achieved partial or complete recanalization [63••]. The EINSTEIN-Jr trial randomized (2:1) 520 children with symptomatic VTE to a bodyweight-adjusted 20-mg-equivalent dose of rivaroxaban versus VKA or ongoing parental treatment following 5–9 days of parenteral anticoagulation. The primary efficacy outcome was recurrent VTE at 3 months, and the primary safety outcome was major or clinically relevant non-major bleeding. In the substudy examining the 114 children enrolled with neuroimaging-confirmed CVT, none of the 73 receiving rivaroxaban and 1 in the standard therapy group experienced recurrent VTE. There were no major bleeding events in the rivaroxaban group; five children in the group had clinically relevant non-major bleeding events. Partial or complete recanalization occurred in 78% in the rivaroxaban group and 74% in the standard therapy group [64••].

Whether DOACs may be an acceptable choice for initial therapy in place of parenteral anticoagulation in selected CVT patients is not established. Further studies are additionally needed to clarify whether VTE initiation dosing or atrial fibrillation dosing is more optimal. The reported experiences in case series are variable [57•]. The ongoing SECRET trial, which is randomizing individuals with CVT 1:1 to rivaroxaban 20 mg daily versus standard therapy (VKA or parenteral anticoagulation) within 14 days of diagnosis, permits use of 20 mg rivaroxaban as initial therapy (clinicaltrials.gov NCT03178864) [65].

DOACs will not be suitable in some patients, including those who are pregnant, breastfeeding (11–59% of cases depending on cohort) [21] or those with antiphospholipid antibody syndrome (APLAS), especially high-risk patients with triple-antibody-positive disease. The TRAPS trial randomized individuals with high-risk APLAS (i.e. triple antibody-positive with prior venous or arterial thromboembolism) to rivaroxaban versus VKA and was terminated early due to an excess of recurrent arterial events in the rivaroxaban group [66•]. This has raised concerns about the safety of using DOACs in APLAS [67], though other DOAC trials are ongoing in lower-risk patients [68]. The rate of APLAS-associated CVT is uncertain. A previous systematic review found a 6–17% prevalence of antiphospholipid antibodies, though rates of those meeting true diagnostic criteria for APLAS were not consistently reported [21]. Prevalence of incidental antiphospholipid antibodies in the general population is approximately 2–4% [69].
Duration and Therapy and Recanalization

American and European guidelines for duration of anticoagulation mirror recommendations for other types of VTE: 3–6 months of anticoagulation for provoked CVT, 6–12 months for unprovoked CVT and indefinite anticoagulation for severe thrombophilias and recurrent VTE [7, 8]. Previous physician surveys indicate that practice is variable, though most tend towards 6 months of treatment for uncomplicated cases [70, 71]. The EX-COA study, which is examining efficacy and safety (recurrent VTE, bleeding and death) of 3–6 months versus 12 months of VKA anticoagulation in CVT, may help to clarify the optimal duration of antithrombotic over the shorter term [72].

The role and timing of repeat neuroimaging in assessing recanalization and thrombus burden is unclear. The recent prospective PRIORITy-CVT study, which imaged 68 individuals with CVT with standardized MRI/MR venography at 48 h, 8 days and 90 days following initiation of anticoagulation, found that 74% had partial (68%) or full (6%) recanalization within 8 days of initiating therapy, and 95% had partial (41%) or complete (54%) recanalization by 90 days [73••]. While early recanalization was associated with regression of non-haemorrhagic lesions, there was no association between recanalization status and new or enlarged haemorrhagic lesions, or recanalization status and favourable functional outcome.

There is inconsistent evidence for whether recanalization is associated with functional outcome, and what the directionality and time-dependence of that relationship may be. Neither PRIORITy-CVT [73••] nor a prospective substudy of RESPECT-CVT found an association between recanalization and functional outcome [74]; however, both were likely unpowered for this outcome. A recent meta-analysis examining the association between recanalization and prognosis found that complete or partial recanalization was associated with an increased odds of functional independence (mRS 0–1) [75]. However, all 19 studies included were appraised as having moderate or low methodological quality, and definitions of recanalization and timing of clinical and imaging assessments were variable between studies. The significance and prognostic implications of recanalization status are yet to be fully determined.

In PRIORITY-CVT, residual headache was not associated with recanalization status. A large prospective series of 325 individuals with CVT from China described an association between severe headache (residual headache requiring bed rest or readmission to hospital 1 month or less prior to follow-up assessment, with a median time to follow-up of 13 months) and absence of recanalization, though follow-up neuroimaging was not systematic [76].

While extended antithrombotic therapy is of benefit in reducing risk of recurrent VTE after DVT/PE, it is not known whether this should be extrapolated to the CVT population, who are younger and likelier to have had a provoked event. In all comers, the risk of recurrent VTE after CVT averages approximately 2–4% per year [77•], with risk increasing somewhat linearly over time. In those without high-risk thrombophilias, risk of recurrence appears to be lower. One prospective cohort of 203 patients without high-risk thrombophilia followed over a median of 36 months found a recurrence risk of 1.6/100 person-years [78•]. Risk was higher in men, and in those who were heterozygotes for Factor V Leiden or prothrombin gene mutation. Those with unprovoked events have also been identified as higher risk for recurrence in other series [77•]. Prophylactic anticoagulation is indicated in women with a history of CVT in the context of oral contraception or pregnancy [7]. Whether some individuals with a history of CVT would benefit from targeted prophylaxis in other higher-risk scenarios is not known.

Prognosis

Large observational series of CVT have reported an approximate 10–15% rate of death and dependence (mRS 3–6) [3, 4]. Previous risk factors identified for poorer prognosis include older age, male sex, presence of intracranial haemorrhage on presentation, and depressed level of consciousness or coma [3, 4]. Although most CVT survivors will retain functional independence, retrospective surveys of CVT survivors report high rates of sequelae impacting quality of life, including pain, mood, fatigue and cognitive residua, even several years following their events. Retrospective series in CVT survivors have found that over half do not return to work, or have difficulty after returning to work, following their event [5, 6].

A recent prospective study describing late seizures in CVT, defined as seizures occurring later than 1 week after diagnosis, found that 11% of 1127 experienced at least one event over a median follow-up of 2 years, with a median time to seizure of 5 months. Predictors included status epilepticus in the acute phase of presentation, decompressive hemi-craniectomy and intracerebral haemorrhage. Of those with late seizures, although 94% were started on antiepileptic therapy, 70% experienced at least one recurrent event [79••].

Dural arteriovenous fistula is a known complication of cerebral venous thrombosis in addition to an identified precipitant, but the prevalence is not well characterized, and there are no recommendations with respect to follow-up for this indication. A recent prospective substudy of the 120 participants from the RESPECT-CVT trial found no dural AV fistulas at 6-month follow-up contrast-enhanced MR angiography [80]. Follow-up, however, was brief, and 95% confidence interval estimates for this cohort would be
0–2.5% [81]. Other smaller series using variable approaches identification of dAVF and with variable timing after CVT have reported rates of 0.9–13% [43, 82, 83].

Conclusions

Several recent and ongoing studies are contributing to a fuller state of understanding with respect to treatment and prognosis of this rare cause of stroke. Further progress will be in the context of ongoing international collaboration, which will help to generate sufficiently large cohorts to identify subgroups that may benefit from variations in acute and longer-term treatment strategies. A fuller picture of prognosis after CVT beyond mRS-focused outcomes is emerging, and ongoing collaboration with CVT survivors in identifying and characterizing patient-centred outcomes will help to better support survivors of this rare cause of stroke.

Compliance with Ethical Standards

Conflict of Interest  Dr. Field is PI for the SECRET (Study of rivaroxaban for ceREbral venous Thrombosis) trial and receives in-kind study medication from Bayer Canada for the study. She is supported by the Vancouver Coastal Health Research Institute, the Michael Smith Foundation for Health Research, the Heart and Stroke Foundation of Canada. The other authors declare that they have no conflict of interest.

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●● Of major importance

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