AHA Scientific Statement

Diagnosis and Management of Cerebral Venous Thrombosis

A Scientific Statement from The American Heart Association

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ABSTRACT

Cerebral venous thrombosis (CVT) accounts for 0.5–3% of all strokes. Most vulnerable populations include young individuals, women at reproductive age, and patients with a prothrombotic state. The clinical presentation of CVT is diverse and may mimic other neurological disorders (e.g., headaches, seizures). A high level of clinical suspicion is required. Its diagnosis is primarily based on MRI/MR-venography or CT/CT venography. The clinical course of CVT is difficult to predict as death or dependence occurs in 10-15% of patients despite intensive medical treatment.

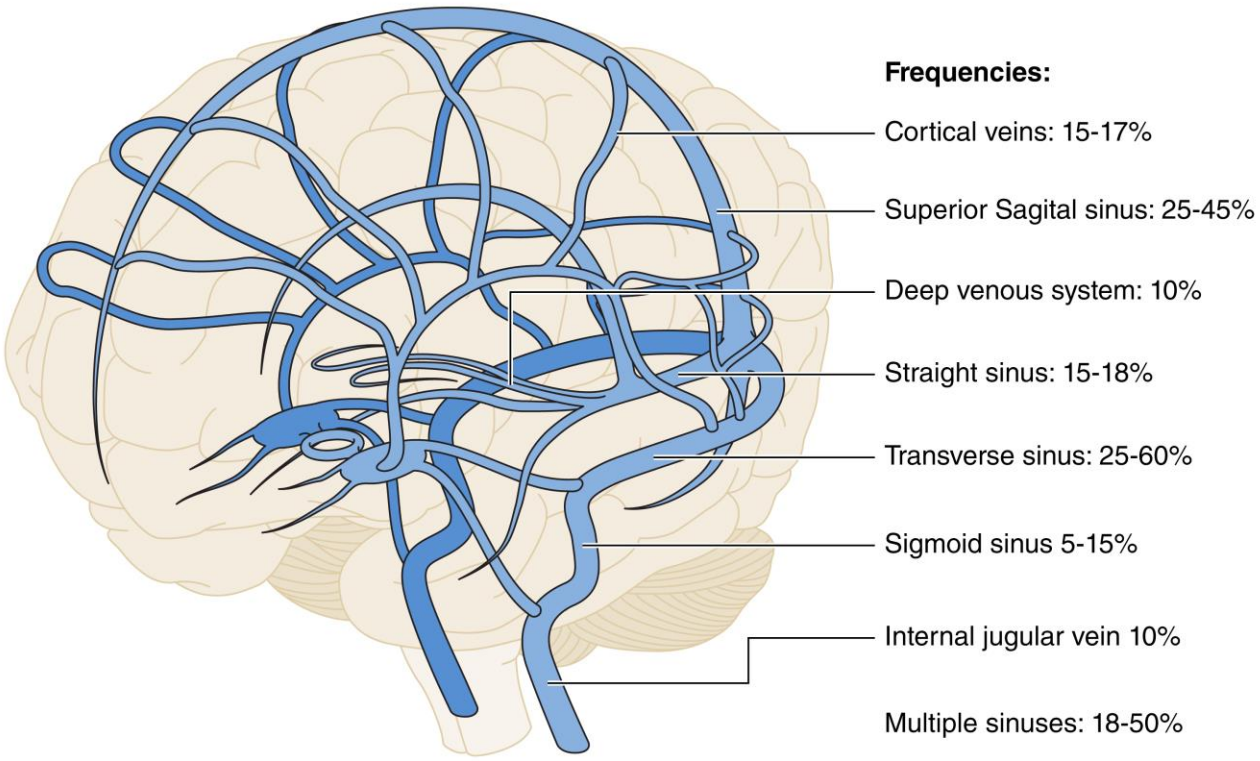
This scientific statement provides an update of the 2011 AHA Scientific Statement for the diagnosis and management of CVT. Our focus is on advances in the diagnosis and management decisions of patients with suspected CVT. We discuss evidence for the use of anticoagulation, endovascular therapies, and considerations for hemicraniectomy. Additionally, we provide an algorithm to optimize the management of patients with CVT and those with progressive neurological deterioration or thrombus propagation despite maximal medical therapy.

Introduction

Cerebral venous thrombosis (CVT) is the presence of a blood clot in the dural venous sinuses, the cerebral veins, or both.[1] Among those with stroke, CVT represents only 0.5% to 3%.[2] The largest registry-based and cohort studies suggest that CVT predominantly affects individuals younger than 55 years old, with two thirds occurring in women.[2] With regards to location, the most commonly affected sinuses are illustrated in Figure 1.[1-3]

The following sections describe the clinical presentation, predisposing factors, advances in imaging modalities and therapies, and the management of CVT in special populations (pediatric, pregnancy and puerperium, and vaccine-induced CVT). The current statement is strengthened by new evidence since our previous publication in 2011.[1] Future areas of research are highlighted.

Figure 1. Anatomy of the Cerebral Venous System and Distribution of CVT



Legend: Prevalence of sinus involvement in CVT. Percentages may be higher than 100% as many patients may have more than one sinus involved.[1-3]

Clinical Presentation

Presenting symptoms of cerebral venous thrombosis (CVT) can be due to increased intracranial pressure or focal parenchymal injury, with or without mass effect.[1] Headache is the most common symptom of CVT, occurring in nearly 90% of cases.[4] Other signs and symptoms related to increased intracranial pressure involve vision, including transient visual obscurations or vision loss (13-27%) and diplopia (6-14%).[2,4-6] Other cranial neuropathies can also occur from increased ICP (6-11%). Approximately 20-40% have seizures at the time of presentation, and 20-50% have focal neurological deficits.[2,4-8] Encephalopathy and coma have been reported in up to

20%.[2,4-7] Symptoms tend to occur more insidiously than other stroke types and the majority will present later than 48 hours following onset. A minority may have more acute presentations with thunderclap headache or subarachnoid hemorrhage (<5%) or acute onset of focal neurologic deficits (5-40%).[2,4-7] Further details are summarized in the Supplemental file (Table e1).

Predisposing Factors

Predisposing factors for CVT are identified in the majority of those with the disease, and may be transient or chronic (Table 1).[9,10] Rates of cerebral venous thrombosis are highest in younger females, with both oral contraception and pregnancy/puerperium being major risk factors. Oral contraception may increase the odds of CVT nearly 8-fold,[10] with possible additional synergistic effects with obesity.[11] Other well-established risk factors include acquired thrombophilias, such as antiphospholipid antibody syndrome, and malignancy, particularly myeloproliferative disorders, and autoimmune disease including Behcet's and inflammatory bowel disease. Genetic thrombophilias such as protein C and protein S deficiency, Factor V Leiden and Prothrombin G20210A polymorphism can be associated with CVT.[1,4,6,12] Other transient provoking factors commonly reported in previous series include infections (including Covid-19)[13,14], and other medications such as corticosteroids, L-asparaginase, and Covid- 19 vaccines.[1,4] Mechanical provoking factors, such as head trauma, neurosurgical procedures and compressive lesions such as meningiomas impinging on venous sinuses, are also associated with CVT.[1,4,15]

Table 1: Predisposing factors or medical conditions associated with CVT

	Transient	Chronic
Sex-specific	Oral contraceptive (54-71%) Pregnancy/Post-partum (11-59%) Hormone replacement therapy (4%)	
Other morbidity	Head and neck infections (8-11%) Dehydration (2%) Sepsis Respiratory infections (Covid-19)	Obesity (23%) Anemia (9-27%) Other systemic diseases (thyroid disease, nephrotic syndrome, inflammatory bowel disease) 1-2%
Other medications	Corticosteroids L-asparaginase	
Malignancy		Myeloproliferative disorders (2-3%) Other malignancy (7%)
Auto-immune		Antiphospholipid antibody syndrome (6-17%) Connective tissue disease (Systemic lupus erythematosus, Behcet's. Sarcoidosis) (1%)
Other genetic thrombophilia (31-41%)		Prothrombin 20210A mutation Factor V Leiden mutation MTHFR (C677T) polymorphism Antithrombin deficiency, Protein C or Protein S deficiency (can be genetic or acquired)
Mechanical	Head trauma (1-3%) Neurosurgical procedures Jugular vein catheterizations (1-2% iatrogenic)	Compressive lesions of venous sinus (meningioma)

Legend: Percentages may be higher than 100% as many patients may have more than one predisposing condition

Long-term Symptoms, CVT Recurrence, and Prognosis

Overall, approximately 80-90% of patients with CVT achieve functional independence (modified Rankin Score of 0-2).[1,4,16] However, several retrospective series reported a high prevalence of residual symptoms related to cognition, mood, fatigue and headache that may impede return to previous level of activity.[17-19] A retrospective study from China including 303 CVT patients who were employed or students prior to their index event found that 42% had not returned to work or school at six months, despite 87% reaching functional independence at the time of assessment.[20]

Epilepsy may affect over 10% of individuals with CVT, with risk factors including seizures at the time of onset, decreased level of consciousness or focal deficits, hemorrhagic lesions at baseline or superior sagittal sinus involvement, and hemicraniectomy.[21,22] Dural arteriovenous fistula (dAVF) is a reported complication of CVT, though CVT can also be a sequela of dAVF. A large retrospective series of 1218 individuals with CVT found the incidence of new dAVF was 2.4% at a median follow-up of 8 months (IQR 5-23 months), although there was no systematic timing or neuroimaging protocol involved in the study.[23]

The incidence of recurrent venous thromboembolism (VTE) after CVT ranges from 1-4%/year, with rates of CVT recurrence generally reported as <1-2% per year.[5,24] A higher risk of recurrence has been reported in individuals with severe thrombophilias (including malignancy), history of VTE, individuals with events without identified precipitants and, inconsistently, with male sex.[5,24] A recent retrospective study of VTE recurrence (including CVT) reported rates of 5.68/100 patient-years, over half of which were CVT.[7] A recent study from Norway found that individuals with CVT (N=654, median age 41, 67% women) compared to general population age- and sex-matched controls were at increased risk of recurrent VTE, ischemic stroke, major

bleeding and mortality at 10 years. Risks of recurrent VTE were higher in younger individuals (ages 18-54) with CVT compared to the general population, while risks of ischemic stroke, major bleeding and mortality (risk difference 11.5% for women ≥55 years and 5.8% for men ≥55 years) were highest in older patients.[25]

Brain and Vascular Imaging for the Diagnosis of CVT

Conventional CT or MRI is often the first test obtained in patients with non-specific acute presentations and may show signs that increase suspicion for CVT. For example, CVT on CT or MRI may be suspected by (1) direct visualization of the thrombus, (2) the absence of venous filling and (3) imaging of the consequences of venous obstruction at the tissue level (venous infarction, edema and hemorrhagic transformation, intracranial hypertension and hydrocephalus) and at the vascular level (dilated veins).[1,26] Common challenges of brain imaging are summarized in Table e2 (Supplemental material).

Direct imaging of thrombus is possible on CT, especially with the increased use of thin slice CT.[1,27] On non-contrast CT (NCCT) this is observed as hyperattenuation due to increase of hemoglobin and red blood cells within the thrombus (dense vessel sign) (Figure 2, Panels A-D). The traditional cord or string sign, a serpiginous or linear hyperdensity within a vein, or dense triangle sign can be present up to 14 days after onset of symptoms (Figure 2, Panel E). Indirect signs that raise the suspicion on NCCT include areas of hypodensity not conforming to typical wedge-shaped infarctions or which are not limited to specific arterial territories or which spare the overlying cortex. Bilateral hypodensities may occur when the sagittal sinus or the deep cerebral veins are involved. Hemorrhages are present in up to 40% of CVT and include areas of hemorrhagic

transformation within regions of hypodensity or frank intracerebral hemorrhage associated with subarachnoid or subdural hemorrhages.[2,4,12] Isolated subarachnoid hemorrhage and basal ganglia hemorrhages are uncommon.[4] The cashew nut sign, a juxtacortical C-shaped hyperdensity, is reported to have a high specificity for CVT but has low sensitivity (Figure 2, Panel A).[28] Bilateral or multifocal hemorrhages also frequently occur (Figure 2, Panel F). In a recent meta-analysis of 27 publications with 2812 cases CT had a sensitivity of 0.79 (95% CI: 0.76, 0.82) and specificity of 0.90 (95% CI: 0.89, 0.91).[27] This is lower than previously reported in the 2011 AHA Statement.[1]

Thrombi can also be directly observed on conventional MRI sequences.[1,29] As the evolution of a thrombus on MRI is dynamic, changes in the signal intensity of the thrombus over time are similar to that of a hematoma. As the thrombus ages, oxyhemoglobin is converted to deoxyhemoglobin and methemoglobin leading to changes in signal characteristics on the T1 and T2 sequences. In these early stages, it is difficult to diagnose thrombosis, considering that T2 may be isointense or hypointense, which mimics a normal flow void of a venous sinus. Similarly, time-of-flight MRV is susceptible to misdiagnosis as absent flow is not always corroborated on T1//T2 sequences (See supplemental file, Table e2). Consequently, it is often helpful to corroborate findings using gradient-recalled echo (GRE), susceptibility-weighted imaging (SWI) sequences or contrast enhanced-MRV.[26,29] Thrombosed blood creates a blooming artifact on GRE or SWI sequences which is especially useful in the identification of inconspicuous findings (Figure 3, Panel B and D), such as thrombosed cortical veins, where they have a sensitivity and specificity approaching 100%.[26,29] Advanced MRI techniques such as T1 based black blood imaging (where signal from flowing blood is suppressed) are promising. MRI is more sensitive than CT in the detection of parenchymal brain lesions secondary to venous occlusion, such as venous infarctions (Figure 3,

Panels A and C). Radiologically, these lesions cross arterial vascular territories and may be bilateral in nature.

A meta-analysis of 21 studies with 1773 patients with CVT showed conventional MRI sequences to have a sensitivity of 0.82 (95% CI: 0.78, 0.85) and a specificity of 0.92 (95% CI 0.91, 0.94).[27]

Confirming the diagnosis of CVT

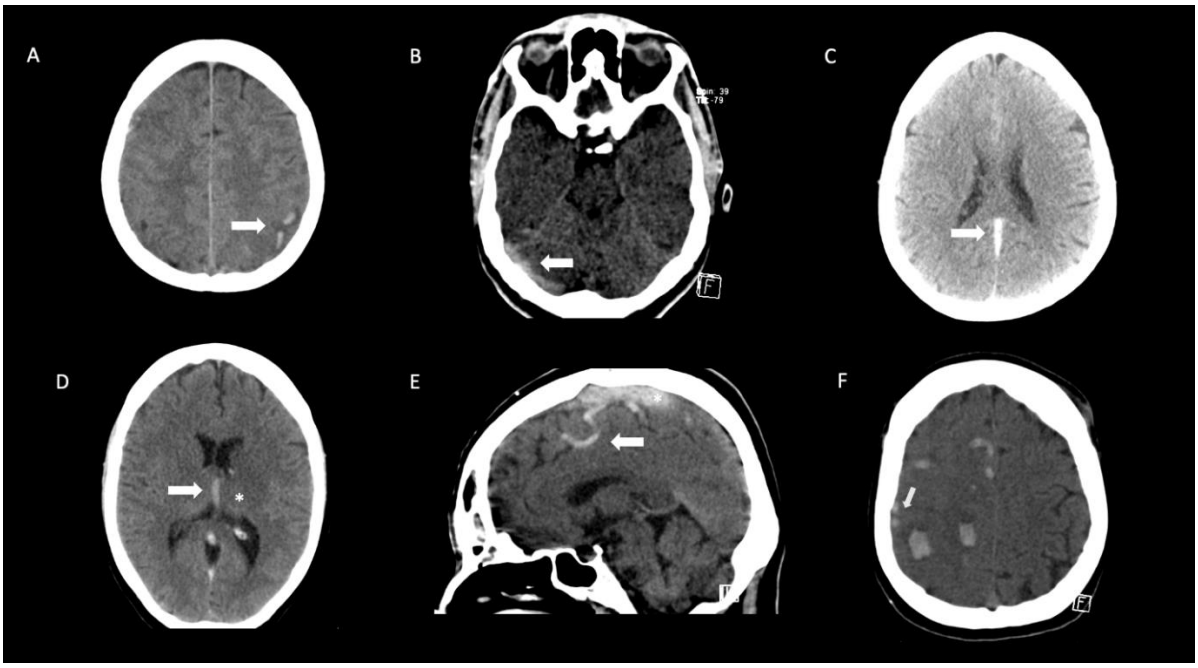
CT venography or MR venography are the optimal tests to confirm a diagnosis of CVT. Digital subtraction angiography (DSA) is typically only used when invasive treatments are considered.[1]

CT venography allows for clear depiction of the superficial and deep cerebral venous system. Thrombi present as filling defects and can usually be easily distinguished from arachnoid granulations. Several small to moderately sized studies have demonstrated a high sensitivity and specificity of CTV compared with DSA or a consensus reading of other imaging modalities. Compared to MRI, CTV has a lower sensitivity for cortical vein thrombosis.[29]

MR venography can either be performed without contrast, using time-of-flight (TOF) or phase-contrast techniques, or with a contrast-enhanced technique (Figure 3, Panels E and F). The use of gadolinium with contrast-enhanced technique allows for direct assessment of luminal filling and increases sensitivity of detection of thrombus within the smaller veins.[1,29] TOF and phase-contrast MRV techniques can both be prone to artifact secondary to complex flow. TOF is however still commonly used and is especially useful in situations that may preclude gadolinium administration, such as in pregnant or breastfeeding patients or in patients with severe renal failure. Compared to 3D TOF, 2D TOF has higher sensitivity in the setting of slow flow. Phase-contrast MRI is used less frequently since defining the velocity of the encoding parameter is not only difficult but

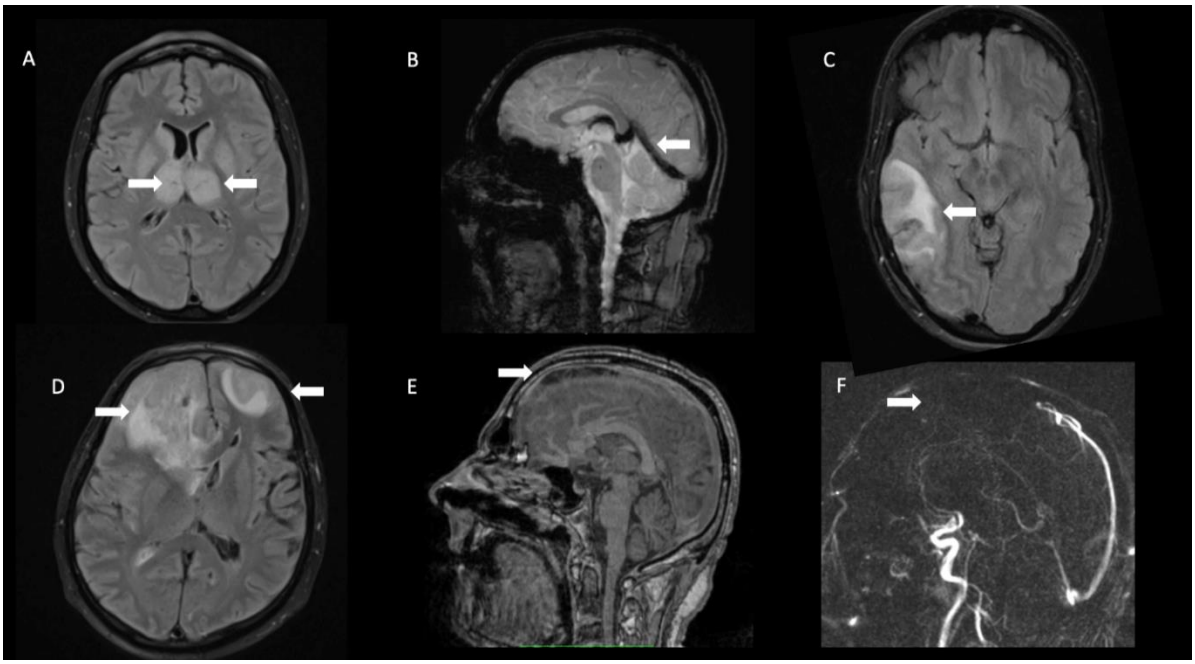
operator-dependent and requires longer acquisition times. Contrast-enhanced MRV has comparable sensitivity and specificity to CTV. Contrast-enhanced techniques and GRE or SWI are recommended for diagnosing cortical vein thrombosis (new evidence since the 2011 AHA Statement).[1,26,29]

Figure 2. Typical findings of CVT on CT



Legend: Panel A: Left sided juxtacortical C-shaped hemorrhages; Panel B: Transverse sinus thrombosis; Panel C: Straight sinus thrombosis; Panel D: Internal cerebral vein thrombosis (arrow) and left thalamic hypodensity (star). Panel E: Cord sign (arrow) and hyperdense sagittal sinus thrombosis (star); Panels F: Multiple small hemorrhages in same patient as E, arrows indicate cord sign

Figure 3. Typical findings of CVT on MRI



Legend: Panel A: Bilateral thalamic hyperintensity (arrows) on FLAIR in a patient with deep cerebral vein thrombosis; Panel B: Susceptibility weighted imaging shows hypointensity of the straight sinus (arrow), vein of Galen and internal cerebral veins; Panel C: Venous infarction due to transverse sinus thrombosis with heterogenous FLAIR hyperintensity (arrow); Panel D: Bilateral FLAIR hyperintensities (arrows) with mass effect in a patient with superior sagittal sinus thrombosis (arrow), shown in E on a contrast-enhanced T1 sequence and F. absent venous filling defect (arrow) with a phase-contrast MRA

Therapeutic Advances in the Management of CVT

Oral Anticoagulation

The objectives of anticoagulation therapy in CVT are to prevent thrombus growth, to facilitate recanalization and to prevent recurrent VTE events. Previous AHA/ASA and European guidelines for the management of CVT recommend the initial use of parenteral heparin followed by transition to oral vitamin K antagonists (VKA) for 3-12 months in the context of transient risk factors, or indefinitely in the context of chronic major risk factors for thrombosis or recurrent VTE (Figure 4).[1,12,30] Whether degree of venous recanalization should inform duration of anticoagulation remains an area of uncertainty.[31-33]

An emerging body of evidence suggests that direct oral anticoagulants (DOACs), which have demonstrated efficacy and safety compared to VKA for individuals with deep venous thrombosis and pulmonary embolism, may also be a reasonable choice for oral anticoagulation in selected individuals with CVT.

RE-SPECT CVT (A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis) was an international prospective clinical trial that randomized 120 individuals with CVT 1:1 to warfarin VKA with target INR 2.0-3.0 or dabigatran 150 mg twice daily for 6 months following 5-15 days of lead-in parenteral anticoagulation.[34] The trial excluded individuals with malignancy, central nervous system infection, trauma, and pregnancy. There were no recurrent VTEs in either group, with one (1.7%; 95%CI 0.0-8.9%) major hemorrhages (gastrointestinal bleeding) in the dabigatran group and two ([3.3%; 95%CI 0.4-11.5%], both intracerebral hemorrhages) in the warfarin group.

ACTION-CVT (Anticoagulation in the Treatment of Cerebral Venous Thrombosis), a large retrospective international study, compared events in 845 consecutive individuals with CVT who were prescribed VKA versus DOAC as part of their routine clinical care between 2015 and 2020.[7] DOACs used included apixaban (67%), rivaroxaban (18%) and dabigatran (14%), or multiple DOACs (3%). Individuals with malignancy, antiphospholipid antibody syndrome and those who were pregnant were excluded. The study found no significant difference in rates of recurrent VTE (aHR 0.94, 95%CI 0.15 - 1.73), and there was a reduced risk of major hemorrhage (aHR 0.35, 95%CI 0.15 - 0.82), primarily driven by a lower risk of ICH, in the DOAC group.[7]

There were no differences in recanalization rates between groups in both studies.[7,34]

A recent systematic review summarizing 3 randomized trials and 16 observational studies comparing DOACs to VKAs found similar risks with both treatments of recurrent VTE, major hemorrhage and complete recanalization.[35] Additional clinical trials and prospective observational studies are ongoing (clinicaltrials.gov NCT03178864, NCT04660747). Persistent areas of controversy include timing of initiation with or without lead-in heparin, whether acute VTE dosing is initially required, and optimal candidates for DOAC therapy. DOACs are not suitable in women who are pregnant (both DOAC and warfarin are contraindicated and only low-molecular weight heparin is recommended) or breastfeeding (DOACs are contraindicated) (Figure 4). DOACs have also been associated with higher risks of recurrent thromboembolic events compared to warfarin in individuals with antiphospholipid antibody syndrome.[36,37]

Reperfusion therapies

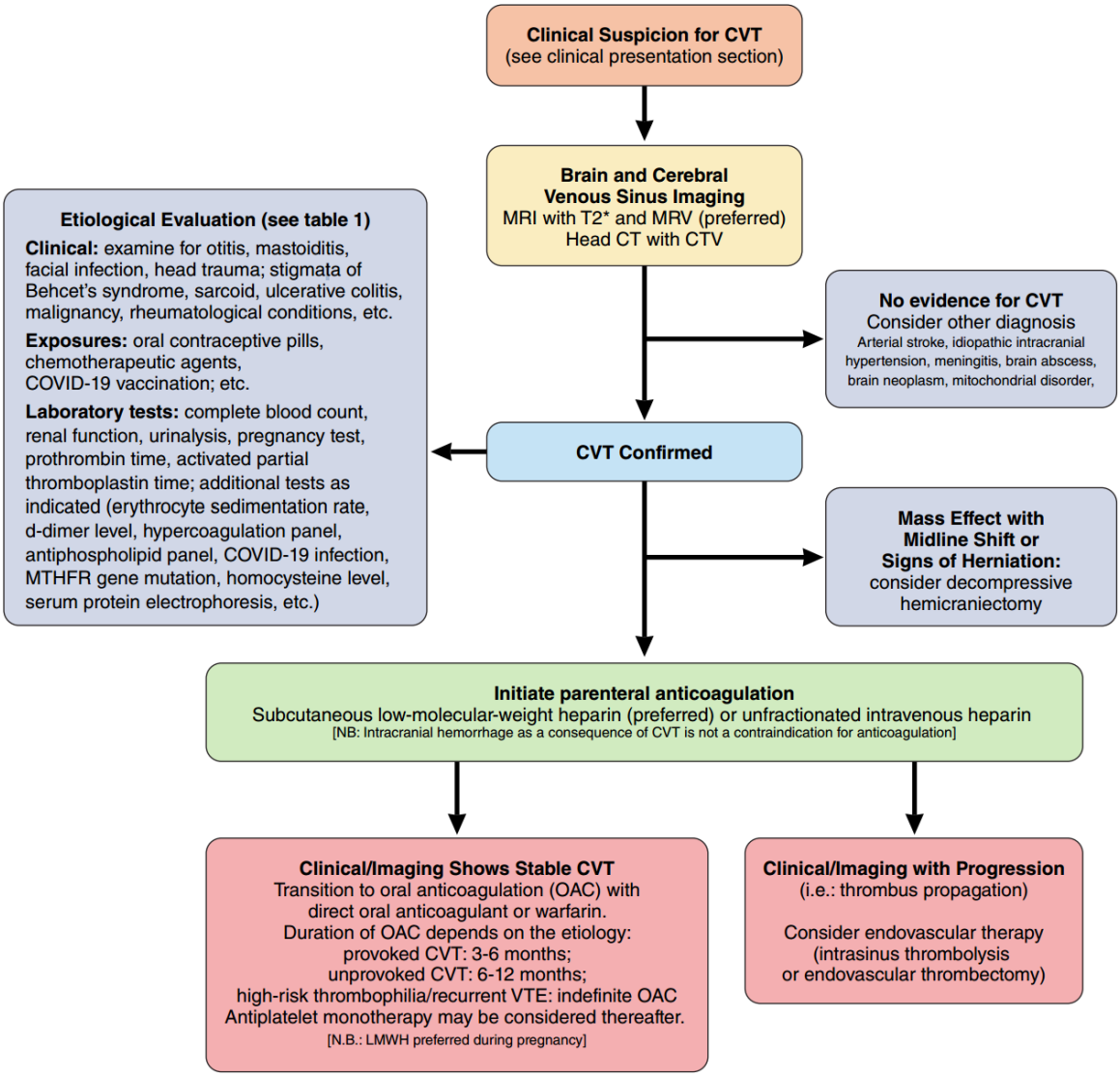
Endovascular treatment (EVT) options for the management of CVT could theoretically offer faster recanalization, although its association with a more favorable outcome in medical therapy, particularly in an unselected population, is uncertain.[38] Several studies reported in the last decade on the use of mechanical thrombectomy (MT) (either balloon-assisted or through aspiration or vacuum aspiration systems), intrasinus thrombolysis (IST), combination of MT and IST, intraarterial thrombolysis (IAT) and intrasinus stenting provide controversial evidence regarding safety, and complication rates.[39,40] The multicenter, randomized clinical trial TO-ACT (Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis) showed that patients with severe CVT did not benefit clinically from EVT when compared to the patients receiving standard anticoagulation therapy.[41] Larger studies and meta-analyses showed that EVT is associated with higher mortality and no evidence of benefit with EVT.[42-45]

Currently, EVT is used as a "rescue treatment" for patients who are experiencing clinical deterioration or failed standard therapy (Figure 4).[40] In a systematic review including 10 studies comprising 339 patients who underwent EVT for CVT, the authors found a complete and partial postoperative recanalization in 90.0% of patients, increasing to 95.2% during the follow-up.[46] The complication rate was 10.3%. There is no current evidence to determine which EVT technique (e.g., stent retriever, microcatheters, aspiration catheters, aspiration pump systems) is superior to other therapeutic strategies.

Decompressive hemicraniectomy

The evidence regarding decompressive hemicraniectomy for CVT remains unchanged since the previous AHA Statement.[1] It should be offered to patients with acute severe CVT and parenchymal lesions with impending herniation as a life-saving therapeutic approach (Figure 4).[47] Factors associated with poorer outcomes included age over 50, midline shift >10 mm, and total effacement of basal cisterns.[48] There are no randomized controlled trials of this surgical approach in the literature.

Figure 4. Proposed algorithm for the management of CVT



Legend: This figure summarizes the suggested approach for the diagnosis and management of CVT.

CVT in Special Populations:

Pediatric Population

CVT is more common in neonates (6.4/100,000) than in children and adolescents.[49] The key to successful management is to consider the diagnosis early in the context of acute presentation with headache, seizures, focal neurological deficits, or coma, and in typical situations such as

sepsis (including mastoiditis and Lemierre's syndrome as well as COVID-19 and meningitis), head trauma (including abuse), hypoxia and/or dehydration. Awareness is especially important in children with pre-existing conditions (congenital heart disease and its surgical treatment, cancer and its treatment, anemia due to iron deficiency or hemoglobinopathies, and inflammatory conditions such as nephrotic syndrome and inflammatory bowel disease). Emergency imaging to diagnose or exclude dural and/or cortical venous thrombosis with or without parenchymal involvement or hemorrhage typically requires anesthesia. Initial blood work may reveal low platelets associated with PF4 mutations or high platelets and high hemoglobin associated with JAK2 mutations, as well as, indices of iron deficiency with or without anemia.[49,50]

There have been no randomized clinical trials of acute CVT treatment in children but management typically involves low molecular weight heparin or unfractionated heparin. As for adults, if there is deterioration in level of consciousness, more invasive procedures should be considered and may potentially be life-saving (Figure 4). Anticoagulation in the acute phase is more controversial in premature and term neonates but is reasonable as there is no evidence of post-treatment hemorrhage, whereas lack of anticoagulation may lead to thrombus propagation.[51,52] CVT in children carries a mortality of 3%, and recurrent venous thrombosis occurs in about 6%, usually associated with non-administration of anticoagulation and lack of venous recanalization.[50] In the EINSTEIN-Jr trial (Oral Rivaroxaban in Children With Venous Thrombosis) involving 114 children with confirmed CVT, after initial heparinization were randomized (2:1) to 3 months of rivaroxaban or standard anticoagulation (either continuing heparin or switching to oral vitamin K antagonists).[53] The primary efficacy outcome was symptomatic recurrent venous thromboembolism (VTE) and the principal safety outcome was major or clinically relevant non-major bleeding. With 100% follow-up, none of the 73 children

treated with rivaroxaban compared with 1 of the 41 children treated with standard anticoagulation had symptomatic recurrent VTE (absolute difference 2.4%; 95%CI -2.6 to 13.5%). Five patients on rivaroxaban had non-major and non-cerebral bleeding while one patient on standard anticoagulation had a major subdural bleed. Complete or partial recanalization was similar in each arm, 18 (25%) and 39 (53%) for rivaroxaban and 6 (15%) and 24 (59%) for standard anticoagulation, respectively. No children died by the end of the 3-month study treatment period. Focal neurologic deficits were observed in 5 (6.8%) and 3 (7.3%) children in the rivaroxaban and standard anticoagulation group, respectively at the end of the study. Long-term studies suggest that one in four children may develop late epilepsy,[54] infantile spasms post-neonatal-CVT, cognitive impairment, or intracranial hypertension.[55]

CVT during Pregnancy and Puerperium

Pregnancy induces changes in the coagulation system that persist into the puerperium and result in a hypercoagulable state, which increases the risk of CVT. Incidence estimates for CVT during pregnancy and the puerperium range from 1 in 2,500 deliveries to 1 in 10,000 deliveries in Western countries, and ORs range from 1.3 to 13.0. The greatest risk periods for CVT include the third trimester and the first 6 postpartum weeks. Around 80% of pregnancy related CVT cases occur after delivery.[56] In fact, a case-control study found that the risk of CVT is only increased in the puerperium (OR 10.6, 95%CI 5.6-20.0), while there was no statistically significant increase of the risk of CVT during pregnancy (OR 1.2, 95%CI 0.6-2.3).[9] Cesarean delivery appears to be associated with a higher risk of CVT after adjustment for age, vascular risk factors, presence of infections, hospital type, and location (OR 3.10, 95%CI 2.26 to 4.24).[9]

Overall, studies published since the prior scientific statement[1] have found that the prognosis of women with pregnancy related CVT is better or the same compared to CVT patients in general.[57] Vitamin K antagonists, including warfarin, are associated with fetal embryopathy and bleeding in the fetus and neonate and thus are contraindicated in pregnancy. Therefore, anticoagulation for CVT during pregnancy and early in the puerperium consists of LMWH in the majority of women.[56,58,59] There is limited evidence regarding endovascular therapies in this population. As in nonpregnant women, thrombolysis or thrombectomy are reserved for patients with neurological deterioration or propagation of the thrombus despite medical therapy (Figure 4).

Future Pregnancies and Recurrence

Women with a history of VTE appear to have an increased risk of thrombotic events (i.e., DVT, PE) in future pregnancies.[50] A systematic review comprising 17 studies and 393 pregnancies found a recurrence rate of 8 per 1,000 pregnancies (95% CI 3-22). The rate of noncerebral VTEs was 22 per 1,000 pregnancies (95% CI 11-43).[60] There was a trend towards a lower rate of recurrent thrombotic events in women who used antithrombotic prophylaxis.[60]
According to the available evidence, CVT is not a contraindication for future pregnancies.[56,58,61] Considering the additional risk that pregnancy confers to women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period is probably beneficial.[61]

Vaccine Induced Thrombotic Thrombocytopenia (VITT) and CVT

In 2021, reports from Europe and the US described thrombocytopenia and cerebral venous thrombosis after vaccination with the ChAdOx1 nCoV-19 vaccine (AstraZeneca) and the

Ad26.COV2.S (Janssen) adenovirus-based SARS-CoV-2 vaccine.[62-64] The age range of affected patients was 18 to 77 years; primarily women. Symptoms began 5-24 days after vaccination.[62] Headache was the most common presenting feature. All patients had thrombocytopenia. In the UK, 23 patients with antibodies to platelet factor 4 (PF4) after ChAdOx1 nCoV-19 vaccination were described. It is believed that DNA from the adenovirus infected cells bonded to platelet factor 4 (PF4) and triggered the production of autoantibodies.[65,66] Although CVT in VITT is a rare condition,[67] it carries a poor prognosis with mortality rates ranging from 39% to 61% in initial cohort studies.[66,68,69]

There is an anecdotal association between CVT and mRNA SARS-CoV-2 vaccines. For example, a pharmacovigilance study comprising over 1.7 million adverse reactions showed a disproportionately lower incident risk of CVT after mRNA SARS-CoV-2 vaccines (1-5/10,000 for BNT162b2 and mRNA-1273 vs. 13/10,000 for ChAdOx1 nCoV-19 vaccine).[70] Also, there is no evidence of VITT after mRNA vaccines.[62,70]

In cases of suspected VITT, laboratory testing for PF4 antibodies is recommended. Despite the lack of evidence, given the similarity to autoimmune heparin-induced thrombocytopenia, avoidance of heparin products, intravenous immunoglobulin 1 g/kg body weight daily for 2 days, and administration of steroids have been advised. Platelet transfusions are not recommended.[71] Non-heparin anticoagulants (argatroban, fondaparinux, etc.) or a direct oral anticoagulant (DOAC) have been used, with transition to an oral anticoagulant once there is full platelet count recovery. [66]

Key points for Clinical Practice

- CVT requires a high level of suspicion among patients presenting with common symptoms and known predisposing conditions (pregnancy, puerperium, use of oral contraceptives, thrombophilia) or demographic factors (young women).
- New predisposing conditions (obesity, Covid-19, vaccine-induced thrombocytopenia)[2,11,14] were identified since our previous report.[1] [New]
- MRI/MRV is the recommended non-invasive study of the cerebral venous system to confirm the diagnosis. CT/CTV is a reasonable alternative among centers with limited resources.
- Contrast-enhanced MRI, GRE, and SWI sequences are the recommended techniques for the diagnosis of cortical venous thrombosis. [New]
- The mainstream initial treatment of CVT includes parental heparin followed by transition to oral vitamin K antagonists (VKA) for 3 to 12 months depending on the underlying etiology, or indefinitely in the presence of thrombophilia or recurrent VTE (Figure 4).
- The use of direct oral anticoagulants appears to be a safe and effective alternative option to VKA as per open-label retrospective and prospective studies [New].
- The benefits of identifying venous recanalization in subsequent CT venograms or MRV to guide the duration of anticoagulation remains uncertain. [New]
- Given the lack of controlled studies (and poorer outcomes in meta-analyses), endovascular therapies are reserved for patients with evidence of thrombus propagation, neurological deterioration despite medical therapy or for those with contraindications for anticoagulation (Figure 4). [New]
- For women with CVT during pregnancy, LMWH in full anticoagulant doses should be continued throughout pregnancy, and LMWH or vitamin K antagonist with a target INR of

2.0 to 3.0 should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 3 months)

- It is reasonable to advise women with a history of CVT that future pregnancy is not contraindicated. Prophylaxis with LMWH during future pregnancies and the postpartum period is usually recommended.
- CVT in the pediatric population is more common in neonates than children, usually exposed to infections, dehydration or head trauma. Parenteral anticoagulation is also the first line treatment.
- Vaccine Induced Thrombotic Thrombocytopenia and CVT may occur (rarely) days or a few weeks after receiving adenovirus-based SARS-CoV-2 usually presenting with new onset of headaches and thrombocytopenia; it requires the expert management by a hematologist and multidisciplinary team. [New]

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Article Information

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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