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Diagnosis and Management of Cerebral Venous Thrombosis: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

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AHA Scientific Statement

Diagnosis and Management of Cerebral Venous Thrombosis

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

The American Association of Neurological Surgeons and Congress of Neurological Surgeons have reviewed this document and affirm its educational content.

The Ibero-American Stroke Society (Sociedad Iberoamericana de Enfermedad Cerebrovascular) endorses the recommendations contained in this report.

Endorsed by the Society of NeuroInterventional Surgery

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Background—The purpose of this statement is to provide an overview of cerebral venous sinus thrombosis and to provide recommendations for its diagnosis, management, and treatment. The intended audience is physicians and other healthcare providers who are responsible for the diagnosis and management of patients with cerebral venous sinus thrombosis.

Methods and Results—Members of the panel were appointed by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and represent different areas of expertise. The panel reviewed the relevant literature with an emphasis on reports published since 1966 and used the American Heart Association levels-of-evidence grading algorithm to rate the evidence and to make recommendations. After approval of the statement by the panel, it underwent peer review and approval by the American Heart Association Science Advisory and Coordinating Committee.

Conclusions—Evidence-based recommendations are provided for the diagnosis, management, and prevention of recurrence of cerebral venous thrombosis. Recommendations on the evaluation and management of cerebral venous thrombosis during pregnancy and in the pediatric population are provided. Considerations for the management of clinical complications (seizures, hydrocephalus, intracranial hypertension, and neurological deterioration) are also summarized. An algorithm for diagnosis and management of patients with cerebral venous sinus thrombosis is described. **(*Stroke*. 2011;42:00-00.)**

Key Words: AHA Scientific Statements ■ venous thrombosis ■ sinus thrombosis, intracranial ■ brain infarction, venous ■ stroke ■ disease management ■ prognosis ■ outcome assessment ■ anticoagulants ■ pregnancy ■ children

Author order is alphabetical after the writing group chair. All authors have contributed equally to the present work.

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.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on October 26, 2010. A copy of the statement is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. KB-0186). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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Thrombosis of the dural sinus and/or cerebral veins (CVT) is an uncommon form of stroke, usually affecting young individuals.[1] Despite advances in the recognition of CVT in recent years, diagnosis and management can be difficult because of the diversity of underlying risk factors and the absence of a uniform treatment approach. CVT represents ≈0.5% to 1% of all strokes.[2] Multiple factors have been associated with CVT, but only some of them are reversible. Prior medical conditions (eg, thrombophilias, inflammatory bowel disease), transient situations (eg, pregnancy, dehydration, infection), selected medications (eg, oral contraceptives, substance abuse), and unpredictable events (eg, head trauma) are some predisposing conditions.[3,4]

Given the diversity of causes and presenting scenarios, CVT may commonly be encountered not only by neurologists and neurosurgeons but also by emergency physicians, internists, oncologists, hematologists, obstetricians, pediatricians, and family practitioners. Our purpose in the present scientific statement is to review the literature on CVT and to provide recommendations for its diagnosis and management. Writing group members were appointed by the American Heart Association (AHA) Stroke Council's Scientific Statement Oversight Committee and the Council on Epidemiology and Prevention. The panel included members with several different areas of expertise. The panel reviewed relevant articles on CVT in adults and children using computerized searches of the medical literature through July 2010. These articles were supplemented by other articles known to the authors. The evidence is organized within the context of the AHA framework and is classified according to the joint AHA/American College of Cardiology Foundation and supplementary AHA Stroke Council methods of classifying the level of certainty and the class and level of evidence (Tables 1 and 2).[5] After review by the panel members, the manuscript was reviewed by expert peer reviewers and members of the Stroke Council Leadership Committee and was subsequently approved by the AHA's Science Advisory and Coordinating Committee.

Although information about the cause and clinical manifestations of CVT is included for the convenience of readers who may be unfamiliar with these topics, the group's recommendations emphasize issues regarding diagnosis, management, and treatment. The recommendations are based on the current available evidence and were approved by all members of the writing group. Despite major progress in the evaluation and management of this rare condition in recent years, much of the literature remains descriptive. In some areas, evidence is lacking to guide decision making; however, the writing group made an effort to highlight those areas and provide suggestions, with the understanding that some physicians may need more guidance, particularly in making decisions when extensive evidence is not available. Continued research is essential to better understand issues related to the diagnosis and treatment of CVT. Identification of subgroups at higher risk would allow a more careful selection of patients who may benefit from selective interventions or therapies.

Epidemiology and Risk Factors for CVT

CVT is an uncommon and frequently unrecognized type of stroke that affects approximately 5 people per million annually and accounts for 0.5% to 1% of all strokes.[1] CVT is more commonly seen in young individuals. According to the largest cohort study (the International Study on Cerebral Venous and Dural Sinuses Thrombosis [ISCVT]), 487 (78%) of 624 cases occurred in patients <50 years of age (Figure 1).[1,6] Clinical features are diverse, and for this reason, cases should be sought among diverse clinical index conditions. A prior pathological study found a prevalence of CVT of 9.3% among 182 consecutive autopsies.[7] No population studies have reported the incidence of CVT. Very few stroke registries included cases with CVT. This may result in an overestimation of risk associated with the various conditions owing to referral and ascertainment biases. In the Registro Nacional Mexicano de Enfermedad Vascular Cerebral (RENAMEVASC), a multihospital prospective Mexican stroke registry, 3% of all stroke cases were CVT.[8] A clinic-based registry in Iran reported an annual CVT incidence of 12.3 per million.[9] In a series of intracerebral hemorrhage (ICH) cases in young people, CVT explained 5% of all cases.[9]

Cause and Pathogenesis: Underlying Risk Factors for CVT

Predisposing causes of CVT are multiple. The risk factors for venous thrombosis in general are linked classically to the Virchow triad of stasis of the blood, changes in the vessel wall, and changes in the composition of the blood. Risk factors are usually divided into acquired risks (eg, surgery, trauma, pregnancy, puerperium, antiphospholipid syndrome, cancer, exogenous hormones) and genetic risks (inherited thrombophilia).

Table 3 summarizes the evidence for a cause-and-effect relationship[10,11] between prothrombotic factors and CVT.[12–55] Evidence for the strength and consistency of association, biological plausibility, and temporality is summarized. These criteria are most closely met for deficiency of antithrombin III, protein C, and protein S; factor V Leiden positivity; use of oral contraceptives; and hyperhomocysteinemia, among others.

Prothrombotic Conditions

The most widely studied risk factors for CVT include prothrombotic conditions. The largest study, the ISCVT, is a multinational, multicenter, prospective observational study with 624 patients. Thirty-four percent of these patients had an inherited or acquired prothrombotic condition.[10] The prevalence of different prothrombotic conditions is summarized in Table 3. Recently, another group in the United States reported that 21% of 182 CVT case subjects in 10 hospitals had a prothrombotic condition.[11]

Antithrombin III, Protein C, and Protein S Deficiency

Two studies have analyzed the role of natural anticoagulant protein deficiencies (antithrombin III, protein C, and protein S) as risk factors for CVT. One study compared 121 patients with a first CVT with 242 healthy control subjects.[36] The other study compared 51 patients with CVT with 120 healthy control subjects.[12] Only 1 patient (2%) had antithrombin III deficiency. The combined odds ratio (OR) of CVT when these 2 studies were combined was 11.1 for protein C deficiency (95% confi-

Table 1. Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT →

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†For recommendations (Class I and IIa; Level of Evidence A and B only) regarding the comparative effectiveness of one treatment with respect to another, these words or phrases may be accompanied by the additional terms "in preference to" or "to choose" to indicate the favored intervention. For example, "Treatment A is recommended in preference to Treatment B for. . . " or "It is reasonable to choose Treatment A over Treatment B for…." Studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

dence interval [CI] 1.87 to 66.05; $P=0.009$) and 12.5 for protein S deficiency (95% CI 1.45 to 107.29; $P=0.03$).

Antiphospholipid and Anticardiolipin Antibodies

The first study mentioned above found a higher prevalence of antiphospholipid antibodies in patients with CVT (9 of 121) than in control subjects (0 of 242).[36] In another study from India with 31 CVT patients, anticardiolipin antibodies were detected in 22.6% of CVT patients compared with 3.2% of normal control subjects.[12] Similar findings (5.9%) were observed in the ISCVT study.[10]

Factor V Leiden Gene Mutation and Resistance to Activated Protein C

Resistance to activated protein C is mainly caused by the presence of the factor V Leiden gene mutation, which is a common inherited thrombophilic disorder. A recent meta-analysis of 13 studies, including 469 CVT cases and 3023 control subjects,[28] reported a pooled OR of CVT of 3.38 (95% CI 2.27 to 5.05) for factor V Leiden, which is similar to its association with venous thromboembolism (VTE) in general.[28]

Prothrombin G20210A Mutation

The prothrombin G20210A mutation is present in ≈2% of whites and causes a slight elevation of prothrombin level.[55,56]A meta-analysis of 9 studies,[38] including 360 CVT patients and 2688 control subjects, reported a pooled OR of CVT of 9.27 (95% CI 5.85 to 14.67) for this mutation,[28] which is stronger than its association with VTE in general.

Hyperhomocysteinemia

Hyperhomocysteinemia is a risk factor for deep vein thrombosis (DVT) and stroke but has not been clearly associated with an increased risk of CVT. Five case-control studies evaluated

Table 2. Definition of Classes and Levels of Evidence Used in AHA Stroke Council Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or ≥1 case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

hyperhomocysteinemia in patients with CVT.[13,16,17,29,30] Researchers from Milan[13] reported on 121 patients with a first CVT and 242 control subjects, finding hyperhomocysteinemia in 33 patients (27%) and 20 control subjects (8%; OR 4.2, 95% CI 2.3 to 7.6). Low levels of serum folate and the 677TT methylenetetrahydrofolate reductase genotype were not associated with CVT risk, independent of homocysteine level.[13]

A study of 45 patients with CVT and 90 control subjects in Mexico reported an adjusted OR of CVT of 4.6 (95% CI 1.6 to 12.8) associated with high fasting homocysteine and an OR of 3.5 (95% CI 1.2 to 10.0) associated with low folate.[29] A small Italian study of 26 consecutive patients with CVT and 100 healthy control subjects reported that 38.5% of case subjects and 13% of control subjects had hyperhomocysteinemia (OR 4.2, 95% CI 1.6 to 11.2).[16] No significant differences were found in the prevalence of prothrombin or methylenetetrahydrofolate reductase mutation. No factor V Leiden mutation was found. Another Italian group[17] found a strong and significant association of the prothrombin G20210A mutation (30% versus 2.5% in patients versus control subjects, respectively, $P=0.001$; OR 16.2, $P=0.002$) and hyperhomocysteinemia (43.3% versus 10%, $P=0.002$; OR 6.9, $P=0.002$).

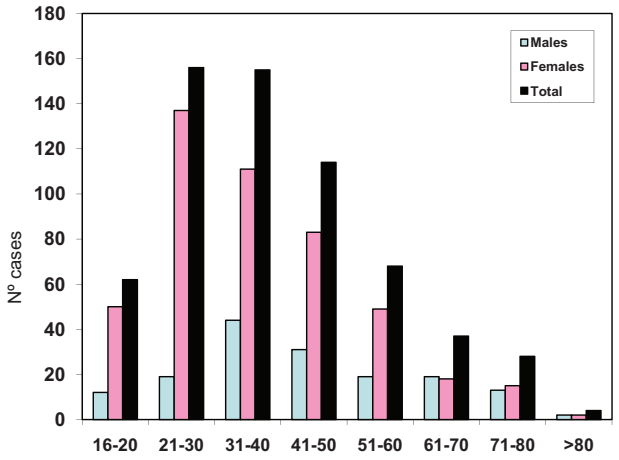

Figure 1. Age and sex distribution of cerebral venous and sinus thrombosis (CVT) in adults. Bars represent the number of patients with CVT for the specific age/sex category. Data provided by Dr Jose Ferro from the International Study on Cerebral Venous and Dural Sinuses Thrombosis.

Pregnancy and Puerperium

Pregnancy and the puerperium are common causes of transient prothrombotic states.[57] Approximately 2% of pregnancy-associated strokes are attributable to CVT.[31] The frequency of CVT in the puerperium is estimated at 12 cases per 100 000 deliveries, only slightly lower than puerperal arterial stroke.[58]

In a study from Mexico, ≈50% of CVT occurred during pregnancy or puerperium.[32] Most pregnancy-related CVT occurs in the third trimester or puerperium. Seven of 8 CVTs among 50 700 admissions for delivery in Canada occurred postpartum.[33] During pregnancy and for 6 to 8 weeks after birth, women are at increased risk of venous thromboembolic events.[34] Pregnancy induces several prothrombotic changes in the coagulation system that persist at least during early puerperium. Hypercoagulability worsens after delivery as a result of volume depletion and trauma. During the puerperium, additional risk factors include infection and instrumental delivery or cesarean section. One study reported that the risk of peripartum CVT increased with increasing maternal age, increasing hospital size, and cesarean delivery, as well as in the presence of hypertension, infections, and excessive vomiting in pregnancy.[35] Recently, it was reported that in pregnant women, hyperhomocysteinemia was associated with increased risk of puerperal CVT (OR 10.8, 95% CI 4.0 to 29.4) in a study of 60 case subjects and 64 control subjects.[30]

Oral Contraceptives

A 1998 study compared the prevalence of several risk factors, including use of oral contraceptives, among 40 female patients with CVT, 80 female patients with DVT of the lower extremities, and 120 female control subjects.[36] Nearly all CVT case subjects were using oral contraceptives (96%), which conferred 22.1-fold increased odds of CVT (95% CI 5.9 to 84.2). The OR for women with the prothrombin G20210A mutation who used oral contraceptives was 149.3 (95% CI 31.0 to 711.0) compared with those with neither characteristic. Stratification for the presence of factor V Leiden or prothrombin mutation and the use

Table 3. Predisposing Conditions for CVT and Principles in Favor of a Cause-and-Effect Relationship

Condition	Prevalence, %*	Consistency[1]†	Strength of Association[2]† OR (95% CI)	Biological Plausibility[3]†	Temporality[4]†	Biological Gradient[5]†
Prothrombotic conditions	34.1					
Antithrombin III deficiency		Yes[12,13]	NA	Yes	Yes	Yes‡
Protein C deficiency		Yes[12,13]	11.1 (1.9–66.0)	Yes	Yes	Yes‡
Protein S deficiency		Yes[12,13]	12.5 (1.5 to 107.3)	Yes	Yes	Yes‡
Antiphospholipid and anticardiolipin antibodies	5.9	Yes[12,14,15]*	8.8 (1.3–57.4)*	Yes	Yes	Yes‡
Resistance to activated protein C and factor V Leiden		Yes[16–27]	3.4 (2.3 to 5.1)	Yes	Yes	Yes‡
Mutation G20210A of factor II		Yes[28]	9.3 (5.9 to 14.7)	Yes	Yes	Yes[55]‡
Hyperhomocysteinemia	4.5	Yes[13,16,17,29,30]	4.6 (1.6–12.0)	Yes	Yes	Yes[13]
Pregnancy and puerperium	21	Yes[31–35]	NA	Yes	Yes	NA
Oral contraceptives	54.3	Yes[13,17,18,23,27,32,36–38]	5.6 (4.0−7.9)*	Yes	Yes	Yes
Drugs						
Androgen, danazol, lithium, vitamin A, IV immunoglobulin, ecstasy	7.5		NA	Yes	Yes	NA
Cancer related	7.4	Yes[39–41]	NA	Yes	Yes	NA
Local compression						
Hypercoagulable						
Antineoplastic drugs (tamoxifen, L-asparaginase)						
Infection	12.3		NA	Yes	Yes	NA
Parameningeal infections (ear, sinus, mouth, face, and neck)		Yes[2,42–44]				
Mechanical precipitants	4.5	Yes[45–47]	NA	Yes	Yes	NA
Complication of epidural blood patch						
Spontaneous intracranial hypotension						
Lumbar puncture	1.9					
Other hematologic disorders	12	Yes[48–51]	NA	Yes	Yes	NA
Paroxysmal nocturnal hemoglobinuria						
Iron deficiency anemia		Yes	NA	Yes	Yes	NA
Nephrotic syndrome	0.6					
Polycythemia, thrombocythemia	2.8					
Systemic diseases	7.2	Yes[52,53]	NA	Yes	Yes	NA
Systemic lupus erythematosus	1					
Behçet disease	1					
Inflammatory bowel disease	1.6					
Thyroid disease	1.7					
Sarcoidosis	0.2					
Other	1.7					
None identified	12.5		NA	NA	NA	NA

CVT indicates cerebral venous thrombosis; OR, odds ratio; CI, confidence interval; NA, nonapplicable/nonavailable; and IV, intravenous.

*Prevalence as per Ferro et al.[10] Percentages for CVT associated with oral contraceptives or pregnancy/puerperium are reported among 381 women ≤50 years of age.

†Cause-and-effect relationship determined as follows: (1) Consistency of association: Has the association been repeatedly observed by different investigators (yes/no)? (2) Strength of association: How strong is the effect (relative risk or OR)? (3) Biological plausibility: Does the association make sense, and can it be explained pathophysiologically (yes/no)? (4) Temporality: Does exposure precede adverse outcome (yes/no)? (5) Biological gradient: Does a dose-response relationship exist (yes/no)? Evidence of a strong and consistent association, evidence of biological plausibility, a notable risk of recurrent events, and detection of a biological gradient are suggestive of causation rather than association by chance alone. Modified from Grimes and Schulz[54] with permission of the publisher. Copyright © 2002, Elsevier.

‡Evidence for the biological gradient is not specific for CVT but for VTE: Anticardiolipins and CVT—based on a case-matched control study (Christopher et al)[15]; oral contraceptives—from Dentali et al[28]; cancer—results among 7029 patients with cancer, 20 of whom (0.3%) developed CVT, combined with results from Ferro et al (OR 27.9, 95% CI 16.5 to 47.2)[10]; hyperhomocysteinemia and CVT—Martinelli et al.[13] For patients with the prothrombin 20210 mutation, having a heterozygous mutation increases the risk of developing a first venous thrombotic event by approximately 2 to 3 times the background risk (or 2 to 3 in 1000 people each year). Having homozygous prothrombin mutations increases the risk further, but it is not yet well established how much the risk is increased (Varga et al).[55]

of oral contraceptives showed similar point estimates for the coagulation abnormalities alone and the use of oral contraceptives alone, whereas the presence of both risk factors gave an OR of 30.0 (95% CI 3.4 to 263.0) for factor V Leiden and 79.3 (95% CI 10.0 to 629.4) for the prothrombin mutation. A study in the Netherlands[37] found that of 40 female CVT patients, 85% used oral contraceptives, with an adjusted OR of 13 (95% CI 5 to 37). The combination of oral contraceptives with a prothrombotic condition also dramatically increased the risk of CVT. A study from Brazil showed similar results.[18] In a meta-analysis that included 16 studies, the authors reported an increased risk of CVT in oral contraceptive users (relative risk 15.9, 95% CI 6.98 to 36.2).[59] In another meta-analysis of 17 studies,[28] an increased risk of CVT was found in patients who used oral contraceptives (OR 5.59, 95% CI 3.95 to 7.91; $P<0.001$). It is clear that the use of oral contraceptives is associated with an increased risk of CVT, that the great majority of younger nonpregnant women with CVT are oral contraceptive users, and that the risk of CVT with oral contraceptive use in women is greater among those with a hereditary prothrombotic factor.

Cancer

In the ISCVT,[10] 7.4% of cases of CVT were associated with cancer. It has been speculated that CVT could be more frequent in cancer patients, particularly in patients with hematologic malignancies; however, there are no studies with a control group. Potential mechanisms for an association of cancer with CVT include direct tumor compression, tumor invasion of cerebral sinuses,[39–41] or the hypercoagulable state associated with cancer.[60] Chemotherapeutic and hormonal agents used for cancer treatment may also play a role.

Other Uncommon Causes

New neuroimaging procedures have increased the ability to detect CVT in recent years and have also helped to identify other potential causes, including infections, mainly in parameningeal locations (ear, sinus, mouth, face, and neck). These causes only explained 8.2% of all cases in the ISCVT series.[2] In contrast, CVT caused by infection is more common in children. In a recent series of 70 children with CVT in the United States, 40% had infection-related CVT.[16] Conversely, a French study of 62 adults with isolated lateral sinus thrombosis found that only 3 cases were related to parameningeal infections.[42]

Other conditions have been associated with CVT in case reports or small series, including paroxysmal nocturnal hemoglobinuria,[48] iron deficiency anemia,[49] thrombocythemia,[50] heparin-induced thrombocytopenia,[61] thrombotic thrombocytopenic purpura,[14] nephrotic syndrome,[51] inflammatory bowel disease,[10,62] systemic lupus erythematosus,[52] Behçcet disease,[53] mechanical precipitants, epidural blood patch,[45] spontaneous intracranial hypotension,[46] and lumbar puncture.[47]

Clinical Diagnosis of CVT

Principal Clinical Findings

The diagnosis of CVT is typically based on clinical suspicion and imaging confirmation. Clinical findings in CVT usually fall into 2 major categories, depending on the mechanism of neurological dysfunction: (1) Those that are related to increased intracranial pressure attributable to impaired venous drainage and (2) those related to focal brain injury from venous ischemia/infarction or hemorrhage. In practice, many patients have clinical findings due to both mechanisms, either at presentation or with progression of the underlying disease. Headache, generally indicative of an increase in intracranial pressure, is the most common symptom in CVT and was present in nearly 90% of patients in the ISCVT.[10] Similar headache frequency has been reported in other populations studied.[63] The headache of CVT is typically described as diffuse and often progresses in severity over days to weeks. A minority of patients may present with thunderclap headache, suggestive of subarachnoid hemorrhage, and a migrainous type of headache has been described.[64] Isolated headache without focal neurological findings or papilledema occurs in up to 25% of patients with CVT and presents a significant diagnostic challenge.[65] CVT is an important diagnostic consideration in patients with headache and papilledema or diplopia (caused by sixth nerve palsy) even without other neurological focal signs suggestive of idiopathic intracranial hypertension. When focal brain injury occurs because of venous ischemia or hemorrhage, neurological signs and symptoms referable to the affected region are often present; most common are hemiparesis and aphasia, but other cortical signs and sensory symptoms may occur. Psychosis, in conjunction with focal neurological signs, has also been reported.[66]

Clinical manifestations of CVT may also depend on the location of the thrombosis (Figure 2). The superior sagittal sinus is most commonly involved, which may lead to headache, increased intracranial pressure, and papilledema.[67] A motor deficit, sometimes with seizures, can also occur. Scalp edema and dilated scalp veins may be seen on examination.[68] For lateral sinus thromboses, symptoms related to an underlying condition (middle ear infection) may be noted, including constitutional symptoms, fever, and ear discharge. Pain in the ear or mastoid region and headache are typical. On examination, increased intracranial pressure and distention of the scalp veins may be noted. Hemianopia, contralateral weakness, and aphasia may sometimes be seen owing to cortical involvement.[69] Approximately 16% of patients with CVT have thrombosis of the deep cerebral venous system (internal cerebral vein, vein of Galen, and straight sinus), which can lead to thalamic or basal ganglial infarction. Most patients present with rapid neurological deterioration. CVT may be confused with other medical conditions.[70–75] Cortical vein thrombosis is also uncommon, and specific clinical syndromes related to the larger cortical veins are rarely seen (eg, temporal lobe hemorrhage associated with vein of Labbé thrombosis).[76]

Several important clinical features distinguish CVT from other mechanisms of cerebrovascular disease. First, focal or generalized seizures are frequent, occurring in ≈40% of patients. Second, an important clinical correlate to the anatomy of cerebral venous drainage is that bilateral brain involvement is not infrequent. This is particularly notable in cases that involve the deep venous drainage system, when bilateral thalamic involvement may occur, causing alterations in level of consciousness without focal neurological findings. Bilateral motor signs, including paraparesis, may also be present due to sagittal sinus thrombosis and bihemispheric injury. Finally, patients with

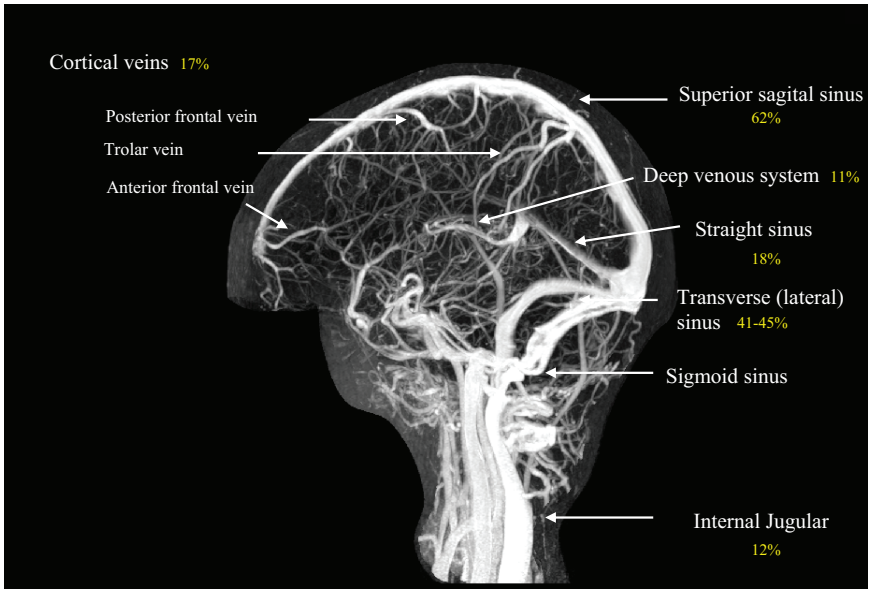

Figure 2. Magnetic resonance venogram showing the cerebral venous system and most frequent (%) location of cerebral venous and sinus thrombosis, as reported in the International Study on Cerebral Venous and Dural Sinuses Thrombosis (n=624).[44]

CVT often present with slowly progressive symptoms. Delays in diagnosis of CVT are common and significant. In the ISCVT, symptom onset was acute (<48 hours) in 37% of patients, subacute (>48 hours to 30 days) in 56% of patients, and chronic (>30 days) in 7% of patients. The median delay from onset of symptoms to hospital admission was 4 days, and from symptom onset to diagnosis, it was 7 days.[10]

Other Clinical and Laboratory Findings

Routine Blood Work

A complete blood count, chemistry panel, sedimentation rate, and measures of the prothrombin time and activated partial thromboplastin time are indicated for patients with suspected CVT. These studies may demonstrate abnormalities suggestive of an underlying hypercoagulable state, an infectious process, or an inflammatory state, all of which may contribute to the development of CVT.

Recommendations

1. **In patients with suspected CVT, routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed *(Class I; Level of Evidence C)*.**
2. **Screening for potential prothrombotic conditions that may predispose a person to CVT (eg, use of contraceptives, underlying inflammatory disease, infectious process) is recommended in the initial clinical assessment (specific recommendations for testing for thrombophilia are found in the long-term management section of this document) *(Class I; Level of Evidence C)*.**

Lumbar Puncture

Unless there is clinical suspicion of meningitis, examination of the cerebrospinal fluid (CSF) is typically not helpful in cases with focal neurological abnormalities and radiographic confirmation of the diagnosis of CVT. Elevated opening pressure is a frequent finding in CVT and is present in >80% of patients.[10] An elevated opening pressure may be a clue for diagnosing CVT in patients who present at the emergency department with headaches. Elevated cell counts (found in ≈50% of patients) and protein levels (found in ≈35%) are often present, but their absence should not discourage consideration of the diagnosis of CVT.[10] There are no specific CSF abnormalities in CVT. Therapeutic considerations are described in "Management and Prevention of Early Complications (Hydrocephalus, Intracranial Hypertension, Seizures)."

D-Dimer

Measurement of D-dimer, a product of fibrin degradation, has a diagnostic role in exclusion of DVT or pulmonary embolus when used with pretest probability assessment. A number of small studies, all with methodological limitations, demonstrated high sensitivity for the identification of patients with CVT and a potential role for exclusion of the diagnosis, although this finding was not universal.[77–81] As is the case with its use in DVT and pulmonary embolism (PE), the specificity of D-dimer was poor, because there are many causes of elevated D-dimer. In a well-designed prospective, multicenter study of 343 patients presenting to the emergency department with symptoms that suggested CVT, a positive D-dimer level (defined as a level >500 μg/L) was found in 34 of 35 patients with confirmed CVT and 27 of 308 patients without CVT.[82] This yielded a sensitivity of 97.1%, a specificity of 91.2%, a negative predictive value of 99.6%, and a positive predictive value of 55.7%, which supports a clinically useful role of D-dimer in excluding CVT. A normal D-dimer level according to a sensitive immunoassay or rapid ELISA may help identify patients with a low probability of CVT.[82,83] A subsequent study of 73 patients with confirmed CVT found normal D-dimer levels in 7 patients (10%).[83] Five of the 7 patients with confirmed CVT and negative D-dimer presented with isolated headache, which suggests that this subgroup might be particularly at risk of false-negative results of D-dimer testing. In contrast, of the 57 patients with confirmed CVT who presented with isolated intracranial hypertension or encephalic signs, only 2 (3.5%) had negative D-dimer testing.

Several factors may account for some of the discrepant findings noted above. First, D-dimer levels decline with time from onset of symptoms, which suggests that patients who

present with subacute or chronic symptoms are more likely to have negative D-dimer levels.[82] Second, the anatomic extent of thrombosed sinuses may correlate with D-dimer levels, which suggests that patients with lesser clot burden may have false-negative D-dimer testing results.[82] Finally, a number of different D-dimer assays are available with variable test performance characteristics.

Recommendation

1. **A normal D-dimer level according to a sensitive immunoassay or rapid enzyme-linked immunosorbent assay (ELISA) may be considered to help identify patients with low probability of CVT[82,83] *(Class IIb; Level of Evidence B)*. If there is a strong clinical suspicion of CVT, a normal D-dimer level should not preclude further evaluation.**

Common Pitfalls in the Diagnosis of CVT

There are several clinical scenarios in which misdiagnosis, or delay in diagnosis, of CVT frequently occurs.

Intracranial Hemorrhage

Approximately 30% to 40% of patients with CVT present with ICH.[14,84] Identification of these patients is critical given that the pathophysiology underlying hemorrhage in such cases is distinct from other causes of ICH, and this has important treatment implications. Features suggestive of CVT as a cause of ICH include prodromal headache (which is highly unusual with other causes of ICH), bilateral parenchymal abnormalities, and clinical evidence of a hypercoagulable state. These features may not be present, however, and a high index of clinical suspicion is necessary. Isolated subarachnoid hemorrhage may also occur due to CVT, although this is rare (0.8% of patients in ISCVT). Hemorrhage location is an important consideration in estimating the likelihood of CVT and is discussed elsewhere in this statement (see "Imaging in the Diagnosis of CVT" for further details).

Recommendation

1. **In patients with lobar ICH of otherwise unclear origin or with cerebral infarction that crosses typical arterial boundaries, imaging of the cerebral venous system should be performed *(Class I; Level of Evidence C)*.**

Isolated Headache/Idiopathic Intracranial Hypertension

In 1 series, 25% of patients with CVT presented with isolated headache, and another 25% presented with headache in conjunction with papilledema or sixth nerve palsies suggestive of idiopathic intracranial hypertension.[65] In a series of 131 patients who presented with papilledema and clinically suspected idiopathic intracranial hypertension, 10% had CVT when magnetic resonance imaging (MRI)/magnetic resonance venography (MRV) was performed.[85] Imaging of the cerebral venous system has been recommended for all patients with the clinical picture of idiopathic intracranial hypertension, because the distinction between CVT and idiopathic intracranial hypertension has important prognostic and treatment implications, and the yield of imaging is significant.[67,85] For patients with isolated headache, the proper strategy for identification of CVT is much less clear. Headache is an extremely common symptom, and the vast majority of patients with isolated headache will not have CVT. The cost-effectiveness and yield of routine imaging are highly uncertain. Factors that may suggest the diagnosis, and thus prompt imaging evaluation, include a new, atypical headache; headache that progresses steadily over days to weeks despite conservative treatment; and thunderclap headache.[64] In addition, a greater level of clinical suspicion for CVT should be maintained in patients with a hypercoagulable state.

Recommendations

1. **In patients with the clinical features of idiopathic intracranial hypertension, imaging of the cerebral venous system is recommended to exclude CVT *(Class I; Level of Evidence C)*.**
2. **In patients with headache associated with atypical features, imaging of the cerebral venous system is reasonable to exclude CVT *(Class IIa; Level of Evidence C)*.**

Isolated Mental Status Changes

Occasionally, patients with CVT will present with somnolence or a confusional state in the absence of obvious focal neurological abnormalities.[86–88] Such clinical presentations are more common in the elderly and with thrombosis of the deep venous system.[89,90] Although a number of mechanisms may underlie this clinical presentation, an important cause is bilateral thalamic lesions due to involvement of the deep venous system. Computed tomography (CT) scanning, especially if performed early in the clinical course, may be unremarkable; MRI will usually demonstrate abnormalities in such cases.

Imaging in the Diagnosis of CVT

Over the past 2 decades, diagnostic imaging has played an increasing role in the diagnosis and management of CVT.[2,3,55,91–97] Diagnostic imaging of CVT may be divided into 2 categories, which will be reviewed in more detail below: Noninvasive modalities and invasive modalities. The goal is to determine vascular and parenchymal changes associated with this medical condition. In some cases, the diagnosis is made only with cerebral digital subtraction angiography.[72,91,98–100]

Noninvasive Diagnostic Modalities: CT, MRI, and Ultrasound

Computed Tomography

CT is widely used as the initial neuroimaging test in patients who present with new-onset neurological symptoms such as headache, seizure, mental alteration, or focal neurological signs. CT without contrast is often normal but may demonstrate findings that suggest CVT.[92,93] Anatomic variability of the venous sinuses makes CT diagnosis of CVT insensitive, with results on a plain CT being abnormal only in ≈30% of CVT cases.[1,28,70,94,95,98] The primary sign of acute CVT on a noncontrast CT is hyperdensity of a cortical vein or dural sinus. Acutely thrombosed cortical veins and dural sinuses appear as a homogenous hyperdensity that fills the vein or sinus and are most clearly visualized when CT slices are perpendicular to the dural sinus or vein (Figure 3). However, only approximately one third of CVT demonstrates direct signs of hyperdense dural sinus.[70,94,96] Thrombosis of the posterior portion of the superior sagittal sinus may appear as

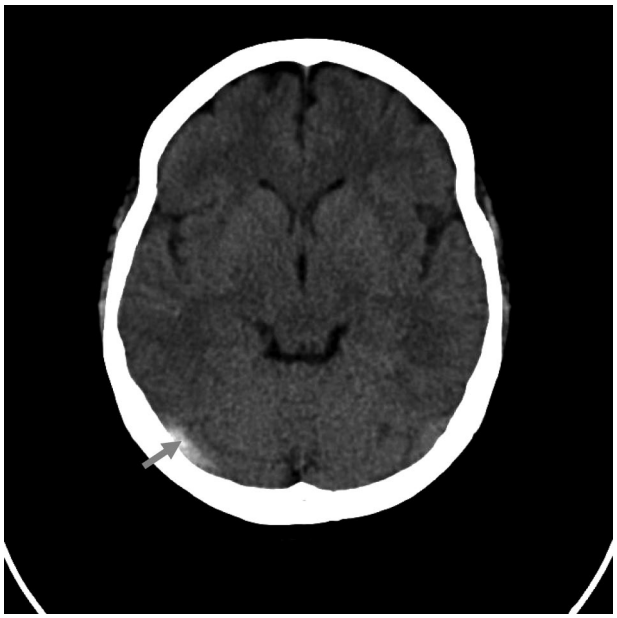

Figure 3. Noncontrast computed tomography head scan showed spontaneous hyperdensity of right transverse sinus.

a dense triangle, the dense or filled delta sign. An ischemic infarction, sometimes with a hemorrhagic component, may be seen. An ischemic lesion that crosses usual arterial boundaries (particularly with a hemorrhagic component) or in close proximity to a venous sinus is suggestive of CVT.[93] Subarachnoid hemorrhage and ICH are infrequent.[99] Subarachnoid hemorrhage was found in only 0.5% to 0.8% of patients with CVT,[10,14,99] and when present, it was localized in the convexity as opposed to the area of the circle of Willis usually observed in patients with aneurysmal rupture.

Contrast-enhanced CT may show enhancement of the dural lining of the sinus with a filling defect within the vein or sinus. Contrast-enhanced CT may show the classic "empty delta" sign, in which a central hypointensity due to very slow or absent flow within the sinus is surrounded by contrast enhancement in the surrounding triangular shape in the posterior aspect of the superior sagittal sinus.[93] This finding may not appear for several days after onset of symptoms but does persist for several weeks.

Because symptoms of CVT may be overlooked or associated with delays in seeking medical attention, CVT may be seen only during the subacute or chronic stage. Compared with the density of adjacent brain tissue, thrombus may be isodense, hypodense, or of mixed density. In this situation, contrast CT or CT venography (CTV) may assist the imaging diagnosis.[70–74,94,97,100–105]

Magnetic Resonance Imaging

In general, MRI is more sensitive for the detection of CVT than CT at each stage after thrombosis (Table 4; Figure 4).[1,70,96,97,101,106,107] CVT is diagnosed on MRI with the

Table 4. Comparison of the Advantages and Disadvantages of CT and MRI in the Diagnosis of CVT

	CT+CTV	MRI+MRV
Advantages	Good visualization of major venous sinuses	Visualization of the superficial and deep venous systems
	Quick (5–10 min)	Good definition of brain parenchyma
	Readily available	Early detection of ischemic changes
	Fewer motion artifacts	No radiation exposure
	Can be used in patients with a pacemaker, defibrillator, or claustrophobia	Detection of cortical and deep venous thrombosis
		Detection of macrobleeding and microbleeding
Disadvantages	Exposure to ionizing radiation	Time consuming
	Risk of contrast reactions	Motion artifacts
	Risk of iodinated contrast nephropathy (eg, in patients with diabetes, renal failure)	Availability
		Limited use in patients with cardiac pacemaker or claustrophobia
	Low resolution for small parenchymal abnormalities	Confers a low risk of gadolinium-induced nephrogenic systemic fibrosis
	Poor detection of cortical and deep venous thrombosis	Slow flow states, complex flow patterns, and normal anatomic variations in dural sinus flow can affect the interpretation
Sensitivity/specificity	Small studies comparing multiplanar CT/CTV vs DSA showed 95% sensitivity and 91% specificity*	The sensitivity and specificity of MRI/MRV are not known owing to the lack of large MRI/MRV head-to-head studies with DSA.
	Overall accuracy 90% to 100%, depending on vein or sinus	Echoplanar T2 susceptibility-weighted imaging combined with MRV are considered the most sensitive sequences
Practical application	Acute onset of symptoms	Acute or subacute onset of symptoms
	Emergency setting	Emergency or ambulatory setting
	Multidetector CTV can be used as the initial test when MRI is not readily available	Patients with suspected CVT and normal CT/CTV
		In patients with suspected deep CVT, because complex basal dural sinuses and their emissary channels are more commonly seen

CT indicates computed tomography; MRI, magnetic resonance imaging; CVT, cerebral venous thrombosis; CTV, CT venography; MRV, magnetic resonance venography; and DSA, digital subtraction angiography. *Wetzel et al.[93]

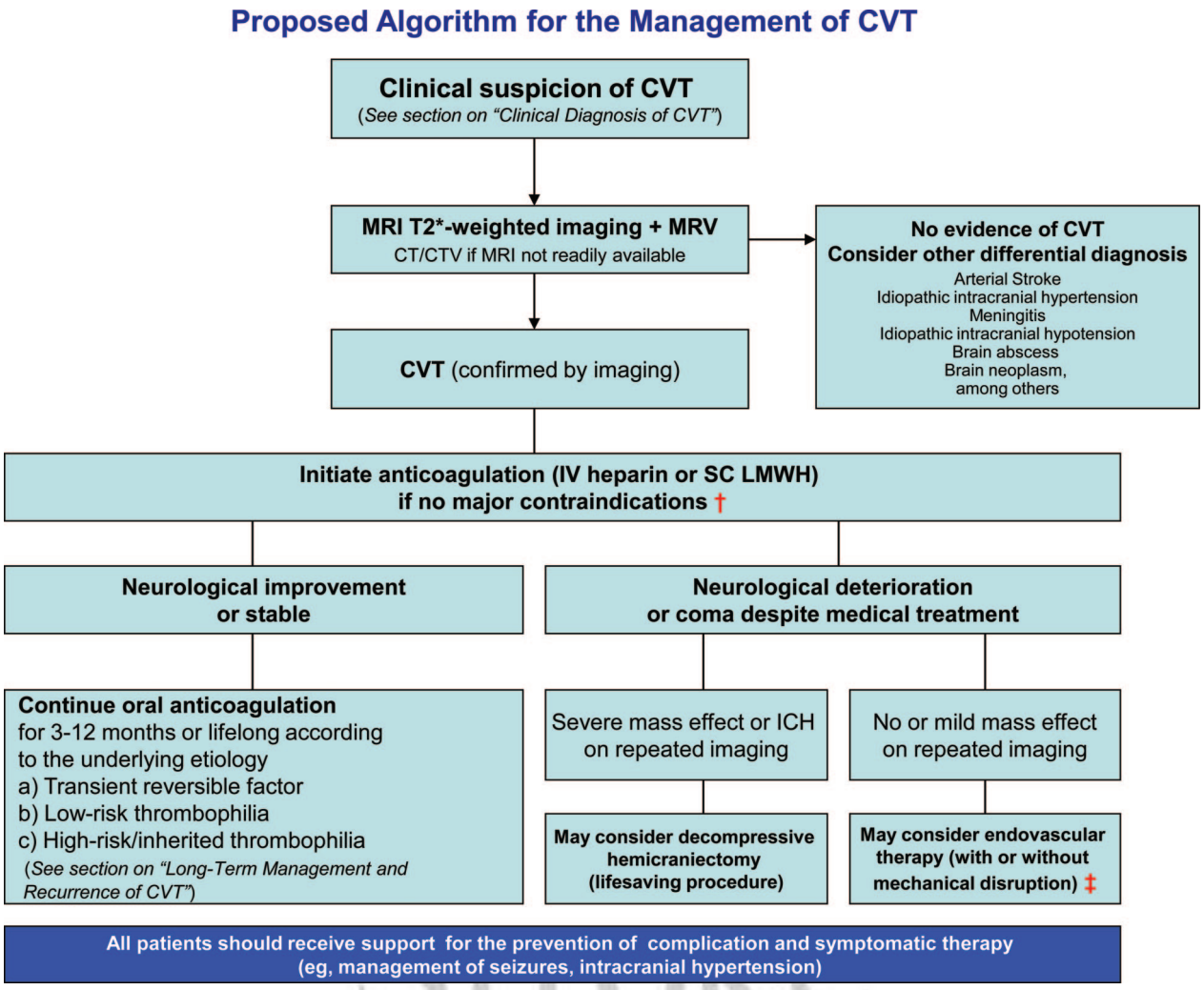

Figure 4. Proposed Algorithm for the Management of CVT. The CVT Writing group recognize the challenges facing primary care, emergency physicians and general neurologists in the diagnosis and management of CVT. The aim of this algorithm is to provide guidance to physicians in the initial management of CVT. Anticoagulation remains the principal therapy and is aimed at preventing thrombus propagation and increasing recanalization. This algorithm is not comprehensive, nor applicable to all clinical scenarios and patient management must be individualized. Limited evidence is available on the benefits of decompressive hemicraniectomy and endovascular therapy for the management of CVT as reflected by the low grade and level of recommendations. Anticipated future advances in imaging techniques, new pharmacological agents and endovascular procedures may provide other therapeutic alternatives to be considered in patients with CVT, and in the future these guidelines will be periodically updated to reflect the changing evidence. CVST indicates cerebral venous and sinus thrombosis; LMWH, low molecular weight heparin; Tx, therapy; ICH, intracerebral hemorrhage; CTV, CT venogram; MRV, MR venogram.
†Intracranial hemorrhage that occurred as the consequence of CVST is not a contraindication for anticoagulation.
‡Endovascular therapy may be considered in patients with absolute contraindications for anticoagulation therapy or failure of initial therapeutic doses of anticoagulant therapy.

detection of thrombus in a venous sinus. Findings are variable but may include a "hyperintense vein sign."[105,108–113] Isolated cortical venous thrombosis is identified much less frequently than sinus thrombosis. The magnetic resonance signal intensity of venous thrombus varies according to the time of imaging from the onset of thrombus formation.[6,65,94,101–107] Acute thrombus may be of low intensity. In the first week, venous thrombus frequently appears as isointense to brain tissue on T1-weighted images and hypointense on T2-weighted images owing to increased deoxyhemoglobin. By the second week, thrombus contains methemoglobin, which results in hyperintensity on T1- and T2-weighted images (Figure 5).[2,10,42,70,71,73,74,91,98–100,105,106,108,113–128] With evolution of the thrombus, the paramagnetic products of deoxyhemoglobin and methemoglobin are present in the sinus. A thrombosed dural sinus or vein may then demonstrate low signal on gradient-echo and susceptibility-weighted images of magnetic resonance images.[70,119,129]

The principal early signs of CVT on non–contrast-enhanced MRI are the combination of absence of a flow void with alteration of signal intensity in the dural sinus. MRI of the brain is suggestive of CVT by the absence of a fluid void signal in the sinus, T2 hypointensity suggestive of a thrombus, or a central isodense lesion in a venous sinus with surrounding enhancement.[120] This appearance is the MRI equivalent of the CT empty delta sign. An acute venous thrombus may have hypointense signal that mimics a normal flow void. The nature of the thrombus then evolves through a subacute and chronic phase.[128]

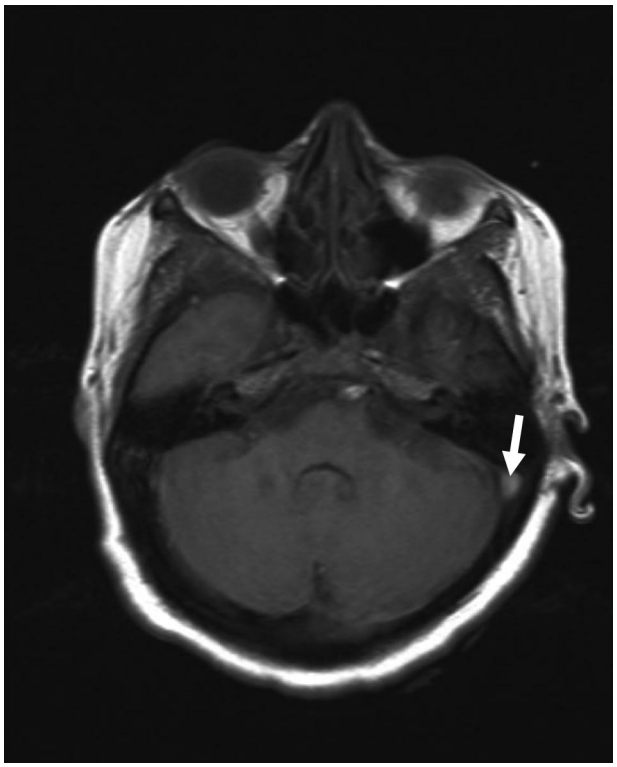

Figure 5. Flair magnetic resonance image showing hypersensitivity signal at left sigmoid sinus (arrow).

Thus, contrast-enhanced MRI and either CTV or MRV may be necessary to establish a definite diagnosis.

The secondary signs of MRI may show similar patterns to CT, including cerebral swelling, edema, and/or hemorrhage.[91,130–134] Occasionally, diffusion-weighted imaging (DWI) and perfusion-weighted MRI may assist in making the diagnosis. DWI may show high signal intensity as restricted diffusion- and perfusion-weighted MRI with prolonged transit time.[70,104,107,109,110,115,120,124,130–135]

Brain parenchymal lesions of CVT are better visualized and depicted on MRI than at CT (Figure 6). Focal edema without hemorrhage is visualized on CT in ≈8% of cases and on MRI in 25% of cases.[70,95,102,111,119,128,133,136–138] Focal parenchymal changes with edema and hemorrhage may be identified in up to 40% of patients.[70,73,98,110,111,120,128,138] The discrepancy in frequency of detection may be due in part to varying timing of imaging after thrombosis.[2,10,14,70,74,95,128,139] Petechial or confluent hemorrhage may also represent an underlying hemorrhagic venous infarction. This may include DWI abnormalities consistent with acute infarction, but the degree of DWI findings may be reduced in venous infarction compared with arterial infarction (Figure 7).[124] An altered enhancement pattern suggestive of collateral flow or of venous congestion may be seen. There are some characteristic patterns of brain parenchymal changes that distinguish CVT from other entities. Also, to some extent, lesions related to specific sinuses are regionally distributed. Brain parenchymal changes in frontal, parietal, and occipital lobes usually correspond to superior sagittal sinus thrombosis (Figure 8). Temporal lobe parenchymal changes correspond to lateral (transverse) and sigmoid sinus thrombosis. Deep parenchymal abnormalities, including thalamic hemorrhage, edema, or intraventricular hemorrhage, correspond to thrombosis of the vein of Galen or straight sinus. MRI signal can also predict radiographic outcome to some extent, because DWI abnormality within veins or sinus predicts poor recanalization.[71,105,110,117–119,131–133,135,140,141]

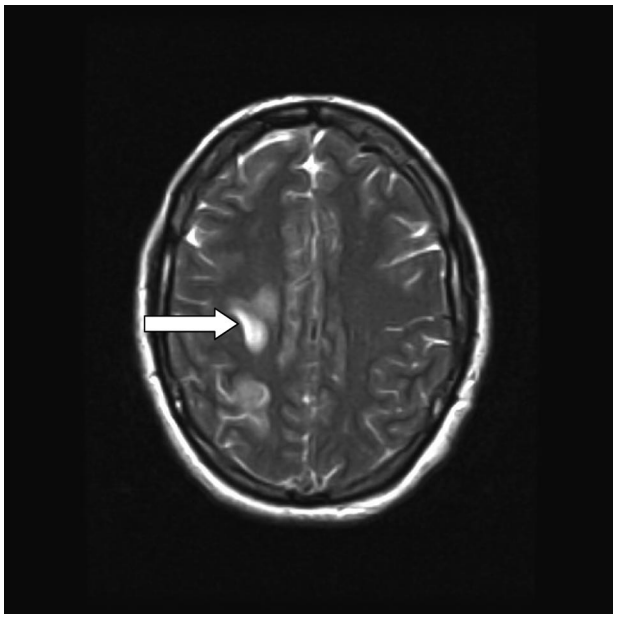

Figure 6. T2-weighted magnetic resonance image showing high-intensity bland venous infarct in frontal lobe.

CT Venography

CTV can provide a rapid and reliable modality for detecting CVT (Figure 9). CTV is much more useful in subacute or chronic situations because of the varied density in thrombosed

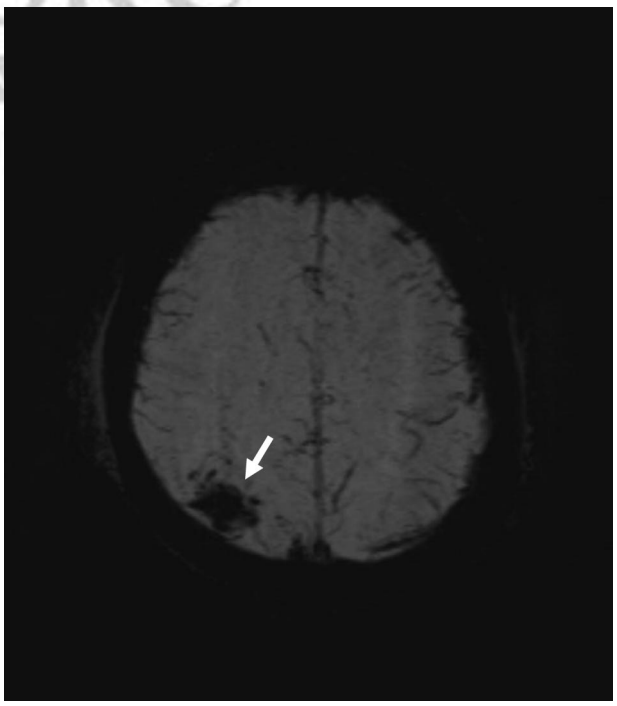

Figure 7. Susceptibility-weighted magnetic resonance image showing hemorrhagic venous infarct in the right parietal lobe.

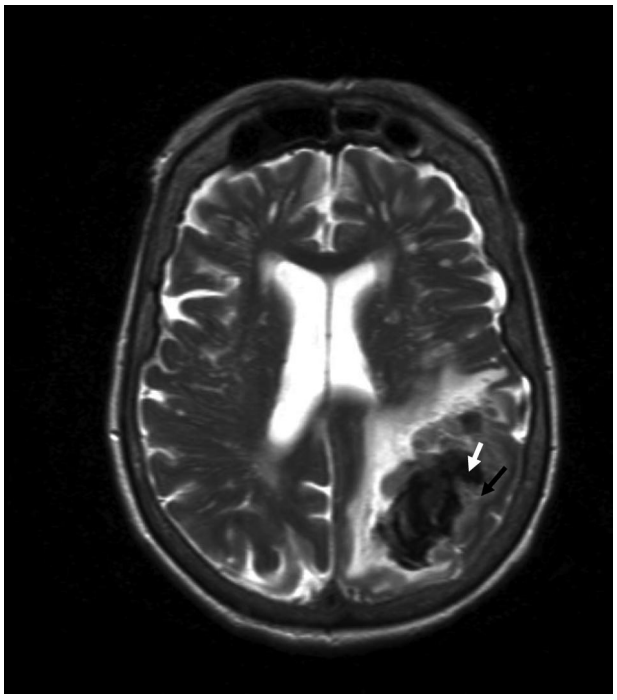

Figure 8. T2-weighted magnetic resonance image showing mixed hypointensity (white arrow) and isointensity (black arrow) signals representing an acute hemorrhage at left parietal lobe.

sinus (Figure 10). Because of the dense cortical bone adjacent to dural sinus, bone artifact may interfere with the visualization of enhanced dural sinus. CTV is at least equivalent to MRV in the diagnosis of CVT.[94,97,100,101,103,106] However, drawbacks to CTV include concerns about radiation exposure, potential for iodine contrast material allergy, and issues related to use of contrast in the setting of poor renal function.[2,70,72,74,97,99–101,103,109,115,116,141]

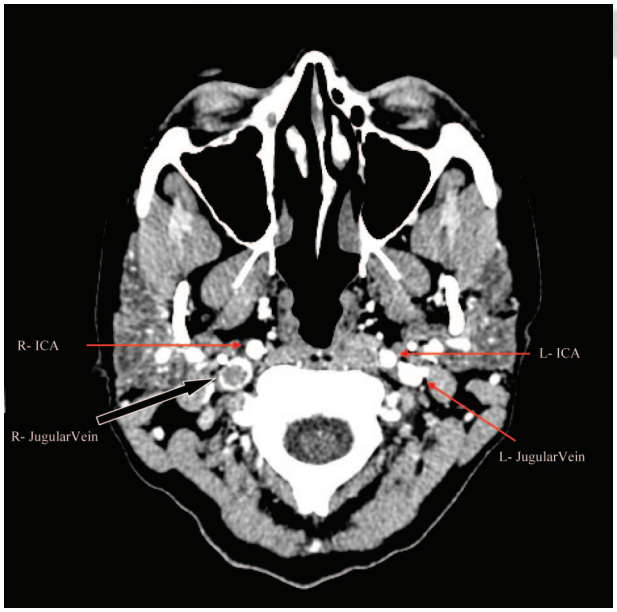

Figure 9. Computed tomographic venogram (axial) showing extension of the cerebral venous thrombosis down to the jugular vein (black arrow). R-ICA indicates right internal carotid artery; L-ICA, left internal carotid artery; R, right; and L, left.

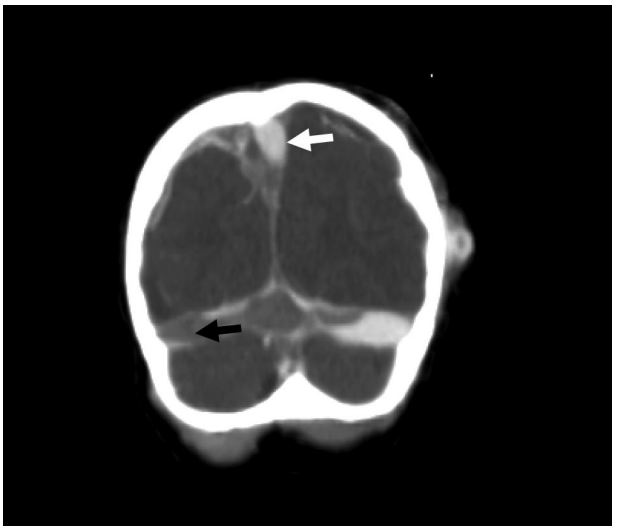

Figure 10. Computed tomographic venogram showing mixed density within venous sinuses (high-density contrast in patent segments (white arrow) and low density (black arrow) in nonperfusing thrombosed segments).

In some settings, MRV is preferable to CTV because of these concerns (Table 4).

Magnetic Resonance Venography

The most commonly used MRV techniques are time-of-flight (TOF) MRV (Figures 11 and 12) and contrast-enhanced magnetic resonance. Phase-contrast MRI is used less frequently, because defining the velocity of the encoding parameter is both difficult and operator-dependent.

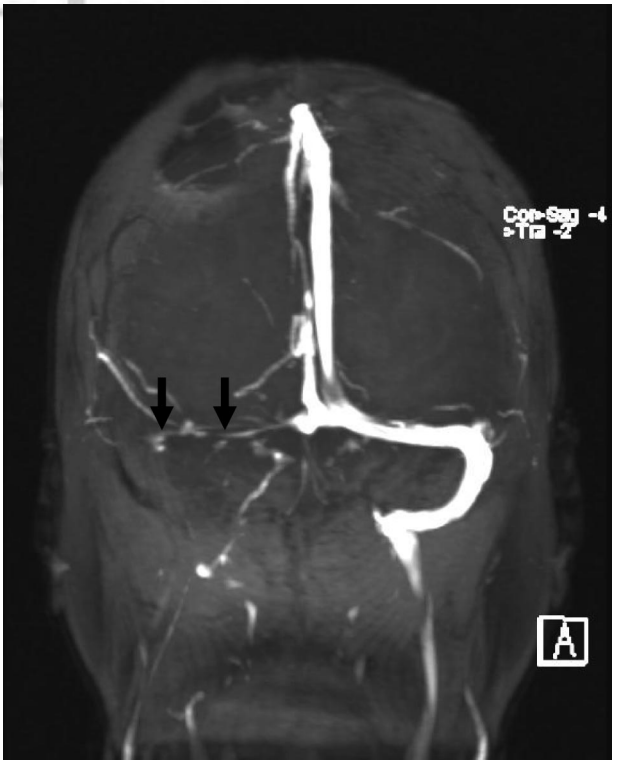

Figure 11. Magnetic resonance venography confirmed thrombosis (black arrows) of right transverse and sigmoid sinuses and jugular vein.

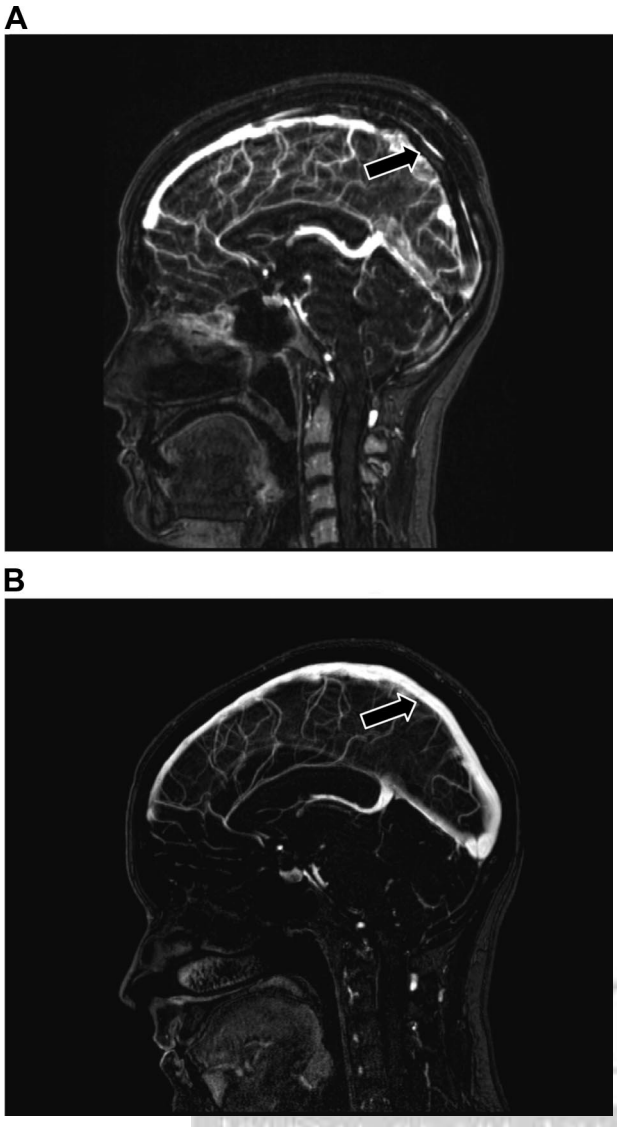

Figure 12. Magnetic resonance venogram showing thrombosis (black arrows) of the superior sagittal sinus and sigmoid sinuses. **A,** 2 days after symptom onset. **B,** 1 year follow-up after oral anticoagulation therapy (OAC).

The 2-dimensional TOF technique is the most commonly used method currently for the diagnosis of CVT, because 2-dimensional TOF has excellent sensitivity to slow flow compared with 3-dimensional TOF. It does have several potential pitfalls in imaging interpretation (see "Potential Pitfalls in the Radiological Diagnosis of CVT: Anatomic Variants, Thrombus Signal Variability, and Imaging Artifacts" below).[2,71,72,95,97,106,108,109,125,142–150] Despite the challenges, other sequences such as gradient echo, susceptibility-weighted imaging, and contrast MRI/MRV may assist in these situations.[129,151] Nonthrombosed hypoplastic sinus will not have abnormal low signal in the sinus on gradient echo or susceptibility-weighted images. The chronic thrombosed hypoplastic sinus will have marked enhanced sinus and no flow on 2-dimensional TOF venography. Contrast-enhanced MRI offers improved visualization of cerebral venous structures.

In patients with persistent or progressive symptoms despite medical treatment, repeated neuroimaging (including a CTV or MRV) may help identify the development of a new ischemic lesion, ICH, edema, propagation of the thrombus, or other brain parenchymal lesions.[97,110,111,120,128,136–138,140,141]

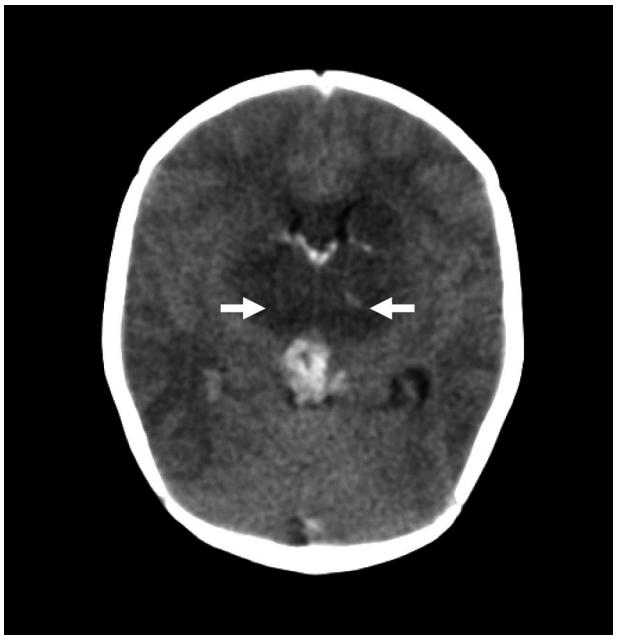

Figure 13. Noncontrast computed tomographic scan in a newborn with deep cerebral venous thrombosis and bilateral thalamic (white arrows) infarcts.

Deep CVT

The deep venous system is readily seen on CT and MRI and may be less impacted by artifact because of the separation from bony structures (Figure 13). A potential pitfall at the junction of the straight sinus and vein of Galen on TOF MRI is the appearance of absence of flow if image acquisition is in an axial plane to the skull. This pitfall may be overcome with contrast-enhanced MRI and DWI.[70–74,102,120,123,124] Table 4 compares the advantages and disadvantages of CT/CTV and MRI/MRV.

Invasive Diagnostic Angiographic Procedures

Cerebral Angiography and Direct Cerebral Venography

Invasive cerebral angiographic procedures are less commonly needed to establish the diagnosis of CVT given the availability of MRV and CTV.[109,125,133] These techniques are reserved for situations in which the MRV or CTV results are inconclusive or if an endovascular procedure is being considered.

Cerebral Angiography

Arteriographic findings include the failure of sinus appearance due to the occlusion; venous congestion with dilated cortical, scalp, or facial veins; enlargement of typically diminutive veins from collateral drainage; and reversal of venous flow. The venous phase of cerebral angiography will show a filling defect in the thrombosed cerebral vein/sinus (Figure 14). Because of the highly variable cerebral venous structures and inadequate resolution, CT or MRI may not provide adequate visualization of selected veins, especially cortical veins and in some situations the deep venous structures. Hypoplasia or atresia of cerebral veins or dural sinuses may lead to inconclusive results on MRV or CTV and can be

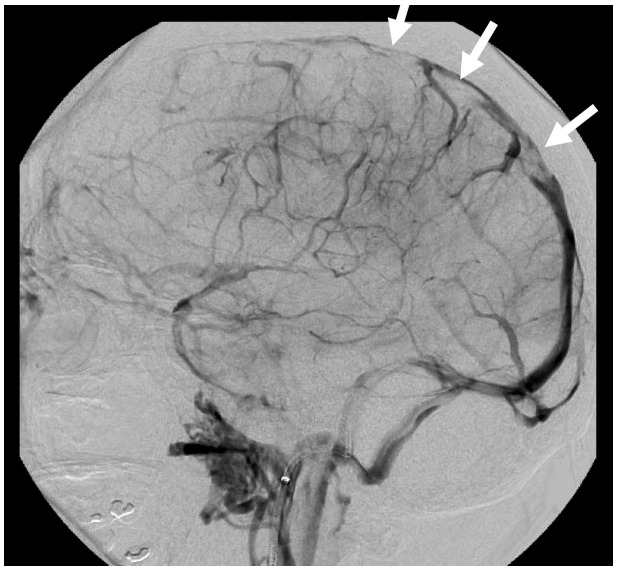

Figure 14. Venous phase of direct carotid angiogram and catheter venogram showed extensive thrombosed superior sagittal sinus (white arrows) and cortical veins. The direct venogram also showed collateral cortical veins.

clarified on the venous phase of cerebral angiography. Acute dural sinus and cortical vein thrombosis typically causes a delay in cerebral venous circulation, and cerebral angiography will demonstrate delayed and slow visualization of cerebral venous structures. Normally, the early veins begin to opacify at 4 to 5 seconds after injection of contrast material into the carotid artery, and the complete cerebral venous system is opacified in 7 to 8 seconds.[74,91,124,152] If cerebral veins or dural sinuses are not visualized in the normal sequences of cerebral angiography, the possibility of acute thrombosis is suspected. This finding accounts for the observed delayed cerebral perfusion seen with perfusion-weighted MRI with prolonged transit time.[74,91,104,124,130,132,153]

Direct Cerebral Venography

Direct cerebral venography is performed by direct injection of contrast material into a dural sinus or cerebral vein from microcatheter insertion via the internal jugular vein. Direct cerebral venography is usually performed during endovascular therapeutic procedures.[74,91] In direct cerebral venography, intraluminal thrombus is seen either as a filling defect within the lumen in the setting of nonocclusive thrombosis or as complete nonfilling in occlusive thrombosis. Complete thrombosis may also demonstrate a "cupping appearance" within the sinus. Venous pressure measurements may be performed during direct cerebral venography to identify venous hypertension. Normal venous sinus pressure is <10 mm H_2O. The extent of parenchymal change correlates with increased venous pressure and with the stage of thrombosis, with changes being maximal in acute thrombosis.

Other Diagnostic Modalities

Transfontanellar ultrasound may be used to evaluate pediatric patients, including newborn or young infants with open anterior or posterior fontanels. Ultrasound, along with transcranial Doppler, may be useful to support the diagnosis of

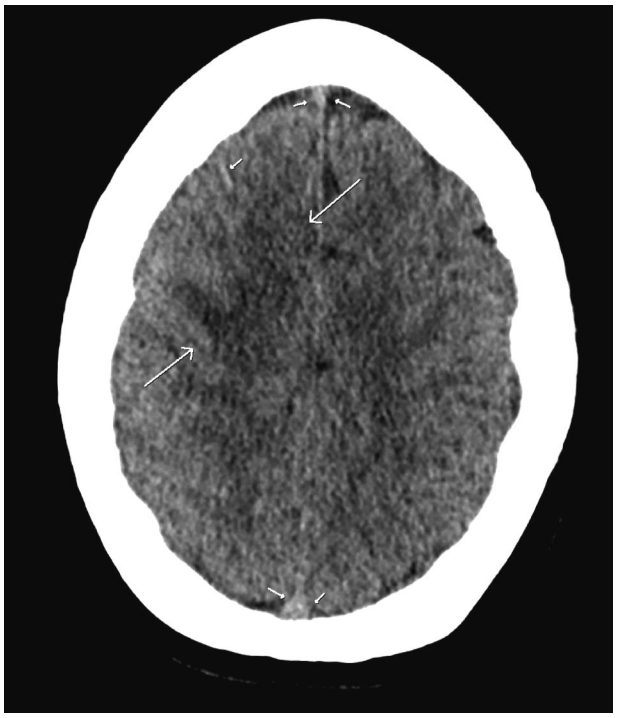

Figure 15. Superior sagittal sinus thrombosis. CT Head showing a subtle decreased attenuation at right frontal lobe (arrows), an isodensity in superior sagittal sinus (short arrows) and right frontal cortical vein (a short arrow).

CVT and for ongoing monitoring of thrombus and parenchymal changes.[152,154,155]

Perfusion Imaging Methods

Anecdotal evidence using positron emission tomography showed a reduction of the cerebral blood flow after ligation of the superior sagittal sinus with a concomitant venous infarction.[156] An increased regional cerebral blood volume was also observed in a young adult with sagittal sinus thrombosis.[157] A prolonged mean transit time and increased cerebral blood volume have been suggested as venous congestion, contrary to the pattern observed in patients with an ischemic arterial stroke (prolonged mean transit time with reduction in cerebral blood volume).[111,124]

Potential Pitfalls in the Radiological Diagnosis of CVT: Anatomic Variants, Thrombus Signal Variability, and Imaging Artifacts

The positive findings of intraluminal thrombus are the key to a confident diagnosis of CVT by CT or MRI. Unfortunately, these findings are not always evident, and the diagnosis rests on nonfilling of a venous sinus or cortical vein (Figure 15). Given the variation in venous anatomy, it is sometimes impossible to exclude CVT on noninvasive imaging studies. Anatomic variants of normal venous anatomy may mimic sinus thrombosis, including sinus atresia/hypoplasia, asymmetrical sinus drainage, and normal sinus filling defects related to prominent arachnoid granulations or intrasinus septa.[2,71,72,95,97,106,108,109,125,142–150,158] Angiographic examination of 100 patients with no venous pathology[159] showed a high prevalence of asymmetrical lateral

(transverse) sinuses (49%) and partial or complete absence of 1 lateral sinus (20%).

Flow gaps are commonly seen on TOF MRV images, which sometimes affects their interpretation. The hypoplastic dural sinus may have a more tapering appearance than an abrupt defect in contrast-enhanced images of the sinus. The lack of identification of a thrombus within the venous sinus on MRI or contrast-enhanced MRV or CTV is helpful to clarify the diagnosis.[160]

As mentioned, sinus signal-intensity variations may also affect the interpretation of imaging in the diagnosis of CVT.[70] Direct cerebral venography may be difficult to interpret owing to retrograde flow of contrast from the point of injection, and the venous pressure may not be accurate because of relative compartmentalization within the system.[70]

Recommendations

1. **Although a plain CT or MRI is useful in the initial evaluation of patients with suspected CVT, a negative plain CT or MRI does not rule out CVT. A venographic study (either CTV or MRV) should be performed in suspected CVT if the plain CT or MRI is negative or to define the extent of CVT if the plain CT or MRI suggests CVT (*Class I; Level of Evidence C*).**
2. **An early follow-up CTV or MRV is recommended in CVT patients with persistent or evolving symptoms despite medical treatment or with symptoms suggestive of propagation of thrombus *(Class I; Level of Evidence C)*.**
3. **In patients with previous CVT who present with recurrent symptoms suggestive of CVT, repeat CTV or MRV is recommended *(Class I; Level of Evidence C)*.**
4. **Gradient echo T2 susceptibility-weighted images combined with magnetic resonance can be useful to improve the accuracy of CVT diagnosis[70,129,151] *(Class IIa; Level of Evidence B)*.**
5. **Catheter cerebral angiography can be useful in patients with inconclusive CTV or MRV in whom a clinical suspicion for CVT remains high *(Class IIa; Level of Evidence C)*.**
6. **A follow-up CTV or MRV at 3 to 6 months after diagnosis is reasonable to assess for recanalization of the occluded cortical vein/sinuses in stable patients *(Class IIa; Level of Evidence C)*.**

Management and Treatment

Acute Management and Treatment of CVT

To address treatment of CVT in adults, we reviewed systematic reviews and guideline statements of the Cochrane Collaboration,[161] the American College of Chest Physicians,[162,163] and the European Federation of Neurological Sciences,[164] in addition to performing a literature review using search terms in PubMed: ("cerebral vein thrombosis" OR "cerebral venous thrombosis" OR "sinus thrombosis") AND randomized trial; ("cerebral vein thrombosis" OR "cerebral venous thrombosis" OR "sinus thrombosis") AND treatment guideline. Secondary sources of data included reference lists of articles reviewed and cohort studies that related treatment to outcomes. A summary algorithm for the diagnosis and management of patients with CVT is provided (Figure 4).

Setting

Organized care has been defined as collaborative, high-quality, standardized, effective and cost-effective care given by an interdisciplinary team using protocols based on best practices.[165] According to the Stroke Unit Trialists' Collaboration, the most important components of organized stroke care are assessment by a stroke neurologist, admission to a stroke unit with stroke-directed nursing care, physiotherapy, and occupational therapy.[166–169] Organized care is one of the most effective interventions to reduce mortality and morbidity after acute stroke.[166,167] For example, stroke unit care was associated with a 14% reduction in the odds of death at 1 year (OR 0.86, 95% CI 0.76 to 0.98; $P=0.02$), death or institutionalization (OR 0.82, 95% CI 0.73 to 0.92; $P<0.001$), and death or dependency (OR 0.82, 95% CI 0.73 to 0.92; $P=0.001$). These benefits were independent of age, sex, stroke severity, and stroke subtype.[167,169,170]

CVT is an uncommon but potentially serious and life-threatening cause of stroke. On the basis of findings for stroke unit care in general, management of CVT in a stroke unit is reasonable for the initial management of CVT to optimize care and minimize complications. Additional specialist input as needed to provide therapeutic anticoagulation is appropriate.

Initial Anticoagulation

There are several rationales for anticoagulation therapy in CVT: To prevent thrombus growth, to facilitate recanalization, and to prevent DVT or PE. Controversy has ensued because cerebral infarction with hemorrhagic transformation or ICH is commonly present at the time of diagnosis of CVT, and it may also complicate treatment. A summary table is provided with data from observational studies and randomized clinical trials[10,84,136,171–181] (Table 5) of CVT.

There are 2 available randomized controlled trials comparing anticoagulant therapy with placebo or open control in patients with CVT confirmed by contrast imaging. Taken together, these trials included only 79 patients. One trial of 20 patients assessed intravenous unfractionated heparin (UFH) using dose adjustment to achieve an activated partial thromboplastin time twice the pretreatment value compared with placebo.[171] This study used a heparin bolus of 3000 U followed by continuous intravenous infusion. The primary outcome was a CVT severity scale at 3 months, which evaluated headache, focal signs, seizures, and level of consciousness. The secondary outcome was ICH. The trial was stopped early after 20 of the planned 60 patients were enrolled because there was a benefit of treatment. Among 10 patients in the heparin group, 8 recovered completely and 2 had mild deficits at 3 months. Among 10 patients in the placebo group, 1 recovered completely, 6 had minor deficits, and 3 died by 3 months. Two patients treated with placebo and none treated with heparin developed ICH. One patient in the placebo group had unconfirmed pulmonary embolus.

The other trial of 59 patients compared subcutaneous nadroparin dosed on the basis of body weight (180 anti-factor Xa units per kilogram daily in 2 divided doses) with placebo for 3 weeks followed by 3 months of oral anticoagulation (without placebo control) in those randomized to nadroparin.[172] The study was blinded during the first 3 weeks and

Table 5. Data From Observational Studies and Clinical Trials of CVT That Addressed Anticoagulation Therapy

First Author	N	Years Recruited	Regimen	F/U Duration	Died, n	Fully Recovered, n*	Disabled, n	ICH	Other Hemorrhage	VTE
Einhaupl[171]	20	1982–4	RCT:	3 mo						
			10-UFH 2×PTT		0-UFH	8-UFH	2-UFH	0	NR	0-UFH
			10-Placebo		3-Placebo	1-Placebo	6-Placebo	2		1-Placebo
De Bruijn[172]	60	1992–6	RCT:	3 mo						
			30-Nadroparin		2-UFH	20-UFH	8-UFH	0	1-UFH	0-UFH
			29-Placebo		4-Placebo	21-Placebo	4-Placebo	0	0-Placebo	1-Placebo
De Bruijn[173]	47	1992–6	RCT as above	18.5 mo	0	16†	3			
Ferro[136]	142	1980–98	112-UFH or AVK‡	Hospital stay	9	96§	6 (Rankin ≥3)	4‖ UFH-AVK	2 Systemic	NR
			30-None					2	0	
Daif[174]	40	1985–94	4-UFH		1-UFH	1-UFH	2-UFH	NR	NR	NR
			36-No ACO		3-No ACO	28-None¶	5-None¶			
Preter[175]	77	1975–90	62-UFH+AVK	63 mo	Not included	66 Overall	11	0	NR	11 (14%)#
			15-None¶					NR		
Maqueda[176]	54	1985–2002	30-UFH	3.5 y	3 (5.6%)	NR	NR	NR	NR	8 (6 off AVK)
			48-AVK ≥3 mo							
Breteau[177]	55	1995–8	UFH+AVK:	36 mo	7	15 (31%)	23	NR	NR	3
			6 mo in 56%, entire F/U in 31%							
Cakmak[178]	16	1996–2000	UFH/LMWH+AVK	3 mo	0	14	2	NR	NR	NR
Ferro[10] and Girot[84]	624	1998–2001	64% UFH 35% LMWH	16 mo	8.3%	57%	2.2%	36 (6%) de novo	NR	4.3%
			Most AVK 80% at 6 mo**					17 ACO; 19 no ACO		
Stolz[179]	79	1985–2001	63-UFH 2×PTT	12 mo+	12 in hospital;	57	10	NR		5
			5-Lysis		2 later (cancer)				2	
			9-LDUFH						NR	
			2-None						NR	
			54 had AVK ×1 y						NR	
Mak[180]	13	1995–1998	12 (3 Heparin)	5–36 mo	1	NR	1	0	NR	1
Brucker[181]	42		42 Heparin+OAC		1	40	1	1	1	1

CVT indicates cerebral venous thrombosis; F/U, follow-up; ICH, new intracerebral hemorrhage during follow-up; VTE, venous thromboembolism; RCT, randomized controlled trial; UFH, unfractionated heparin; PTT, partial thromboplastin time; NR, not reported; AVK, anti-vitamin K; ACO, anticoagulation; LMWH, low-molecular-weight heparin; LDUFH, low-dose unfractionated heparin; and OAC, oral anticoagulation.

*Definitions for disability vary among studies.

†Recovered completely.

‡Thirty-one of 49 patients with ICH received anticoagulation; 81 of 93 without ICH received anticoagulation.

‖One patient was asymptomatic.

§Anticoagulation was associated with a 3.8-fold (95% CI, 1.5–9.6) increased odds of full recovery; not associated with death risk.

¶No comparisons made by treatment status. Nine patients developed recurrent CVT (11.7%), all while not taking anticoagulation therapy.

#Seven had a predisposing condition; it is unknown whether they had stopped anticoagulation therapy.

**A total of 12.7% died or were dependent with early anticoagulation vs 18.3% without early anticoagulation ($P>0.05$).

open label thereafter. Primary outcomes were scores for activities of daily living, the Oxford Stroke Handicap Scale, and death. Secondary end points were symptomatic ICH and other major bleeding. At 3 months, 13% of patients in the nadroparin group had a poor outcome compared with 21% given placebo (treatment difference in favor of nadroparin −7%; 95% CI −26% to 12%). There was no symptomatic ICH in either group (1 nonfatal hemorrhage with nadroparin and 1 fatal unconfirmed pulmonary embolus with placebo). Six patients on active treatment (12%) and 8 control subjects (28%) had full recovery over 3 months.

Meta-analysis of these 2 trials[161] revealed a nonstatistically significant relative risk of death or dependency with anticoagulation (relative risk 0.46, 95% CI 0.16 to 1.31), with a risk difference in favor of anticoagulation of −13% (95% CI −30% to 3%). The relative risk of death was 0.33 (95% CI 0.08 to 1.21), with a risk difference of −13% (95% CI −27% to 1%).

A third trial randomized 57 women with puerperal CVT confirmed only by CT imaging and excluded those with hemorrhage on CT.[182] Treatment was with subcutaneous heparin 5000 IU every 6 hours, dose adjusted to an activated partial thromboplastin time 1.5 times baseline for at least 30 days after delivery. Outcome assessment was not blinded. Three patients in the control group either died or had residual paresis compared with none in the heparin group.

In the special situation of CVT with cerebral hemorrhage on presentation, even in the absence of anticoagulation, hemorrhage is associated with adverse outcomes. Highlighting this, in 1 trial of nadroparin, all 6 deaths in the trial overall occurred in the group of 29 patients with hemorrhage on their pretreatment CT scan. None of the deaths were attributed to new or enlarged hemorrhage. These 29 patients were equally divided between treatment groups. Thus, cerebral hemorrhage was strongly associated with mortality but not with cerebral bleeding on treatment. Other studies[171,175] suggested low rates of cerebral hemorrhage after anticoagulation for CVT.

In the special situation of a patient with a major contraindication for anticoagulation (such as recent major hemorrhage), the clinician must balance the risks and benefits of anticoagulation, depending on the clinical situation. In these settings, as for venous thrombosis in general, consultation with an expert in anticoagulation management may be appropriate, and low-intensity anticoagulation may be considered if possible in favor of no anticoagulation until such time as it might be safe to use full-intensity anticoagulation.

Data From Observational Studies

A number of observational studies, both prospective and retrospective, are available, primarily from single centers.[10,136,175–178] Not all studies reported specifically on outcomes of anticoagulation treatment, because the majority of patients in most studies were treated with intravenous UFH or low-molecular-weight heparin (LMWH) at the time of diagnosis, with eventual use of vitamin K antagonists. Data are summarized in Table 5. Mortality rates were low, typically <10%, often due to the underlying disease (eg, cancer) rather than CVT and rarely due to ICH. The majority of patients fully recovered neurological function, and few became disabled.

In a retrospective study of 102 patients with CVT, 43 had an ICH. Among 27 (63%) who were treated with dose-adjusted intravenous heparin after the ICH, 4 died (15%), and 14 patients (52%) recovered completely. Of the 13 patients who did not receive heparin, mortality was higher (69%) with lower improvement in functional outcomes (only 3 patients completely recovered).[171]

The largest study by far was the ISCVT, which included 624 patients at 89 centers in 21 countries. Nearly all patients were treated with anticoagulation initially, and mortality was 8.3% over 16 months; 79% had complete recovery (modified Rankin scale [mRS] score of 0 to 1), 10.4% had mild to moderate disability (mRS score 2 to 3), and 2.2% remained severely disabled (mRS score 4 to 5).[10] Few studies had sufficient numbers of patients not treated with anticoagulation to adequately address the role of anticoagulation in relation to outcome. Data from observational studies suggest a range of risks for ICH after anticoagulation for CVT from zero to 5.4%.[136,171,181,183]

In conclusion, limited data from randomized controlled clinical trials in combination with observational data on outcomes and bleeding complications of anticoagulation support a role for anticoagulation in treatment of CVT, regardless of the presence of pretreatment ICH. On the basis of the available data, it is unlikely that researchers will have equipoise on this question, so a new randomized trial may not be feasible. Anticoagulation appears safe and effective. There was consensus in the writing group to support anticoagulation therapy in the management of patients with CVT. If anticoagulation is given, there are no data supporting differences in outcome with the use of UFH in adjusted doses or LMWH in CVT patients. However, in the setting of DVT or PE, a recent systematic review and meta-analysis of 22 studies showed a lower risk of major hemorrhage (1.2% versus 2.1%), thrombotic complications (3.6% versus 5.4%), and death (4.5% versus 6.0%) with LMWH.[184]

Other Treatments

Fibrinolytic Therapy

Although patients with CVT may recover with anticoagulation therapy, 9% to 13% have poor outcomes despite anticoagulation. Anticoagulation alone may not dissolve a large and extensive thrombus, and the clinical condition may worsen even during heparin treatment.[2,6,10,74,84,95,164,170,172,185–191] Incomplete recanalization or persistent thrombosis may explain this phenomenon. Partial or complete recanalization rates for CVT ranged from 47% to 100% with anticoagulation alone.[110,178,192–194]

Unfortunately, most studies reporting partial or complete recanalization at 3 to 6 months have a small sample size. When 4 studies that included 114 CVT patients were combined, partial or complete recanalization at 3 to 6 months was observed in 94 (82.5%).[110,178,192,193] Recanalization rates may be higher for patients who receive thrombolytic therapy.[14] In general, thrombolytic therapy is used if clinical deterioration continues despite anticoagulation or if a patient has elevated intracranial pressure that evolves despite other management approaches.

Many invasive therapeutic procedures have been reported to treat CVT. These include direct catheter chemical thrombolysis and direct mechanical thrombectomy with or without thrombolysis. There are no randomized controlled trials to support these interventions compared with anticoagulation or with each other. Most evidence is based on small case series or anecdotal reports. Here, we review the studied interventions.

Direct Catheter Thrombolysis

In direct catheter thrombolysis, a standard microcatheter and microguidewire are delivered to the thrombosed dural sinus through a sheath or guiding catheter from the jugular bulb. Mechanical manipulation of the thrombus with the guidewire increases the amount of clot that might be impacted by the thrombolytic agent, potentially reducing the amount of fibrinolytic agent used.[61,113,131,150,170,188,192,195–205]

In a retrospective multicenter study of CVT in the United States, 27 (15%) of 182 patients received endovascular thrombolysis. Ten patients were receiving concomitant anticoagulation therapy. Recanalization was achieved in 26 patients (96%), 4 developed an intracranial hemorrhage, and 1 patient (4%) died.

A systematic review that included 169 patients with CVT treated with local thrombolysis showed a possible benefit for those with severe CVT, which indicates that fibrinolytics may reduce case fatality in critically ill patients. ICH occurred in 17% of patients after thrombolysis and was associated with clinical worsening in 5%.[206]

Mechanical Thrombectomy/Thrombolysis

Balloon-Assisted Thrombectomy and Thrombolysis

Despite systemic thrombolysis or mechanical manipulation of the clot with direct fibrinolytic agent delivery, the sinus thrombosis may persist. Balloon-assisted thrombolysis may be more efficient because the inflated balloon may reduce washout of fibrinolytic agents, potentially lessening the dose of fibrinolytic agents required, the occurrence of hemorrhage,[74,207,208] and procedure time. The balloon may be used to perform partial thrombectomy before thrombolysis.[112,209]

Catheter Thrombectomy

For patients with extensive thrombus that persists despite local administration of a fibrinolytic agent, rheolytic catheter thrombectomy may be considered. One such device is the AngioJet (MEDRAD, Inc, Warrendale, PA), which uses hydrodynamic thrombolytic action occurring at the tip of the catheter via the Venturi effect from high-velocity saline jets. Thrombus is disrupted and directed down the second lumen of the device. Perforation of the venous sinus wall may occur rarely, at a rate that is unknown but reported in the existing small series. It may be avoided by removal of the AngioJet after partial recanalization of the thrombosis and follow-up with additional microcatheter thrombolysis.[187,189,193,198,199,201,202,210,211]

The Merci retrieval device (Concentric Medical, Mountain View, CA) has also been used to remove thrombus in the cerebral venous system. This technique also requires direct catheter access to the venous sinus. The small corkscrew-shaped device is dispensed via the tip of the catheter, advanced into the thrombus, and then slowly pulled back into the catheter with the adherent thrombus. Here again, the device may be used to perform partial recanalization, followed by thrombolysis to avoid damaging the wall or trabeculae of the dural sinus.[195] As mentioned above, the evidence available at the present time is anecdotal.

The Penumbra System (Penumbra, Inc, Alameda, CA) is a new-generation neuroembolectomy device that acts to debulk and aspirate acute clots. It uses a reperfusion catheter that aspirates thrombus while passing a wire-based separator within the catheter to break up the clot and facilitate aspiration. Only anecdotal evidence for its efficacy is available.[212] The risks associated with use of the Penumbra System for cerebral venous thrombosis are likely similar to those seen with the Merci and AngioJet systems.

Surgical Considerations

As endovascular options for management of venous thrombosis have evolved, surgery has played an increasingly limited role. Surgical thrombectomy is needed uncommonly but may be considered if severe neurological or visual deterioration occurs despite maximal medical therapy.[213,214]

In a recent review, among 13 patients with severe CVT who underwent decompressive craniectomy, 11 (84.6%) achieved a favorable outcome (mRS score $\leq$3).[215] Decompressive craniotomy may be needed as a life-saving measure if a large venous infarction leads to a significant increase in intracranial pressure. Likewise, large hematomas rarely may need to be considered for surgical evacuation if associated with a progressive and severe neurological deficit.

Summary

The use of these direct intrasinus thrombolytic techniques and mechanical therapies is only supported by case reports and small case series. If clinical deterioration occurs despite use of anticoagulation, or if the patient develops mass effect from a venous infarction or ICH that causes intracranial hypertension resistant to standard therapies, then these interventional techniques may be considered.

Aspirin

There are no controlled trials or observational studies that directly assess the role of aspirin in management of CVT.

Steroids

Steroids may have a role in CVT by decreasing vasogenic edema, but steroids may enhance hypercoagulability. In a matched case-control study among the 624 patients in the ISCVT,[216] 150 patients treated with steroids at the discretion of their healthcare provider were compared with 150 patients not so treated, matched to those treated on the basis of prognostic factors for poor outcome of CVT. Those treated with steroids thus had similar characteristics as control subjects, except they were more likely to have vasculitis. At 6 months, there was a trend toward a higher risk of death or dependence with steroid treatment (OR 1.7, 95% CI 0.9 to 3.3), and this did not differ after the exclusion of those with vasculitis, malignancy, inflammatory disease, and infection. Among those with parenchymal brain lesions on CT/MRI, results were striking, with 4.8-fold increased odds of death or dependence with steroid treatment (95% CI 1.2 to 19.8). Sensitivity analyses that used different analytic approaches yielded similar findings.

Antibiotics

Local (eg, otitis, mastoiditis) and systemic (meningitis, sepsis) infections can be complicated by thrombosis of the adjacent or distant venous sinuses. The management of patients with a suspected infection and CVT should include administration of the appropriate antibiotics and the surgical drainage of infectious sources (ie, subdural empyemas or purulent collections within the paranasal sinuses).

Management and Prevention of Early Complications (Hydrocephalus, Intracranial Hypertension, Seizures)

Seizures

Seizures are present in 37% of adults, 48% of children, and 71% of newborns who present with CVT.[102,183] No clinical trials have studied either the optimal timing or medication

choice for anticonvulsants in CVT. Whether to initiate anticonvulsants in all cases of CVT or await initial seizures before treatment is controversial. Because seizures increase the risk of anoxic damage, anticonvulsant treatment after even a single seizure is reasonable.[217] In the absence of seizures, the prophylactic use of antiepileptic drugs may be harmful (the risk of side effects may outweigh its benefits).[196,197,209]

A few studies have reported the occurrence and characteristics of patients with seizures accompanying CVT. Among 91 patients, 1 study[218] reported that 32% presented with seizures and 2% developed them during hospitalization; only 9.5% developed late seizures, and seizures were not a predictor of prognosis at 1 year. Early seizures were 3.7-fold more likely (95% CI 1.4 to 9.4) in those with parenchymal lesions on CT/MRI at diagnosis and 7.8-fold more likely (95% CI 0.8 to 74.8) in those with sensory defects. A more recent report from the ISCVT[197] showed 245 (39%) of 624 patients presented with seizures and 43 (6.9%) experienced early seizure within 2 weeks after diagnosis. Besides seizures on presentation, only a supratentorial parenchymal lesion on CT/MRI at diagnosis (present in 58%) was associated with occurrence of early seizures (OR 3.1, 95% CI 1.6 to 9.6). Furthermore, among those with a supratentorial lesion and no presenting seizure, use of antiepileptic drugs was associated with a 70% lower risk of seizures within 2 weeks, although this was not statistically significant (OR 0.3, 95% CI 0.04 to 2.6). On the basis of these findings, the authors suggested the prescription of antiepileptic agents in acute CVT patients with supratentorial lesions who present with seizures.[197]

Hydrocephalus

The superior sagittal and lateral dural sinuses are the principal sites for CSF absorption by the arachnoid granulations, highly vascular structures that protrude across the walls of the sinuses into the subarachnoid space and drain into the venous system. In CVT, the function of the arachnoid granulations may be impaired, potentially resulting in failure of CSF absorption and communicating hydrocephalus (6.6%).[14,198]

Obstructive hydrocephalus is a less common complication of CVT and results from hemorrhage into the ventricular system. This is typically associated with thrombosis that involves the internal cerebral veins and may be associated with thalamic hemorrhage. This syndrome is well described in term neonates but occurs at all ages.[201,205] Neurosurgical evacuation of CSF with ventriculostomy, or in persistent cases, ventriculoperitoneal shunt, is necessary. The brain is under increased venous pressure, and tissue perfusion is at increased risk compared with other situations with obstructive hydrocephalus. Therefore, close monitoring and neurosurgical consultation are important, because intervention may be required at lesser severities of ventricular enlargement.

Intracranial Hypertension

Up to 40% of patients with CVT present with isolated intracranial hypertension.[183] This is characterized by diffuse brain edema, sometimes seen as slit ventricles on CT scanning. Clinical features include progressive headache, papilledema, and third or sixth nerve palsies. Intracranial hypertension is primarily caused by venous outflow obstruction and tissue congestion compounded by CSF malabsorption.

No randomized trials are available to clarify the optimal treatment; however, rational management of intracranial hypertension includes a combination of treatment approaches. First, measures to reduce the thrombotic occlusion of venous outflow, such as anticoagulation and possibly thrombolytic treatment, may result in resolution of intracranial hypertension. Second, reduction of increased intracranial pressure can be accomplished immediately by lumbar puncture with removal of CSF until a normal closing pressure is achieved. Unfortunately, lumbar puncture requires temporary cessation of anticoagulants, with an attendant risk of thrombus propagation. Despite the lack of randomized clinical trials, acetazolamide is a commonly used therapeutic alternative for the treatment of intracranial hypertension with CVT.[139] It may have a limited role in the acute management of intracranial hypertension for patients with CVT. Acetazolamide, a carbonic anhydrase inhibitor, is a weak diuretic and decreases production of CSF. Although used occasionally, corticosteroids are not efficacious[216] and carry risks of associated hyperglycemia and high lactate, which are deleterious to an ischemic brain. Serial lumbar punctures may be necessary when hypertension is persistent. In refractory cases, a lumboperitoneal shunt may be required.[199] Because prolonged pressure on the optic nerves can result in permanent blindness, it is of paramount importance to closely monitor visual fields and the severity of papilledema during the period of increased pressure. Ophthalmologic consultation is helpful for this. Although rarely required, optic nerve fenestration is a treatment option to halt progressive visual loss.

Decompressive craniectomy has been used in patients with malignant arterial stroke to treat elevated intracranial pressure unresponsive to conventional treatment. In a pooled analysis of randomized trials, surgical decompression within 48 hours of stroke onset reduced case fatality and improved functional outcome.[204] Limited evidence is available on the role of decompressive craniectomy in CVT with either brain edema, venous infarction, neurological deterioration, or impending cerebral herniation.[200,202,203] A disadvantage of craniectomy is that it precludes anticoagulation for the immediate postoperative period.

Recommendations

1. **Patients with CVT and a suspected bacterial infection should receive appropriate antibiotics and surgical drainage of purulent collections of infectious sources associated with CVT when appropriate *(Class I; Level of Evidence C)*.**
2. **In patients with CVT and increased intracranial pressure, monitoring for progressive visual loss is recommended, and when this is observed, increased intracranial pressure should be treated urgently *(Class I; Level of Evidence C)*.**
3. **In patients with CVT and a single seizure with parenchymal lesions, early initiation of antiepileptic drugs for a defined duration is recommended to prevent further seizures[218] *(Class I; Level of Evidence B)*.**

4. **In patients with CVT and a single seizure without parenchymal lesions, early initiation of antiepileptic drugs for a defined duration is probably recommended to prevent further seizures *(Class IIa; Level of Evidence C).***
5. **In the absence of seizures, the routine use of antiepileptic drugs in patients with CVT is not recommended *(Class III; Level of Evidence C).***
6. **For patients with CVT, initial anticoagulation with adjusted-dose UFH or weight-based LMWH in full anticoagulant doses is reasonable, followed by vitamin K antagonists, regardless of the presence of ICH[161,171,172,175,181,183] *(Class IIa; Level of Evidence B)*. (For further details, refer to "Acute Management and Treatment of CVT: Initial Anticoagulation.")**
7. **Admission to a stroke unit is reasonable for treatment and for prevention of clinical complications of patients with CVT *(Class IIa; Level of Evidence C).***
8. **In patients with CVT and increased intracranial pressure, it is reasonable to initiate treatment with acetazolamide. Other therapies (lumbar puncture, optic nerve decompression, or shunts) can be effective if there is progressive visual loss. *(Class IIa; Level of Evidence C).***
9. **Endovascular intervention may be considered if deterioration occurs despite intensive anticoagulation treatment *(Class IIb; Level of Evidence C).***
10. **In patients with neurological deterioration due to severe mass effect or intracranial hemorrhage causing intractable intracranial hypertension, decompressive hemicraniectomy may be considered *(Class IIb; Level of Evidence C).***
11. **For patients with CVT, steroid medications are not recommended, even in the presence of parenchymal brain lesions on CT/MRI, unless needed for another underlying disease[216] *(Class III; Level of Evidence B).***

Long-Term Management and Recurrence of CVT

Risk of Recurrence With and Without Anticoagulation

Prevention strategies focus on preventing recurrence of CVT or other VTE in those CVT patients at high risk of these outcomes. There are no available risk stratification schemes in CVT, but patients with certain thrombophilic conditions or medical conditions, such as cancer, might be considered high risk. There are no randomized clinical trials of long-term prevention of first or recurrent CVT. Overall, there is approximately a 6.5% annual risk of any type of recurrent thrombosis.[10,117]

Because there are no secondary prevention trials of anticoagulation in adults with CVT, evaluation of prevention strategies can only be performed with observational studies that evaluate recurrence of CVT or VTE with or without ongoing anticoagulation. In a cohort of 154 patients treated at Mayo Clinic between 1978 and 2001, 56 patients initially received both heparin and warfarin, 12 received heparin only, and 21 received warfarin only.[61] Seventy-seven (50%) were treated with warfarin for an average of 9 months, with 25 committed to lifelong therapy.[61] During 36 months of follow-up (464 patient-years), there were 23 recurrent VTEs in 20 patients (13%), the majority in the first year. Ten patients had recurrent CVT (2.2 per 100 patient-years), and 11 had DVT or PE (2.8 per 100 patient-years). Nine of the recurrent events occurred while the patients were taking warfarin. After 8 years of follow-up, there was no impact of warfarin on survival or recurrence-free survival.[61]

In a cohort of 54 CVT patients treated consecutively at University Hospital Gasthuisberg, Leuven, Belgium, 8 (14.8%) had a recurrence of VTE (7 with DVT or PE, 1 with CVT and mesenteric vein thrombosis) over a median of 2.5 years of follow-up (4.5 per 100 patient-years). Median time to recurrence was 2.5 months (range 2 weeks to 4 years). Only 2 of these 8 patients were taking anticoagulants at the time of recurrence, 1 with an international normalized ratio (INR) of 1.6 and the other with an INR of 2.1. Among the 6 patients with recurrent VTE who were not taking anticoagulants, recurrence occurred between 2 weeks and 10 months after the index event. Those with recurrence more often had a thrombophilic disorder, had a history of DVT, and had not received oral anticoagulation because of perceived contraindications.[176]

In the ISCVT study, among 624 patients with CVT, there were 14 (2.2%) recurrent CVTs and 27 (4.3%) other thrombotic events (16 DVT, 3 PE, 2 ischemic stroke, 2 transient ischemic attack, and 4 acute limb ischemia) over a mean follow-up of 16 months.[10] Seventeen (41.5%) of the 41 patients with recurrent or other thrombotic events were receiving anticoagulants, but the type of anticoagulation and the number who were receiving therapeutic doses of anticoagulation were unknown.[10] It was not reported whether anticoagulation was given long-term and whether recurrent events differed based on its use.

The Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT) evaluated outcomes for 142 CVT patients, of whom 51 were retrospectively enrolled and 91 were prospectively enrolled. There were 2 (2%) recurrent CVTs and 10 (8%) other arterial or venous thrombotic events (maximum 16 years of follow-up for the retrospective cases and 12 months of follow-up for prospective cases).[117] For the prospectively followed cases, the incident risk of a thrombotic event was 4% per year (5 thrombotic events in 4 patients: 2 DVTs, 1 PE, 1 ischemic stroke, and 1 acute limb ischemia). Three of these events occurred with anticoagulation use, although the INR levels were unknown at the time of the event. In addition, all of these events occurred within 12 months of the index CVT.[117]

A cohort of 77 CVT patients diagnosed in France between 1975 and 1990 was followed up for 63 months.[175] Nine (11.7%) had a recurrence of CVT, 8 during the first 12 months, and none were receiving anticoagulation at the time of recurrence. Eleven patients (14.3%) had other thrombotic events, including retinal vein thrombosis, PE, and arterial thromboses.[175] Use of anticoagulation at the time of recurrent thromboses that were not CVTs was not reported.

More recently, 145 patients with a first CVT were followed up for a median of 6 years after discontinuation of anticoagulation therapy. CVT recurred in 5 patients (3%), and other manifestations of VTE (defined as DVT of the lower limbs or PE) were seen in 10 additional patients (7%). The recurrence rate accounted for 3.4% of all VTEs in the first 16 months (or 2.03 per 100 person-years; 95% CI 1.16 to 3.14) and 1.3% of CVTs in the first 16 months (or 0.53 per 100 person-years; 95% CI 0.16 to 1.10). Approximately half of the recurrences occurred

within the first year after discontinuation of anticoagulant therapy. Mild thrombophilia abnormalities were not associated with recurrent CVT, but severe thrombophilia showed an increased risk of DVT or PE.[210] In summary, the prevalence of CVT recurrence was similar in the Italian and ISCVT studies (1.3% and 2.2%, respectively[10,209]) at the 16-month follow-up.

The overall risk of recurrence of any thrombotic event (CVT or systemic) after a CVT is ≈6.5%. The risk of other manifestations of VTE after CVT ranges from 3.4%[209] to 4.3%[10] on the basis of the largest studies of this medical condition.[10] Patients with severe thrombophilia have an increased risk of VTE.

Secondary Prevention of CVT and Other VTE Events

DVT/PE and CVT share some similarities. The chronic and transient risk factors appear to be similar, although women are more likely to have CVT,[61] and selected thrombophilia subtypes may differ between CVT and DVT/PE.[211] In the ISCVT cohort, the overall rate of recurrent CVT or other VTE recurrence was 4.1 per 100 person-years, with male sex and polycythemia/thrombocythemia being the only independent predictors found. The same study reported a steady increase in the cumulative risk of thrombotic recurrences not influenced by the duration of anticoagulation, which emphasizes the need for a clinical trial to assess the efficacy and safety of short versus extended anticoagulant therapy.[219] Given that systemic VTE after CVT is more common than recurrent CVT, one may reasonably adopt the VTE guidelines for prevention of both new VTE and recurrent CVT.[219,220] However, each individual patient should undergo risk assessment (see "Thrombophilias and Risk Stratification for Long-Term Management" below), and the patient's risk level and preferences regarding long-term anticoagulation treatment, the risk of bleeding, and the risk of thrombosis without anticoagulation should then be considered.[220]

Thrombophilias and Risk Stratification for Long-Term Management

Thrombophilias may be hereditary or acquired, and hereditary thrombophilias have been stratified as mild or severe on the basis of the risk of recurrence in very large family cohorts.[221] Among VTE patients, the hereditary thrombophilias with the highest cumulative recurrence rates for VTE in the absence of ongoing anticoagulation have been deficiencies of antithrombin, protein C, and protein S, with a 19% recurrence at 2 years, 40% at 5 years, and 55% at 10 years. Homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; and antiphospholipid syndrome are categorized as severe.

Interestingly, the more common hereditary thrombophilias, such as heterozygous factor V Leiden and prothrombin G20210A or elevated factor VIII, have a much lower risk of recurrence (7% at 2 years, 11% at 5 years, and 25% at 10 years) and could be categorized as mild.[221] Hyperhomocysteinemia, a common hereditary or acquired risk factor for VTE, was not significantly associated with a high risk of recurrence.[10,28] In addition, the annual incidence and the risk of recurrence increased markedly in those with combined thrombophilic defects, described as double heterozygous/homozygous.[221]

There are several important points regarding the hereditary thrombophilia data described above. First, the familial nature of these deficiencies of protein C, S, or antithrombin was clearly established, which distinguishes these patients from those with sporadic or acquired abnormalities. Second, testing for deficiencies of protein C, S, and antithrombin must be performed at least 6 weeks after a thrombotic event and then confirmed with repeat testing and family studies. In addition, protein C and S functional activity and antithrombin levels are difficult to interpret during treatment with warfarin. Therefore, testing for these conditions is generally indicated 2 to 4 weeks after completion of anticoagulation.[222,223] Lastly, clearly established deficiencies of proteins C, S, and antithrombin are relatively uncommon.

Antiphospholipid antibody syndrome is an acquired thrombophilia associated with specific laboratory criteria (lupus anticoagulant, anticardiolipin antibody, and anti-β2-glycoprotein I) and a history of a venous or arterial event or fetal loss.[224] Caution must be taken when the results of antiphospholipid antibody testing are interpreted. A normal result may occur at the time of the clinical presentation, which rules out antiphospholipid antibody syndrome. On the other hand, abnormal tests may occur transiently due to the disease process, infection, certain medications (antibiotics, cocaine, hydralazine, procainamide, quinine, and others), or unknown causes. Approximately 5% of the general population at any given time has evidence of abnormal tests, and these mainly have no clinical consequence.[224,225]

A diagnosis of antiphospholipid syndrome requires abnormal laboratory testing on 2 or more occasions at least 12 weeks apart.[226] Patients diagnosed with antiphospholipid syndrome have an increased risk of recurrent thrombotic events; however, test results cannot predict the likelihood of complications, their type, or their severity in a particular patient.

Although there are no prospective studies that report recurrence rates for CVT specifically, the high risk of recurrent VTE with this disorder meets the definition of severe thrombophilia. The Duration of Anticoagulation Study Group reported a 29% recurrence of VTE in patients with anticardiolipin antibodies versus 14% in those without them (P=0.001) over a 4-year period, and the risk increased with the titer of the antibodies.[227] In a randomized controlled trial of warfarin for 3 months versus extended treatment for 24 months after first-ever idiopathic DVT or PE, the presence of antiphospholipid antibodies was associated with a 4-fold increased risk of recurrence (hazard ratio [HR] 4.0, 95% CI 1.2 to 13), and the presence of a lupus anticoagulant was associated with a 7-fold increased risk (HR 6.8, 95% CI 1.5 to 31) in the placebo group.[228] The current recommendations for VTE patients call for indefinite anticoagulation (adjusted-dose warfarin INR 2.0 to 3.0 or heparin) for patients with antiphospholipid syndrome.[220]

Other Tests That Might Define Risk of Recurrent CVT or VTE After CVT

In patients with DVT or PE, increasing evidence suggests there is clinical utility to D-dimer measurement when used to define risk of recurrent VTE.[224,229,230] For example, in a randomized controlled trial (n=608), patients with an abnormal D-dimer level 1 month after the discontinuation of

anticoagulation had a significant incidence of recurrent VTE (15% versus 2.9%), which was reduced by the resumption of anticoagulation (compared with those not receiving vitamin K antagonists, $P=0.02$).[231] During 1.4 years of follow-up, 120 subjects with an abnormal D-dimer level were randomized to no anticoagulation, and 18 (15%) in this group developed a recurrent VTE. Of the103 patients with abnormal D-dimer randomized to resume anticoagulation, only 3 (2.9%) had a recurrent VTE.[231] Although the study was randomized, it was unblinded, and D-dimer levels were only obtained once. In addition, there were no subjects with CVT and no similar studies in CVT patients. Although the clinical utility of D-dimer for longer-term anticoagulation for VTE secondary prevention appears promising, the lack of standardization of D-dimer assays may limit their clinical applicability and reliability.[232]

Recommendations

1. **Testing for prothrombotic conditions, including protein C, protein S, antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A mutation, and factor V Leiden, can be beneficial for the management of patients with CVT. Testing for protein C, protein S, and antithrombin deficiency is generally indicated 2 to 4 weeks after completion of anticoagulation. There is a very limited value of testing in the acute setting or in patients taking warfarin.[222–226] (*Class IIa; Level of Evidence B*).**
2. **In patients with provoked CVT (associated with a transient risk factor), vitamin K antagonists may be continued for 3 to 6 months, with a target INR of 2.0 to 3.0 (Table 3) *(Class IIb; Level of Evidence C)*.**
3. **In patients with unprovoked CVT, vitamin K antagonists may be continued for 6 to 12 months, with a target INR of 2.0 to 3.0 *(Class IIb; Level of Evidence C)*.**
4. **For patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia (ie, homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; or antiphospholipid syndrome), indefinite anticoagulation may be considered, with a target INR of 2.0 to 3.0 *(Class IIb; Level of Evidence C)*.**
5. **Consultation with a physician with expertise in thrombosis may be considered to assist in the prothrombotic testing and care of patients with CVT *(Class IIb; Level of Evidence C)*.**

Management of Late Complications (Other Than Recurrent VTE)

Headache

Headache is a common complaint during the follow-up of CVT patients, occurring in ≈50% of patients.[193,205] In general, headaches are primary and not related to CVT. In the Lille study,[177] 53% of patients had residual headache, 29% fulfilled criteria for migraine, and 27% had headache of the tension type. In VENOPORT,[205] 55% of patients reported headaches during the follow-up, and these were mild to moderate in 45%. In a series of 17 patients presenting with headache as the only neurological sign of CVT, several patients had headaches at 3 months, which comprised migraine attacks similar to those that occurred previously (4), tension type (2), and new onset of migraine with aura (2).[64] At follow-up, severe headaches that required bed rest or hospital admission were reported in 14% of patients in the ISCVT[10] and 11% in VENOPORT.[117] In patients with persistent or severe headaches, appropriate investigations should be completed to rule out recurrent CVT. Occasionally, MRV may show stenosis of a previously occluded sinus, but the clinical significance of this is unclear. Headache during follow-up is more common among patients who present acutely as having isolated intracranial hypertension. In these patients, if headache persists and MRI is normal, lumbar puncture may be needed to exclude elevated intracranial pressure.

Seizures

Focal or generalized post-CVT seizures can be divided into early or remote (occurring >2 weeks after diagnosis) seizures.[10,197] On the basis of case series, remote seizures affect 5% to 32% of patients. Most of these seizures occur in the first year of follow-up.[175,218] In ISCVT, 11% of the patients experienced remote seizures (36 patients by 6 months, 55 by 1 year, and 66 by 2 years). Risk factors for remote seizures were hemorrhagic lesion on admission CT/MRI (HR 2.62, 95% CI 1.52 to 4.52), early seizure (HR 2.42, 95% CI 1.38 to 4.22), and paresis (HR 2.22, 95% CI 1.33 to 3.69). Five percent of the patients had post-CVT epilepsy (>1 remote seizure). Post-CVT epilepsy was also associated with hemorrhagic lesion on admission CT/MRI (OR 6.76, 95% CI 2.26 to 20.41), early seizure (OR 3.99, 95% CI 1.16 to 11.0), and paresis (OR 2.75, 95% CI 1.33 to 6.54).[234] Initiation of antiepileptic drugs for a defined duration is recommended to prevent further seizures in patients with CVT and parenchymal lesions who present with a single seizure. Recommendations covering different scenarios are provided in the section on the "Management and Prevention of Early Complications."

Visual Loss

Severe visual loss due to CVT rarely occurs (2% to 4%).[55,193,235] Papilledema can cause transient visual impairment, and if prolonged, optic atrophy and blindness may ensue. Visual loss is often insidious, with progressive constriction of the visual fields and relative sparing of central visual acuity. Visual deficits are more common in patients with papilledema and those who present with increased intracranial pressure. Delayed diagnosis is associated with an increased risk of later visual deficit. Patients with papilledema or visual complaints should have a complete neuro-ophthalmological study, including visual acuity and formal visual field testing.

Dural Arteriovenous Fistula

Thrombosis of the cavernous, lateral, or sagittal sinus can later induce a dural arteriovenous fistula.[236] A pial fistula can also follow a cortical vein thrombosis. The relationship between the 2 entities is rather complex, because (1) dural fistulas can be a late complication of persistent dural sinus occlusion with increased venous pressure, (2) the fistula can close and cure if the sinus recanalizes, and (3) a preexisting fistula can be the underlying cause of CVT. The exact frequency of dural fistula after CVT is not known because there are no cohort studies with

long-term angiographic investigation. The incidence of dural arteriovenous fistula was low in cohort studies without systematic angiographic follow-up (1% to 3%).[55,94,201,205,237] A cerebral angiogram may help identify the presence of a dural arteriovenous fistula.

Recommendation

1. **In patients with a history of CVT who complain of new, persisting, or severe headache, evaluation for CVT recurrence and intracranial hypertension should be considered *(Class I; Level of Evidence C)*.**

CVT in Special Populations

CVT During Pregnancy

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 2500 deliveries to 1 in 10 000 deliveries in Western countries, and ORs range from 1.3 to 13.[238–240] The greatest risk periods for CVT include the third trimester and the first 4 postpartum weeks.[240] Up to 73% of CVT in women occurs during the puerperium.[241] 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).[35]

Vitamin K antagonists, including warfarin, are associated with fetal embryopathy and bleeding in the fetus and neonate and thus are generally believed to be contraindicated in pregnancy. Therefore, anticoagulation for CVT during pregnancy and early in the puerperium consists of LMWH in the majority of women.[220]

In contrast to UFH, LMWH is not associated with teratogenicity or increased risk of fetal bleeding. The American College of Chest Physicians guidelines for antithrombosis address prevention and treatment of DVT and pulmonary embolus in pregnancy and the puerperium, recommending LMWH over UFH (recommendation 4.2.1).[241a] They recommend that treatment be continued throughout pregnancy and for at least 6 weeks postpartum (for a total minimum duration of treatment of 6 months). Although these recommendations are directed to systemic venous thrombosis, it is logical to apply them to CVT for several reasons. First, safety in terms of teratogenicity and fetal/newborn/maternal bleeding complications should be similar, and second, the recommendations are concordant with treatment of non–pregnancy-associated CVT. In a retrospective cohort study of 37 high-risk pregnancies, once-daily tinzaparin was studied for the prevention of initial or recurrent cerebral thrombosis. During treatment, no systemic venous thrombosis occurred; however, 1 parietal infarct and 1 postpartum CVT were documented.[242] As in nonpregnant women, fibrinolytic therapy is reserved for patients with deterioration despite systemic anticoagulation, and its use has been reported during pregnancy.[243]

Future Pregnancies and Recurrence

Patients with previous VTE are at increased risk of further venous thrombotic events compared with healthy individuals.[244,245] Similarly, women with a history of VTE appear to have an increased risk of thrombotic events (ie, DVT, PE) in future pregnancies.[57] Pregnancy, and in particular puerperium, are known risk factors for CVT. Six studies investigated the outcome and complications of pregnancy in women who had CVT,[10,117,175,246–248] with a total of 855 women under observation, of whom 83 became pregnant (101 pregnancies) after their CVT.

These studies found that the risk of complications during future pregnancies was low. In fact, 88% of the pregnancies ended in a normal birth, the remainder being terminated prematurely by voluntary or spontaneous abortion. There was only 1 case of recurrent CVT and 2 cases of DVT; however, a high proportion of spontaneous abortion was noted.

On the basis of the available evidence, CVT is not a contraindication for future pregnancies. Considering the additional risk that pregnancy confers to women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period can be beneficial.

Recommendations

1. **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 6 months) *(Class I; Level of Evidence C)*.**
2. **It is reasonable to advise women with a history of CVT that future pregnancy is not contraindicated. Further investigations regarding the underlying cause and a formal consultation with a hematologist and/or maternal fetal medicine specialist are reasonable.[10,117,175,246–248] *(Class IIa; Level of Evidence B)*.**
3. **It is reasonable to treat acute CVT during pregnancy with full-dose LMWH rather than UFH *(Class IIa; Level of Evidence C)*.**
4. **For women with a history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period is probably recommended *(Class IIa; Level of Evidence C)*.**

CVT in the Pediatric Population

The incidence of pediatric CVT is 0.67 per 100 000 children per year.[91] When neonates are excluded, the reported incidence is 0.34 per 100 000 children per year.[249] Neonates present with seizures or lethargy, whereas older infants and children (similar to adults) usually present with seizures, altered levels of consciousness, increasing headache with papilledema, isolated intracranial hypertension, or focal neurological deficits.

Risk Factors

Risk factors for pediatric CVT are age related. Neonates constitute 43% of pediatric patients with CVT.[91] There are several likely reasons for their increased risk. First, considerable mechanical forces are exerted on the infant's head during birth that result in molding of the skull bones along the suture lines. This results in mechanical distortion of and damage to the underlying dural venous sinuses and thrombosis. The neonate also has an increased thrombotic tendency.[250] First, there is a transplacental transfer of circulating maternal antiphospholipids to the fetus, which can persist into the newborn

period.[251] Second, neonates have reduced levels of circulating anticoagulant proteins, including proteins C and S and antithrombin, and higher hematocrit relative to adults. Furthermore, hemoconcentration occurs with the normal fluid loss and relative dehydration of the neonate during the first week of postnatal life. Multiple risk factors are present in more than half of neonates with CVT.[252] Additional complications of gestation and labor and delivery increase the risk of CVT. Maternal preeclampsia/eclampsia is a reported risk factor for neonatal CVT.[253] Neonatal diseases including head and neck infections, meningitis, dehydration secondary to feeding difficulties or gastroenteritis, and congenital heart disease also cause CVT.[91]

A recent meta-analysis of observational studies estimated the impact of thrombophilia on the incident risk of arterial ischemic stroke and CVT. The reported magnitude of association was as follows: Antithrombin deficiency, OR 7.1 (95% CI 2.4 to 22.4); protein C deficiency, OR 8.8 (95% CI 4.5 to 17.0); protein S deficiency, OR 3.2 (95% CI 1.2 to 8.4); factor V G1691A, OR 3.3 (95% CI 2.6 to 4.1); factor II G20210A, OR 2.4 (95% CI 1.7 to 3.5); methylenetetrahydrofolate reductase C677T (arterial ischemic stroke), OR 1.58 (95% CI 1.2 to 2.1); antiphospholipid antibodies (arterial ischemic stroke), OR 7.0 (95% CI 3.7 to 13.1); elevated lipoprotein(a), OR 6.3 (95% CI 4.5 to 8.7); and combined thrombophilias, OR 11.9 (95% CI 5.9 to 23.7). The authors also concluded that further studies are needed to determine the impact of thrombophilias on outcome and recurrence risk.[250]

In older children and adolescents, systemic lupus erythematosus, nephrotic syndrome, leukemia or lymphoma with L-asparaginase treatment, and trauma are reported causes of CVT.[102,245] Iron deficiency anemia is an established risk factor for CVT.[254] Prothrombotic disorders ranged from 33% to 66% of neonatal and pediatric CVTs and are frequently present when there are other risk factors for CVT.[102]

Radiographic Diagnosis

As in adults, a high index of suspicion for CVT and specific venous imaging are required make a diagnosis. This is especially true for neonates, who have nonspecific presentations that consist solely of seizures in the majority. The neuroimaging findings of CVT are similar in children and adults. In neonates, 2-dimensional TOF MRV has several pitfalls, including a focal area of absent flow where the occipital bone compresses the posterior superior sagittal sinus in the supine position. This is present in up to 14% of neonates without CVT.[255,256] Therefore, CTV is frequently required to confirm the presence of CVT suggested by MRV. In neonates, transfontanellar Doppler ultrasound can suggest CVT by demonstrating an absence of flow from an occlusive thrombus; however, in partially occlusive thrombosis, this technique may not be as reliable.[257]

Parenchymal lesions are more likely hemorrhagic in neonates than in children.[102] Intracranial hemorrhage in neonates frequently includes subtentorial subdural hemorrhage. Term neonates with intraventricular hemorrhage have CVT as the cause in 34% of cases, frequently in association with thalamic hemorrhage.[205]

Outcome

CVT is associated with a significant frequency of adverse outcomes in neonates and older infants and children. In neonates, long-term follow-up is required to ascertain the outcomes, because deficits may only become evident with brain maturation over many years. Among neonates with CVT, neurological deficits are observed in 28%[258] to 83%.[102,245,253,259] Differences among studies may relate to treatment protocols: In 1 study of 39 neonates with CVT, neurological deficits were reported in 83%, and only 10% of neonates received anticoagulation. In contrast, in a Canadian Registry that included 160 children with CVT, venous infarction occurred in 42%, and 8% died. Additional outcomes included seizures in 20% and symptomatic recurrent thrombosis in 19 children (13%; CVT in 12 and extracerebral thrombosis in the remaining 7 children). Among the 63 neonates with CVT, neurological deficits were seen in only 34%, anticoagulation was used in 36%, and mortality among neonates was 7%.[102] In CVT occurring beyond the newborn period, neurological deficits are reported in 17% to 46% of cases.[43,175,185,260,261]

One study showed that 18% of children with CVT had residual visual impairment on long-term follow-up. Other studies reported similar findings in children and adults with CVT.[237,235,262]

Management of CVT in the Pediatric Population

Consideration of endovascular treatment for neonates and children with CVT is driven by the high rates of adverse outcomes. No randomized clinical trials have been conducted in pediatric CVT. Therefore, treatment practices have been extrapolated primarily from adult studies.

In children, and increasingly in neonates, the mainstay of CVT treatment is anticoagulation, including LMWH, UFH, and warfarin. Individual and regional practices vary widely in pediatric CVT and particularly in neonatal CVT. Seizures were observed in >50% of the pediatric population with CVT.[102] Given the higher frequency of epileptic seizures in children, continuous electroencephalography monitoring may be considered for unconscious or mechanically ventilated children.

Primary Evidence

Despite the absence of randomized trials, increasing evidence from case series and large observational studies supports the efficacy of anticoagulation in children or neonates with CVT.[72,179,201,236,263] In the Canadian Pediatric Ischemic Stroke Registry, 85 of 160 children with CVT at 16 Canadian children's hospitals received anticoagulation (25 neonates and 60 non-neonates). There were no fatal or severe complications reported; however, follow-up was not systematic.[102]

In a European multicenter study among 396 pediatric patients (75 neonates) with CVT, 250 (63%) received acute anticoagulation. Twenty-two (6%) had recurrent VTE (13 cerebral; 3%) after a median of 6 months of follow-up. In the multivariable survival analysis, nonadministration of an anticoagulant before relapse (HR 11.2, 95% CI 3.4 to 37.0; $P<0.0001$), persistent occlusion on repeat venous imaging (HR 4.1, 95% CI 1.1 to 14·8; $P=0·032$), and heterozygosity for the prothrombin G20210A mutation (HR 4.3, 95% CI 1.1 to 16.2; $P=0.034$) were independently associated with recurrent VTE. Of note, there was no significant difference in recurrence based on medical conditions such as cancers (acute lymphoblastic leukemia, lymphoma, or brain tumor), type I diabetes mellitus, nephrotic syndrome, infectious diseases, or heparin-induced thrombocytopenia. The number

of CVT cases needed to screen to detect at least 1 prothrombin G20210A heterozygote was 16. The number needed to treat for 1 year with anticoagulation to prevent 1 recurrent VTE was 32 for the entire group. The number needed to treat was 3 for those with prothrombin G20210A who were older than 2 years of age at diagnosis of CVT.[245]

A recently published case series from the Netherlands studied anticoagulation use in neonates with CVT, intraventricular hemorrhage, or thalamic hemorrhage.[201] Among the 10 neonates, 1 infant died before therapy could be initiated, and 2 were born before typical use of LMWH therapy. The remaining 7 neonates received 3 months of LMWH (dalteparin) with a target anti-Xa level of 0.5 to 1.0 U/mL. There were no increased or new hemorrhages during treatment. Another pediatric CVT study that included 42 children reported safety and improved outcomes with anticoagulation even in the presence of ICH.[187] Finally, in a prospective single-center study of protocol-based anticoagulation therapy among 162 pediatric patients, approximately half received anticoagulation at diagnosis, including 35% of neonates and 71% of children. Hemorrhagic complications were rare (6%); all were nonfatal and were associated with a favorable clinical outcome in the majority. Propagation of CVT thrombus was observed in more than one quarter of neonates and more than one third of children not treated with anticoagulation.[264] Further studies on optimal dosing of anticoagulation with stratification by cerebral hemorrhage at the time of the diagnosis are in the planning stage through the International Pediatric Stroke Study.[265,266]

Published Pediatric Stroke Guidelines

In the past 5 years, 3 sets of guidelines addressing treatment of pediatric CVT were published.[267–269] All 3 guidelines recommended use of anticoagulation with LMWH, UFH, and/or warfarin for 3 to 6 months in children beyond the newborn period, even in the presence of intracranial hemorrhage.

By contrast, recommendations regarding anticoagulation for neonatal CVT have been discordant. Of the 3 published guidelines, 1 did not address neonatal CVT,[268] 1 recommended acute anticoagulation,[269] and the other recommended no acute anticoagulation.[251] Specifically, the American College of Chest Physicians recommended initial anticoagulation except in the presence of significant hemorrhage, in which case monitoring for propagation was suggested, with initiation of anticoagulation if propagation should occur. Anticoagulation was recommended for a minimum of 6 weeks and no longer than 3 months. It was suggested that a venous imaging study be performed at 6 weeks, and if full recanalization is seen, anticoagulation can be discontinued. The AHA guidelines make no recommendations regarding initial anticoagulation. Anticoagulation is considered reasonable in neonates with thrombus propagation or thrombophilia (which cannot always be diagnosed during acute illness). The reluctance to treat neonatal CVT with anticoagulation was based on several concerns. First, there was an absence of safety data for neonates, and second, there was concern regarding increased susceptibility of the neonatal brain to hemorrhage. Before the current outcome literature, another reason not to treat neonates was the erroneous perception that neonates have a good outcome from CVT and treatment is therefore unnecessary. As noted in previous sections, these assumptions have been refuted in part by studies published in the past few years. However, in the absence of clinical trial evidence, practice variability is understandable.[251]

Recommendations

1. **Supportive measures for children with CVT should include appropriate hydration, control of epileptic seizures, and treatment of elevated intracranial pressure *(Class I; Level of Evidence C)*.**
2. **Given the potential for visual loss owing to severe or long-standing increased intracranial pressure in children with CVT, periodic assessments of the visual fields and visual acuity should be performed, and appropriate measures to control elevated intracranial pressure and its complications should be instituted *(Class I; Level of Evidence C)*.**
3. **In all pediatric patients, if initial anticoagulation treatment is withheld, repeat neuroimaging including venous imaging in the first week after diagnosis is recommended to monitor for propagation of the initial thrombus or new infarcts or hemorrhage *(Class I; Level of Evidence C)*.**
4. **In children with acute CVT diagnosed beyond the first 28 days of life, it is reasonable to treat with full-dose LMWH even in the presence of intracranial hemorrhage *(Class IIa; Level of Evidence C)*.**
5. **In children with acute CVT diagnosed beyond the first 28 days of life, it is reasonable to continue LMWH or oral vitamin K antagonists for 3 to 6 months *(Class IIa; Level of Evidence C)*.**
6. **In all pediatric patients with acute CVT, if initial anticoagulation is started, it is reasonable to perform a head CT or MRI scan in the initial week after treatment to monitor for additional hemorrhage *(Class IIa; Level of Evidence C)*.**
7. **Children with CVT may benefit from thrombophilia testing to identify underlying coagulation defects, some of which could affect the risk of subsequent rethromboses and influence therapeutic decisions[250–252] *(Class IIb; Level of Evidence B)*.**
8. **Children with CVT may benefit from investigation for underlying infections with blood cultures and sinus radiographs[92,237,267] *(Class IIb; Level of Evidence B)*.**
9. **In neonates with acute CVT, treatment with LMWH or UFH may be considered[72,179,201,236,263] *(Class IIb; Level of Evidence B)*.**
10. **Given the frequency of epileptic seizures in children with an acute CVT, continuous electroencephalography monitoring may be considered for individuals who are unconscious or mechanically ventilated *(Class IIb; Level of Evidence C)*.**
11. **In neonates with acute CVT, continuation of LMWH for 6 weeks to 3 months may be considered *(Class IIb; Level of Evidence C)*.**
12. **The usefulness and safety of endovascular intervention are uncertain in pediatric patients, and its use may only be considered in carefully selected patients with progressive neurological deterioration despite intensive and therapeutic levels of anticoagulant treatment *(Class IIb; Level of Evidence C)*.**

Clinical Outcomes: Prognosis

There are several studies and reviews on the outcome and prognosis of CVT.[181,256,257] The majority of such studies are retrospective (totally or in part).[14,63,66,90,136,175,179,190,194,233,270–274] Of the few

Table 6. Variables Associated With Poor Prognosis in Cohort Studies

Demographic	Clinical	Neuroimaging	Risk Factors
Age >37 y[10]	Coma[10,117,277]	Intracerebral hemorrhage[10,277]	Cancer[10,177]
Male sex[10]	Neurological deficit and severity (NIHSS)[177,179]	Involvement of the straight sinus[277]	CNS infection[10]
	Encephalopathy[117]	Thrombosis of the deep venous system[10]	Underlying coagulopathy hereditary thrombophilia[66]
	Decreased level of consciousness[10]		
	Hemiparesis[10]	Venous infarction[66,179]	
	Seizures[10,179]		

NIHSS indicates National Institutes of Health Stroke Scale; CNS, central nervous system.

prospective studies, some did not analyze prognostic factors[178,193,261] or performed only a bivariate analysis of such predictors[275,276] or analyzed specific subgroups of patients.[42,84,89,192] There are only 5 cohort studies[5,55,93,167,203] that analyzed prognostic factors for the short-term[5] and the long-term outcome of CVT patients (Table 6).[6,10,117,177,277]

Neurological Worsening After Diagnosis

Neurological worsening may occur in 23% of patients, even several days after diagnosis. Neurological worsening can feature depressed consciousness, mental status disturbance, new seizure, worsening of or a new focal deficit, increase in headache intensity, or visual loss. Approximately one third of patients with neurological deterioration will have new parenchymal lesions when neuroimaging is repeated. Patients with depressed consciousness on admission are more likely to deteriorate.[1,278]

Early Death

Approximately 3% to 15% of patients die in the acute phase of the disorder.[28] Most early deaths are a consequence of CVT. In the ISCVT,[10] 21 (3.4%) of 624 patients died within 30 days from symptom onset; however, in a recent retrospective/prospective multicenter study[16] from the United States, higher mortality (13%) was reported. Case series from developing countries also have higher figures for early deaths, with 6% reported in a large Pakistan-Middle East registry[63] and 15% in a single-center case series from Iran.[261]

In the largest study, the ISCVT, risk factors for 30-day mortality were depressed consciousness, altered mental status, and thrombosis of the deep venous system, right hemisphere hemorrhage, and posterior fossa lesions. The main cause of acute death with CVT is transtentorial herniation secondary to a large hemorrhagic lesion,[5] followed by herniation due to multiple lesions or to diffuse brain edema. Status epilepticus, medical complications, and PE are among other causes of early death.[136,279]

Late Deaths

Deaths after the acute phase are predominantly related to the underlying conditions, in particular malignancies.[10,14]

Long-Term Outcome

In the ISCVT study,[55] complete recovery at last follow-up (median 16 months) was observed in 79% of the patients; however, there was an 8.3% overall death rate and a 5.1% dependency rate (mRS score ≥3) at the end of follow-up (12.6% if we consider patients who survived with an mRS score ≥2). In a systematic review that included both retrospective and prospective studies, overall mortality was 9.4%, and the proportion of dependency (mRS score ≥3 or Glasgow Outcome Scale score ≥3) was 9.7%.[28] Two retrospective/prospective studies were reported after this review. In the Pakistan-Middle East registry,[63] the dependency rate (mRS score ≥3) was higher (11%), whereas in the US multicenter registry,[16] 28% of patients were dependent at 12 months. Of note, some studies include patients transferred to tertiary care centers, whose strokes are usually more severe, with the potential for a referral bias. Among the 7 cohort studies (including the prospective part of retrospective/prospective studies in which information can be analyzed separately), the overall death and dependency rate was 15% (95% CI 13% to 18%).[10]

Neuropsychological and Neuropsychiatric Sequelae

There is little information on the long-term neuropsychological and neuropsychiatric outcome in CVT survivors.[260,272] Despite the apparent general good recovery in most patients with CVT, approximately one half of survivors feel depressed or anxious, and minor cognitive or language deficits may preclude them from resuming their previous jobs.[260,272]

Abulia, executive deficits, and amnesia may result from thrombosis of the deep venous system, with bilateral panthalamic infarcts. Memory deficits, behavioral problems, or executive deficits may persist.[263,280]

Aphasia, in general of the fluent type, results from left lateral sinus thrombosis with temporal infarct or hemorrhage. Recovery is usually favorable, but minor troubles in spontaneous speech and naming might persist.

Risk Factors for Long-Term Poor Outcomes

Risk factors for poor long-term prognosis in the ISCVT cohort were central nervous system infection, any malignancy, thrombosis of the deep venous system, intracranial hemorrhage on admission CT/MRI, Glasgow Coma Scale score <9, mental status disturbance, age >37 years, and male sex.[55] Brain herniation leading to early death was more frequent in young patients, whereas late deaths due to malignancies and less favorable functional outcome were more frequent in elderly patients.[6,10,89] Table 6 summarizes demographic, imaging, and clinical variables associated with poor prognosis.[281,282] A Glasgow Coma Scale score of 14 to 15 on admission, a complete or partial intracranial hypertension syndrome (including isolated headache) as the only

manifestation of CVT, and absence of aphasia were variables associated with a favorable outcome.[117,177]

Risk Score Models

Despite the overall favorable outcome, ≈15% of CVT patients die or become dependent after CVT.[10,283] Risk stratification scores might improve the ability to inform CVT patients of their individual prognosis and to select those who might benefit most from intensive monitoring and invasive treatments. One study created and validated a risk score model to predict a poor outcome. The risk score model range from 0 (lowest risk) to 9 (highest risk), and a cutoff of ≥3 points indicated a higher risk of death or dependency at 6 months. Two points were assigned for the presence of malignancy, coma, or thrombosis of the deep venous system and 1 point for male sex, presence of decreased level of consciousness, or ICH. The predictive ability (c-statistics) in the derivation cohort was 85.4%, 84.4%, and 90.1% in the validation samples. Sensitivity and specificity in the combined samples were 96.1% and 13.6%, respectively.

Another study[284] incorporated age >37 years and central nervous system infection into this model and assigned a weighted index to each variable. The study validated the score in 90 CVT patients and obtained an area under the receiver operator characteristic curve of 0.81 to predict mortality. With a cutoff score of ≥14, sensitivity was 88% and specificity was 70%. The predictive value for good outcome, defined as an mRS score <2, was 95%, and for bad outcome, it was 39%.

Recanalization

In a systematic review of 5 small studies,[28] recanalization rates of CVT at 3 months and 1 year of follow-up were 84% and 85%, respectively. The highest rates of recanalization are observed in deep cerebral veins and cavernous sinus thrombosis and the lowest rates in lateral sinus thrombosis.[193] In adults, recanalization of the occluded sinus is not related to outcome after CVT.[41,194]

Summary/Future Considerations

This statement provides an extensive and critical review of the literature related to the diagnosis and management of CVT and its most common complications.

A dural sinus or cerebral venous thrombosis (CVT) accounts for 0.5% to 1% of all strokes, mostly affecting young individuals and women of childbearing age.[1,4,6] Patients with CVT commonly present with headache, although some develop a focal neurological deficit, decreased level of consciousness, seizures, or intracranial hypertension without focal neurological signs.[1,4,6] Uncommonly, an insidious onset may create a diagnostic challenge. A prothrombotic factor or a direct cause is identified in approximately two thirds of patients with sinus thrombosis. The diagnosis is usually made by venographic studies with CT (CTV) or MRI (MRV) to demonstrate obstruction of the venous sinuses or cerebral veins by thrombus.[70,96] Management of CVT includes treatment of the underlying condition; symptomatic treatment; the prevention or treatment of complications of increased intracranial pressure, ICH, or venous infarction; and typically, anticoagulation therapy (see algorithm in Figure 4).

Diagnostic and therapeutic techniques in stroke are in continuous evolution. Important advances have been made in the understanding of the pathophysiology of cerebral sinus thrombosis. Yet promising techniques (endovascular procedures, hemicraniectomy for the management of refractory intracranial hypertension in the context of mass effect or ICH, etc) need to be evaluated rigorously before they are widely adopted.

Despite substantial progress in the study of CVT in recent years, much of the literature remains descriptive. The CVT writing group made an effort to highlight areas that require further study (eg, larger randomized clinical trials to determine the benefit of therapeutic interventions) and provided suggestions that reflect the current standard practice. A randomized clinical trial aimed at comparing the benefit of anticoagulation therapy versus endovascular thrombolysis (TO-ACT Trial; Thrombolysis Or Anticoagulation for Cerebral Venous Thrombosis) is under way. The results of TO-ACT may contribute to improving the acute management of patients with CVT.

Management dilemmas in CVT can be complex. Healthcare providers managing these patients may require assistance from appropriate subspecialists given that there is no strong literature evidence to guide some of these challenging clinical decisions. The present statement is unlikely to end the debate about the management of CVT. Rather, the content of the present statement should be seen as a compilation of the best available evidence at the present time. Through a process of innovative research and systematic evaluation, diagnosis, management, and therapeutic alternatives will continue to evolve and consequently lead to better outcomes for patients with CVT.

Appendix

Search Strategy

To address the diagnosis and management of CVT, we systematically searched in PubMed on the following terms: "cerebral vein thrombosis" OR "cerebral venous thrombosis" OR "sinus thrombosis." Then, we refined our search by combining these with "epidemiology," "management," "diagnosis," "imaging," "MRI, "randomized trial," "prognosis," and "outcome." These terms were searched with regard to adults, pregnant women, children, and neonates. Our last search was undertaken on July 7, 2010. No language restriction was placed on the searches. Because the intention was to guide readers on the management of CVT based on a comprehensive review of the literature, including sometimes specific and/or uncommon clinical situations, no formal restrictions or further quality assessment was undertaken.

For the treatment section, we reviewed systematic reviews and guideline statements of the Cochrane Collaboration,[161] the AHA/American Stroke Association,[285] the American College of Chest Physicians,[162,163] and the European Federation of Neurological Sciences,[164] in addition to literature reviews and treatment guidelines. For specific therapeutic alternatives, we combined ("cerebral vein thrombosis" OR "cerebral venous thrombosis" OR "sinus thrombosis") with "hemicraniectomy," "thrombolysis," or "endovascular." Secondary sources of data included reference lists of articles reviewed and cohort studies that related treatment to outcomes.

Authors assigned to each section were responsible for checking for additional references for their specific topic.

For the section on "CVT in the Pediatric Population," we also reviewed the guideline statements of the AHA[267] and the "American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)" on antithrombotic therapy in neonates and children.[269] For the section on "CVT During Pregnancy," we also reviewed the guideline statements from the American College of Chest Physicians.[241a]

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*Modest.

†Significant.

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*Modest.

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