CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Cerebral Venous Thrombosis

7th Edition, 2024

Cerebral Venous Thrombosis Scientific Writing Group:

Leadership: Thalia S. Field (Co-Chair), Jennifer Mandzia (Co-Chair), Patrice Lindsay (Senior Editor), Rebecca Lund (Project Lead), Theodore Wein (Senior Advisor), Chelsy Martin (Project Lead), Anita Mountain (Advisory Co-Chair), Eric E. Smith (Advisory Co-Chair)

Members: Derek B. Debicki, Johnathon Gorman, Manraj KS Heran, Leonard A. Levin, Mahendranath Moharir, Lissa Peeling, Kanjana S. Perera, Deborah Siegal, Steve Verreault, Norine Foley, *on behalf of the Canadian Stroke Best Practice Recommendations Advisory Committee, in collaboration with the Canadian Stroke Consortium.*

Cerebral Venous Thrombosis (CVT), 7th Edition 2024

TABLE OF CONTENTS

INTRODUCTION AND OVERVIEW

Introduction to the Canadian Stroke Best Practice Recommendations

The Canadian Stroke Best Practice Recommendations (CSBPR) provide up-to-date, evidence-based guidelines for the prevention and management of stroke, to promote optimal recovery and reintegration for individuals with stroke and support their families and informal caregivers. The CSBPR are under the leadership of the Heart and Stroke Foundation of Canada (HSF).

The theme of the 7th Edition of the CSBPR is **building connections to optimize individual outcomes**. Individuals with stroke often present to the healthcare system with multiple comorbid conditions – some of which may have contributed to their stroke, some of which may be consequences of it, and some of which may be unrelated. Nelson et al. found that approximately 80% of individuals who survive a stroke have on average five other conditions and a range of psychosocial issues (Nelson et al. 2016). The interactions among complex comorbid conditions must be considered to ensure treatment and ongoing care planning is personalized and person-centred.

The healthcare system is often designed in siloes, with planning and organization for different conditions being done separately rather than being integrated across conditions, even related vascular conditions. As individuals move through different settings and phases of care after a stroke, they often report feeling anxious and overwhelmed. Providing individualized care and ensuring connections are made within the community have a significant impact on a person's short- and long-term outcomes.

The 7th Edition of the CSBPR takes a broad, wholistic focus and takes into consideration issues of multimorbidity and increasing complexity of individuals with stroke. A proportion of individuals will have CVT secondary to a separate known or unknown issue (i.e. post-partum, malignancy, other hypercoagulable state, trauma). Recognition and management of sequelae including epilepsy, vision issues, fatigue, cognitive issues and mood will also help to promote recovery and facilitate wellness after stroke.

The goal of disseminating and implementing these recommendations is to optimize evidence-based stroke care across Canada, reduce practice variations in the care of individuals with stroke, and narrow the gap between current knowledge and clinical practice.

These recommendations have been developed in collaboration with the Canadian Stroke Consortium. We work closely with the Canadian Cardiovascular Society, Thrombosis Canada, and Hypertension Canada to ensure alignment of recommendations across guidelines where possible and appropriate.

Disclaimer: The Canadian Stroke Best Practice Recommendations (CSBPR) are designed to support implementation of best practices in stroke care across Canada. Healthcare systems, health organizations and professional organizations, as well as legislation and standards, vary provincially. The CSBPR provide guidance on a national level; they do not, overall, account for provincial variations in legislation or standards. The CSBPR are not intended to supersede any provincial or local law or organizational or professional standard. In considering and implementing the CSBPR, users are encouraged to consult and follow all appropriate legislation or standards.

Scope of the Cerebral Venous Thrombosis Module

The CSBPR **Cerebral Venous Thrombosis** module provides guidance to healthcare providers caring for adult individuals who present to the healthcare system with current or recent symptoms of cerebral venous thrombosis. This module addresses management and care of individuals with CVT across the continuum of care starting with first presentation to the healthcare system.

Definitions and Descriptions

Cerebral Venous Thrombosis (CVT): Thrombosis of the veins of the brain, including the dural venous sinuses and/or cortical or deep veins.

Individuals with CVT may present with neurological deficits due to increased intracranial pressure with or without mass effect, from parenchymal venous congestion, intracranial hemorrhage, or some combination. In the mildest circumstance, individuals with CVT may present with headache only. Compared with ischemic stroke and primary intracerebral hemorrhage, CVT is a less common cerebrovascular disorder, accounting for <1% of all stroke syndromes.

Acute Stroke: An episode of symptomatic neurological dysfunction caused by focal brain, retinal or spinal cord ischemia or hemorrhage, and regardless of symptomatic duration. In general, "stroke" is a clinical term that refers to persistent neurological deficits due to a cerebrovascular cause that could be arterial or venous. Although stroke is commonly associated with changes on imaging, such as infarction or hemorrhage in the brain, sometimes individuals may have persistent symptoms in the absence of imaging findings. CVT may not always be associated with focal deficits in that some individuals may only have symptoms in keeping with increased intracranial pressure, such as headache, nausea/vomiting or visual changes. Thus, the distinction between not having versus having a "stroke" from CVT can be somewhat arbitrary.

Venous Thromboembolism (VTE): VTE is a general term that refers to thrombosis (commonly called blood clots) in the veins. Common VTE types include deep vein thrombosis (DVT - thrombosis of the deep veins in the leg or arm), or pulmonary embolism (PE – a thrombus that begins elsewhere [typically as a DVT] and embolizes, lodging in one or more of the arteries of the lung). CVT is a type of VTE affecting veins in the brain.

Etiology: Risk factors for CVT can be classified as ***transient*** (e.g. oral contraceptive use, puerperium, infection) or ***persistent*** (e.g. active cancer, inherited/acquired thrombophilia). An event without any apparent identified transient or persistent precipitant is referred to as ***"unprovoked;*** also referred to in the literature as "idiopathic" (Kearon et al. 2016). *Common risk factors associated with CVT, both transient (e.g. oral contraceptive use, puerperium, infection) and persistent (e.g. active cancer, inherited/acquired thrombophilia) are listed in Figure 1.*

Guideline Development Methodology

The CSBPR present high-quality, evidence-based stroke care guidelines in a standardized framework. As healthcare providers across all disciplines implement these recommendations, it is expected that practice variations will be reduced and gaps between evidence and practice will start to close, leading to improved outcomes for individuals with stroke.

The Cerebral Venous Thrombosis module is a new addition to the CSBPR suite of recommendations. The methodology used to develop this module has followed our thorough and rigorous process. *Refer to CSBPR Overview of Methodology for additional detail.* Key steps in our development process have included:

1. Establish an expert interprofessional writing group representing relevant disciplines across the continuum of care and a range of settings and striving for balance regarding gender and overall diversity*. Refer to Appendix One for a list of writing group members and affiliations.*
2. Consult with the Cerebral Venous Thrombosis Community Consultation and Review Panels, comprising individuals with cerebral venous thrombosis, informal caregivers, and family members.

3. Select clinical questions to address in the module using the population/problem, intervention or exposure, comparison, and outcome (PICO) format, where appropriate and applicable.
4. Conduct a systematic search and appraisal of research literature to December 2023, and update evidence summary. Refer to the assigning evidence levels section of this module for more information on the GRADE approach.
5. Conduct a systematic search and appraisal of external reference guideline recommendations.
6. Scientific writing group and the community consultation panels develop, review and finalize a set of recommendations, address clinical questions, review and discuss benefits, risks, and harms of proposed recommendations, and adhere to the elements of the Agree 2 criteria where appropriate (Brouwers et al. 2010). This includes consideration of individual values and preferences, informed by the community consultation panels and available evidence.
7. Scientific Writing Group rates the strength of the recommendations and the quality of evidence following GRADE criteria (Guyatt et al. 2011; Guyatt et al. 2008a; Guyatt et al. 2008b).
8. Review of the proposed module by the Canadian Stroke Best Practices Advisory Committee, and incorporation of edits as required, with further consideration of benefits, risks, and harms.
9. Review of the proposed module by external leading experts in Canada and internationally, and incorporation of edits as required. *Refer to Appendix Two for a list of External expert reviewers*
10. Obtain final approval and endorsement and undertake French translation.
11. Update educational materials and implementation resources.
12. Disseminate through publication and public release knowledge translation activities.
13. Continue with ongoing review and update process.

More detail for each of these steps is available in the CSBPR *Overview, Methods and Knowledge Translation* manual on the Canadian Stroke Best Practices website. www.strokebestpractices.ca

Assigning Evidence Levels

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and terminology has been applied throughout these guidelines. With GRADE, each recommendation was assessed for:

1. The **strength of the guidance** (strong or conditional), based on the balance of desirable and undesirable consequences, quality of evidence, values and preferences of those affected, and resource use.
    - A strong recommendation is one for which the guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects.
    - A conditional recommendation is one for which the guideline panel finds that the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists.

    and
2. The **quality of the evidence** (high, moderate, low) upon which the recommendations are formulated: risk of bias, directness of evidence, consistency and precision of results, risk of publication bias, magnitude of the effect, dose-response gradient, and influence of residual plausible confounding (Guyatt et al. 2008a).

The writing group was provided with comprehensive evidence tables that included summaries of high-quality evidence identified through the structured literature searches. The group discussed and debated the quality of the evidence and through consensus developed a final set of proposed recommendations.

Each recommendation was assigned a rating as to the strength of the recommendation and the quality of the evidence. Where appropriate and feasible, full GRADE review and analysis using relevant GRADE tables has been conducted.

Clinical Considerations

The CSBPR uses the additional category of clinical considerations, consisting of expert opinion statements. These are included when it is determined that guidance related to common clinical issues would be helpful, but the topic lacked sufficient evidence to form an actual recommendation.

Conflicts of Interest

All potential participants in the recommendation development and review process are required to complete confidentiality agreements and declare all actual and potential conflicts of interest prior to participation. Declared conflicts of interest are reviewed by the co-chairs of the CSBPR Advisory Committee and Heart & Stroke staff to assess the potential impact. Those with significant conflicts with respect to the module topic are not selected for writing group or reviewer roles.

Participants who have conflicts for a particular topic area are identified at the beginning of discussions for that topic and are recused from voting. If a co-chair is in conflict, they are recused from their responsibilities for that discussion and another non-conflicted participant assumes the role for that discussion and vote. Heart & Stroke senior staff members participate in all writing group discussions and intervene if they perceive an untoward bias by a writing group member.

Conflict of interest declarations for the Cerebral Venous Thrombosis module writing group members can be found in Appendix One.

Acknowledgements

Heart & Stroke gratefully acknowledges the Cerebral Venous Thrombosis writing group leaders and members, all of whom have volunteered their time and expertise to develop these new recommendations. Members of the Canadian Stroke Consortium were involved in all aspects of the development of these recommendations. These recommendations (in whole or specific parts) underwent external review by Diana Aguiar de Sousa, Lana Castellucci, Luciana Catanese, Johnathon Coutinho, Laura Gioia, Brett Graham, Sherry Hu, Sylvain Lanthier, Neshika Samarasekera, Arturo Tamayo, and Katie White.

We thank the Canadian Stroke Best Practices and Quality Advisory Committee members: Eric E. Smith (Co-Chair), Anita Mountain (Co-Chair), Gord Gubitz, Dar Dowlatshahi, Dylan Blacquiere, Margie Burns, Thalia S. Field, Farrell Leibovitch, Christine Papoushek, Jeffrey Habert, Joyce Fung, Michael D Hill, Eddy Lang, Pascale Lavoie, Beth Linkewich, Colleen O'Connell, Jai Shankar, Debbie Timpson, Theodore Wein, and Katie White. The performance measures were reviewed and updated by the Heart & Stroke health systems quality council including Amy Yu (Chair), Michael D Hill, Aravind Ganesh, Sacha Arsenault, Christine Hawkes, Raed Joundi, Laura Gioia, Noreen Kamal, Shannon MacDonald, Katharine Mckeen, Kathryn Yearwood, Leigh Botly, and Laura Holder.

We acknowledge and thank Norine Foley and the evidence analysis team at workHORSE; Laurie Charest of Heart & Stroke for her coordination of the CSBPR teams and processes; and Francine Forget Marin and the Heart & Stroke internal teams who contributed to the development and publication of these recommendations (Translation, Communications, Knowledge Translation, Engagement, Health Policy, and Digital Solutions).

Community Consultation and Review Panel

Heart & Stroke is especially grateful to the members of the Cerebral Venous Thrombosis Community Consultation and Review Panel who worked in tandem with the scientific writing group for this module and shared their personal experiences and insights on living with cerebral venous thrombosis and

optimizing recovery and health outcomes. CCRP members include Annette Greenwood, Estee Polnau, and Aviva Rappaport.

Funding

The development of the CSBPR is funded by Heart & Stroke. No funds for the development of these recommendations are received from commercial interests, including pharmaceutical and device companies. Scientific writing group members and external reviewers are volunteers who do not receive any remuneration for their participation.

Citing the Cerebral Venous Thrombosis 7th Edition, 2024

Thalia S. Field (Co-Chair), Jennifer Mandzia (Co-Chair), M. Patrice Lindsay (Corresponding Author), Theodore Wein (Senior Advisor), Rebecca Lund, Chelsy Martin, Deborah Siegal, Derek B. Debicki, Johnathon Gorman, Leonard A. Levin, Mahendranath Moharir, Lissa Peeling, Kanjana S. Perera, Steve Verreault, Norine Foley, Anita Mountain and Eric E. Smith; on Behalf of the Canadian Stroke Best Practice Recommendations Advisory Committee, in collaboration with the Canadian Stroke Consortium. *Canadian Stroke Best Practice Recommendations: Cerebral Venous Thrombosis, 7th Edition, 2024;* Toronto, Ontario, Canada: Heart and Stroke Foundation. In M. Patrice Lindsay, Anita Mountain, Rebecca Lund, Chelsy Martin, Theodore Wein, and Eric E. Smith (Editors), on behalf of the Canadian Stroke Best Practices and Advisory Committee in collaboration with the Canadian Stroke Consortium. *Canadian Stroke Best Practice Recommendations, 7th edition, 2024*; Toronto, Ontario, Canada: Heart and Stroke Foundation of Canada.

The recommendations in this module are also published in the Canadian Journal of Neurological Sciences.

Field TS, Lindsay MP, Wein T, Debicki DB, Gorman J, Heran MK, et al. Canadian Stroke Best Practice Recommendations, 7th Edition: Cerebral Venous Thrombosis, 2024. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 2024;1–57. doi:10.1017/cjn.2024.269

English link: https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/canadian-stroke-best-practice-recommendations-7th-edition-cerebral-venous-thrombosis-2024/7CBC520E3EA55FE604E692D340D31CE1

French link: https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/canadian-stroke-best-practice-recommendations-7th-edition-cerebral-venous-thrombosis-2024/7CBC520E3EA55FE604E692D340D31CE1

Comments

The Heart and Stroke Foundation of Canada's stroke team invites your comments, suggestions, and inquiries about the development and application of the CSBPR at strokebestpractices@heartandstroke.ca.

CEREBRAL VENOUS THROMBOSIS RECOMMENDATIONS 2024

Section 1 Diagnosis and Initial Clinical Assessment of Symptomatic Cerebral Venous Thrombosis (CVT)

1. Diagnosis and Initial Clinical Assessment of Symptomatic Cerebral Venous Thrombosis, Recommendations 2024

1.0 Clinical Presentation

i. Awareness of CVT as a possible differential diagnosis is an important part of maintaining an appropriate index of clinical suspicion. Front-line physicians and other healthcare professionals should receive education related to the clinical presentation and diagnosis of this condition [Strong recommendation; Low quality of evidence].

ii. In considering a diagnosis of CVT, healthcare professionals should consider both the individual's symptoms and CVT risk factors [Strong recommendation; Moderate quality of evidence].

Refer to Table 1 – Common Clinical Features at the Time of Presentation with CVT

Refer to Figure 1 – Patient Characteristics, Risk Factors, and Conditions Associated with Cerebral Venous Thrombosis

1.1 Initial Clinical Assessment of Symptomatic CVT

i. Symptomatic CVT is a medical emergency. Individuals with confirmed or suspected CVT should receive urgent and appropriate neuroimaging and clinical evaluation [Strong recommendation; Low quality of evidence]. *Refer to Section 1.2 for more information on imaging.*

ii. Individuals with confirmed or suspected CVT should be assessed for ongoing clinical stability (airway, breathing, circulation), active seizures, and increased intracranial pressure including fundoscopy [Strong recommendation; Moderate quality of evidence].

1.2 Diagnosis of CVT and Other Investigations

1.2.1 Imaging Recommendations

i. Individuals with a suspected diagnosis of CVT should receive both parenchymal and neurovascular imaging (non-contrast CT and CT venography or MRI brain and MR venography as described in 1.2.1.ii) immediately following clinical stabilization to confirm diagnosis [Strong recommendation; Moderate quality of evidence].

ii. Individuals with a suspected diagnosis of CVT should undergo either contrast-enhanced CT venography or contrast-enhanced MR venography for diagnosis of CVT [Strong recommendation; Moderate quality of evidence].

   a. Isolated non-contrast CT head is not recommended as it is not sufficient to rule in or rule out a diagnosis of CVT [Strong recommendation; Moderate quality of evidence].

iii. Contrast-enhanced MR venography is recommended over time-of-flight MR venography due to the possibility of false positive diagnoses as a result of flow-related artefacts [Strong recommendation; Moderate quality of evidence].

   a. Time-of-flight MR venography without contrast is not recommended as it is insufficiently sensitive for the diagnosis of cortical vein thrombosis [Strong recommendation; Moderate quality of evidence].

b. For individuals with a suspected diagnosis of isolated cortical vein thrombosis not confirmed with first-line imaging, additional imaging with MRI gradient echo or susceptibility-weighted imaging is recommended [Strong recommendation, Moderate quality of evidence].

1.2.2 Other Investigations

i. D-dimer measurement has limited diagnostic utility for the assessment of individuals with suspected CVT due to insufficient sensitivity to exclude cases where pre-test probability of a CVT diagnosis is lower. Using the results of D-dimer testing to determine whether neuroimaging should be performed in individuals with suspected CVT is not recommended [Strong recommendation; Moderate quality of evidence].

ii. Routine lumbar puncture is not recommended for the diagnosis of CVT [Strong recommendation; Very low quality of evidence].

iii. The following laboratory investigations should be routinely considered in individuals with CVT as part of the *initial* evaluation: hematology (complete blood count), electrolytes, coagulation (aPTT, INR), renal function (creatinine, estimate glomerular filtration rate), random glucose, ALT, TSH, and beta hCG pregnancy test in individuals able to become pregnant [Strong recommendation; Low quality of evidence].

Section 1.2 Clinical Considerations

1. Symptomatic CVT can be challenging to diagnose in the absence of appropriate clinical suspicion, and without appropriate neurovascular imaging. *Refer to Summary of the Evidence and Table 1 for additional information on diagnosis of CVT. Refer to Section 3.1 for additional laboratory tests related to hypercoagulability workup and recommended timing.*

   Refer to Appendix Three for other laboratory tests which may be considered in specific circumstances, depending on clinical presentation and risk profile.

   Refer to Appendix Four for Antiphospholipid Antibody Testing in CVT flowsheet.

Rationale

Cerebral venous thrombosis (CVT) is a rare but potentially life-threatening type of stroke, representing 0.5–1.0% of all stroke admissions (Bousser and Ferro 2007). The reported rates of CVT vary from 8.7 (Zhou et al. 2023) to 20.3 per million,(Otite et al. 2020) and appear to be increasing over time. The risk of CVT is higher in women, where it is often associated with pregnancy and the puerperium, and with oral contraceptive use (Amoozegar et al. 2015). Other non-genetic factors associated with an increased risk of CVT include antiphospholipid antibodies (7.0-fold increase), autoimmune diseases (5.6-fold increase), anemia (4.0-fold increase) and malignancy (3.2-fold increase) (Green et al. 2018). The most common genetic factors associated with CVT are prothrombotic conditions, such as the presence of factor V Leiden and protein C deficiency (Green et al. 2018). Diagnosis of CVT is frequently delayed in part because it can mimic other acute neurological conditions (Bakradze et al. 2023).

Individuals with lived experience emphasized the importance of recognizing the common presenting signs and symptoms of CVT, as their experience mostly differed from typical presentations of stroke. It is important to readily recognize CVT signs and symptom so that diagnosis is not delayed. Their experiences highlighted the challenge of CVT diagnosis; in some cases, many tests were performed prior to their diagnosis to rule out other causes. People with lived experience also emphasized the importance of imaging in the diagnosis of CVT.

System Implications

To ensure that people who experience CVT receive timely stroke assessments, interventions and management, interdisciplinary teams need to have the education, infrastructure and resources required. These may include the following components established at a systems level.

1. Government funding and support for awareness initiatives to improve the recognition and recall of the signs of CVT, which may present differently from other types of strokes, as well as more typical stroke presentations (e.g., FAST, which is a global best practice) and the importance of contacting 9-1-1 immediately. Awareness and education campaigns should prioritize reaching communities who are less aware of the signs of stroke and most at risk of stroke and should be informed collaboratively through community engagement activities with those audiences.
2. Enhanced collaboration among community organizations and healthcare professionals to ensure consistency in public education of the signs of stroke with a strong emphasis on the urgency of responding when the signs of stroke are recognized. Specific information related to other forms of stroke including CVT should be included as part of awareness and education efforts.
3. Training and education for EMS, emergency department and all in-hospital staff, medical and nursing students, physicians in primary and acute care as well as specialists, nurses, and allied health professionals to increase their ability to recognize potential individuals with stroke, including CVT, and provide rapid assessment and management.
4. Comprehensive systems in place to ensure all people in Canada have access to timely and appropriate emergency medical services, including ambulatory services (e.g., outpatient services, emergency department, community health centres, nursing stations) without financial burden, and quality stroke care regardless of geographic location.
5. Enhanced monitoring and awareness of stroke among all people in Canada. Healthcare systems and provincial/territorial and federal governments should generate linked health and social surveillance population-based and regional data and use it to drive quality improvement through better understanding of the health and social issues facing people in Canada.

Performance Measures

System Indicators:

1. Numbers of individuals presenting to the emergency department ED who receive a diagnosis of CVT.
2. Number of individuals with CVT who are admitted to hospital annually.
3. Number of individuals admitted with an alternate primary diagnosis who are subsequently diagnosed with CVT during their hospital stay (e.g. head trauma with late onset CVT, neurosurgical procedure with post-op CVT, etc.).
4. Number of individuals diagnosed with CVT who receive vascular imaging (CTV or MRV) at time of diagnosis.

Process Indicators:

5. Timing from presentation to medical attention to diagnosis.
6. Timing from first presentation to medical attention and implementation of definitive therapy (eg. antithrombotic therapy, typically with full anticoagulation).
7. Number of presentations to medical attention prior to diagnosis.

Patient-oriented outcome and experience indicators:

8. Mortality rate from CVT at 30 days and one year following diagnosis.

9. Changes in quality of life index measure at 30 days, one year and 5 years following diagnosis with CVT.

Measurement Notes

a. For indicator 9, standardized quality of life measurement tools should be used, and the same measure used over time.

Implementation Resources and Knowledge Transfer Tools

Resources and tools listed below that are external to Heart & Stroke and the Canadian Stroke Best Practice Recommendations may be useful resources for stroke care. However, their inclusion is not an actual or implied endorsement by the Canadian Stroke Best Practices team or Heart & Stroke. The reader is encouraged to review these resources and tools critically and implement them into practice at their discretion.

Healthcare Provider Information

- CSBPR Cerebral Venous Thrombosis Module: Table 1 Common Clinical Features at the Time of Presentation with CVT
- CSBPR Cerebral Venous Thrombosis Module: Figure 1 Patient Characteristics, Risk Factors, and Conditions Associated with Cerebral Venous Thrombosis
- CSBPR Cerebral Venous Thrombosis Module: Appendix Three: Recommended Laboratory Investigations for Individuals with Cerebral Venous Thrombosis
- CSBPR Cerebral Venous Thrombosis Module: Appendix Four: Antiphospholipid Antibody Testing Flowsheet
- Heart & Stroke: Signs of Stroke: https://www.heartandstroke.ca/stroke/signs-of-stroke; https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Stroke Engine: https://strokengine.ca/
- CVT Consortium: https://cerebralvenousthrombosis.com/professionals/

Information for Individuals with Lived Experience of Stroke, Including Family, Friends and Caregivers

- Heart & Stroke: Cerebral Venous Thrombosis Infographic
- CVT Consortium: https://cerebralvenousthrombosis.com/patients/patient-information-in-english/
- Heart & Stroke: Signs of Stroke: https://www.heartandstroke.ca/stroke/signs-of-stroke
- Heart & Stroke: FAST Signs of Stroke... what are the other signs?: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: What is Stroke? https://www.heartandstroke.ca/stroke/what-is-stroke
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/pdf-files/canada/your-stroke-journey/en-your-stroke-journey-v20.pdf
- Heart & Stroke: A Family Guide to Pediatric Stroke: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/a-family-guide-to-pediatric-stroke-en.pdf?rev=ff206495b5a4479da4b1a1d7b54c7734
- Heart & Stroke: Stroke in Young Adults: A Resource for Patients and Families: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/stroke_young_final.pdf?rev=7338abd3dba746dc96180a057e244ce9
- Heart & Stroke: Online and Peer Support: https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Stroke Engine: https://strokengine.ca/

Summary of the Evidence

Cerebral venous thrombosis is distinct from other stroke types. It is relatively uncommon within the general population, presenting symptoms can be gradual and non-focal, and it most commonly affects younger individuals, particularly women (Coutinho et al. 2012; Duman et al. 2017; Ferro et al. 2004; Yaghi et al. 2022b). This combination of factors makes it critical for front-line clinicians to be aware of the disease and its presenting symptoms and risk factors. In general, both younger adults and women with stroke are at increased risk for initial misdiagnosis and/or diagnostic delay, which is common in CVT (Newman-Toker et al. 2014; Yu et al. 2021). With respect to CVT specifically, one retrospective study found that of 53 individuals with CVT, 20.8% had experienced an initial error in diagnosis (Liberman et al. 2019). Another retrospective study using a combination of administrative claims data from the United States and single-centre chart review found that of 5966 individuals with a diagnosis of CVT, 3.6% had been seen in the emergency room in the 14 days prior to diagnosis and discharged with a diagnosis of headache or seizure. Those who were seen and sent home from the emergency department were younger (mean age 38.5 years) than in the remainder of the cohort (44.4 years) (Liberman et al. 2018). Non-focal presentations, such as isolated symptoms and signs of intracranial hypertension, are associated with longer times (>10 days) from symptom onset to diagnosis (Bakradze et al. 2023; Ferro et al. 2009).

Incidence of CVT is approximately 10-20 per million in the general population, (Zhou et al. 2023) although the incidence of CVT in association with pregnancy, approximately 9/100,000, is similar to that of pregnancy-associated ischemic stroke and intracerebral hemorrhage (Swartz et al. 2017). Many population-based series have reported increased incidence of CVT over time (Devasagayam et al. 2016; Otite et al. 2020; Zhou et al. 2023). A recent US-based health services study found increasing rates between 2005 and 2017 in men and older individuals, with stable rates in younger women. There were also increased rates over time of comorbidity codes for malignancy, trauma and inflammatory disease alongside those for CVT (Otite et al. 2020). Thus, increased rates might be due to improved overall ascertainment with more frequent use of vascular neuroimaging, better survival of medically complex individuals who go on to develop CVT, and/or better ascertainment in medically complex individuals.

Sex-specific risk factors for CVT are discussed in detail below (See *Sex, gender and other equity-related considerations*). Risk factors are summarized in Figure 1 and have been explored in detail in a recent meta-analysis of genetic and non-genetic risk factors (Green et al. 2018). A recent large prospective cohort study found that adults with an identified risk factor had an earlier age of onset of CVT than those without (Ranjan et al. 2023). Malignancy in particular was associated with older age of onset of CVT.

The limited available literature examining cancer types associated with CVT specifically include a high representation of some hematologic malignancies (specifically acute lymphoblastic leukemia (ALL), Janus-Kinase-2 (V617F) mutation-associated myeloproliferative neoplasms and Waldenstrom's macroglobulinemia) and some solid organ cancers, including breast, gastrointestinal, lung and CNS cancers (Silvis et al. 2018). Some therapies, such as L-asparaginase for ALL, and steroids, are also known risk factors for CVT. Head and neck infection is a well-established risk factor for CVT; COVID-19 infection has been associated with increased risk of CVT in both community- and hospital-based series (McCullough-Hicks et al. 2022; Taquet et al. 2021). CVT, with and without other venous and arterial thromboembolic events, was a common presentation of Vaccine-induced thrombosis with thrombocytopenia (VITT), a rare (1/26500 to 1/1273000) autoimmune reaction to non-replicant adenovirus vector-based COVID-19 vaccines (ChAdOx1, AstraZeneca/COVISHIELD and Ad26COV2.S, Janssen, Johnson & Johnson) characterized by anti-platelet factor-4 antibodies (Klok et al. 2022).

Presenting symptoms of CVT may also differ from those of arterial strokes. The onset of symptoms is generally more insidious. Overall, in multiple recent large series, less than half of patients present within 48 hours of symptom onset, although more acute presentations can occur with thunderclap headache or stroke-like sudden focal symptom onset in addition to seizures (Duman et al. 2017; Lindgren et al. 2022; Yaghi et al. 2022b). Symptoms may result from increased intracranial pressure, focal parenchymal injury, and/or mass effect. Headache is the most common symptom, reported in approximately 90%, although it may be a less common presenting features in older individuals presenting with CVT (Coutinho et al. 2015). The exact prevalence varies depending on cohort, although the other most common presenting symptoms include focal deficits, seizures, vision loss, encephalopathy or depressed

level of consciousness or cranial neuropathies. (Table 1) Headache types, onset patterns and locations at presentation are variable. One series of 200 consecutive patients with CVT found that headache at presentation was not associated with neuroimaging evidence of hemorrhage or hydrocephalus. There was no association between lateralization of pain and site of thrombosis, and none between thrombus location and headache apart from occipital and neck pain association with transverse and/or sigmoid involvement (Wasay et al. 2010). Characteristic symptoms of headaches due to increased intracranial pressure (ICP), which is associated with papilledema on fundoscopic examination, may include supine or nocturnal headache, associated nausea and/or vomiting, and blurred vision, transient visual obscurations, and/or diplopia.

Several small studies and meta-analyses have examined diagnostic imaging modalities for CVT. Large high-quality studies comparing diagnostic imaging modalities for CVT, particularly current ones comparing contemporary contrast-enhanced CT venography (CTV) and/or contrast-enhanced MRI venography (MRV) against gold-standard digital subtraction angiography, are lacking. A 2020 critical review of English and Dutch neuroimaging studies examining performance of CT/CT venography and MRI for the diagnosis of CVT concluded that studies were observational, mostly small, outdated and with a high risk of bias (van Dam et al. 2020). The accuracy of parenchymal CT and MRI in the differential diagnosis of cerebral venous thrombosis and cerebral venous sinus thrombosis (i.e. CVT with sinus involvement only) was examined in a systematic review using any of MR venography, CT venography, or digital subtraction angiography (DSA) as the standard reference (Xu et al. 2018). Among 2,822 cases, the pooled sensitivity and specificity for the identification of CVT using CT was 0.79 (95% CI 0.76- 0.82), and 0.90 (95% CI 0.89- 0.91), respectively. The corresponding values for the use of MRI were 0.82 (95% CI 0.78- 0.85) and 0.92 (95% CI 0.91-0.94) (Xu et al. 2018). The 2020 critical review found that, using DSA as the reference standard, small observational studies comparing CT venography to DSA have reported sensitivity and specificity of both 100% (van Dam et al. 2020). Other small studies using other imaging modalities and final clinical outcome as reference standard have demonstrated a sensitivity of 100% (95% CI 88-100%) and specificity of 100% (95-100%) for cases of sinus thrombosis, but lower sensitivity for cortical vein thrombosis. Non-contrast-enhanced time-of-flight (TOF) MR venography, compared with digital subtraction angiography also was not sensitive in the assessment of small veins but accurate for larger veins and sinuses. When compared against contrast-enhanced MRI, TOF MRV and non-contrast phase contrast (PC) MRV had a sensitivity of 64-100% and 48-100%, respectively, with wide confidence intervals, and lower accuracy for identifying cortical vein thrombosis (van Dam et al. 2020). Studies comparing contrast-enhanced MRI to DSA reported sensitivities of 86-97% and specificities of 55-97% for diagnosis of CVT. MRI with gradient-echo (GRE) or susceptibility-weighted imaging (SWI) had the most consistently reported adequate sensitivity and specificity for cortical vein thrombosis (97-98% and 100%, respectively) (Altinkaya et al. 2015; Idbaih et al. 2006; Linn et al. 2010).

In summary, larger and contemporary higher-quality studies are needed. Both contrast-enhanced CTV and MRV are acceptable modalities, although additional imaging with MRI, including gradient-echo MRI, may need to be considered if isolated cortical vein thrombosis is suspected. CT venography may be more quickly performed and more easily accessible, and with fewer contraindications to MRI, while MR venography does not expose patients to ionizing radiation. However, MR contrast should be avoided in pregnancy and some patients may have additional contraindications to MR imaging, such as pacemaker or retained ferromagnetic material. Although some groups have reported alternative native-contrast thrombus imaging MRI sequences, such as black-blood thrombus imaging, with high reported diagnostic accuracy for CVT, protocols tend to be site-specific and can be lengthy (Yang et al. 2016). Given these limitations, native-contrast sequences are not recommended for routine use at this time. There is no extensive literature comparing neuroimaging approaches (e.g. time-of-flight versus contrast-enhanced MR venography) to assess venous recanalization in individuals with *known* CVT. (Section 3.2).

D-dimer has been explored as a screening tool to decide who should have neuroimaging to exclude CVT where index of suspicion for CVT might be lower, such as isolated headache. A 2012 systematic review and meta-analysis including 14 studies with 1,134 individuals evaluated for suspected CVT, 363 had a confirmed diagnosis. The weighted mean sensitivity for elevated D-dimer in those with confirmed CVT was 89.1% (95% CI 84.8–92.8). Sensitivities varied and were lower in those with longer duration of symptoms, isolated headache and thrombosis of a single venous sinus. The pooled positive and

negative likelihood ratios were 9.1 (95% CI, 6.8–12.2) and 0.07 (95% CI, 0–0.14), respectively (Dentali et al. 2012b). Another small retrospective study found that presentations with focal neurologic deficits were associated with higher D-dimer levels at baseline (Juli et al. 2020). A more recent prospective study of 359 individuals with suspected CVT, 94 of whom had a subsequent confirmed diagnosis, found the sensitivity and specificity of a D-dimer cut-off of 500 µg/L or above was 89.4% and 66.4%, respectively (Heldner et al. 2020). Thus, given that D-dimer alone cannot reliably identify almost all individuals with the disease, particularly those who may have a less classic presentation for CVT, D-dimer is not recommended at this time as a screening tool. Further studies will determine whether D-dimer in combination with other diagnostic modalities, such as non-contrast CT, might be a suitable approach in lower-resource environments.

Sex, gender and other equity-related considerations

CVT is more common in females, although the greatest disparities in incidence between males and females are in patients aged 50 years and under (Zhou et al. 2023). The most common risk factors for CVT include oral contraceptive use, pregnancy and the puerperium and hormone replacement therapy (Green et al. 2018; Silvis et al. 2016). One large prospective cohort study found that women experienced CVT 9 years earlier than men on average, and that gender-specific risk factors (pregnancy, puerperium or oral contraceptive use) were associated with earlier age of onset in women (Ranjan et al. 2023). Oral contraceptive use may increase the risk of CVT up to 8-fold, and there may possibly be a synergistic risk between oral contraceptive use and obesity (Amoozegar et al. 2015; Zuurbier et al. 2016). Although the general stroke (Bushnell et al. 2014) and venous thromboembolism (Dragoman et al. 2018; Oedingen et al. 2018) literature has compared formulations of hormonal contraceptives and has identified consistent increased risk with estrogen-containing, but not progesterone-only formulations, this has not been examined in detail in CVT specifically. The risk of pregnancy associated CVT is highest in the first six weeks post-partum (Silvis et al. 2019).

Women are at higher risk than men for misdiagnosis of stroke, and the risk may be even higher with CVT, as individuals may be younger (another risk factor for misdiagnosis) and the indolent and often non-focal onset of symptoms may be mistaken for a benign cause of headache, such as migraine, which affects approximately 20% of women (Frederick et al. 2014; Stewart et al. 1995).

There is a dearth of information related to considerations of race-ethnicity and social determinants of health in CVT. One study using US administrative data found that Black individuals had the highest risk of CVT, followed by white and Asian individuals (Otite et al. 2020). This mirrors population-based data related to peripheral VTE (i.e. DVT and PE) (Goldhaber 2014). Another recent study reported that Black race-ethnicity was associated with worse outcomes after CVT, although contributors related to health inequities, structural racism and social determinants of health as opposed to any genetic or other biological factors is not known (Goldhaber 2014; Klein et al. 2022). Data from lower- and middle-income countries, particularly from Africa and South America, is under-represented, and to date, the only genome-wide association study data is from European patients (Baduro and Ferro 2021; Ken-Dror et al. 2021; Zhou et al. 2023).

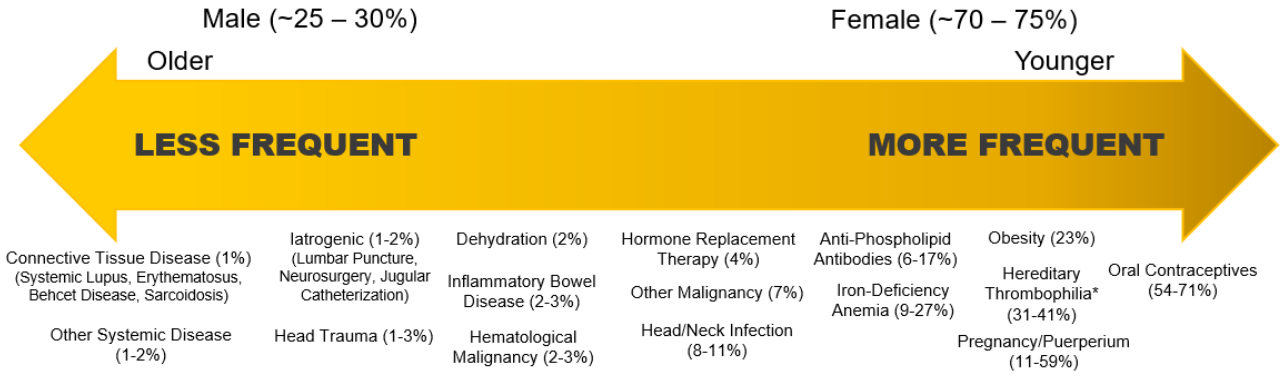
Evidence Table and Reference List: Cerebral Venous Thrombosis

TABLE 1: Common Clinical Features at The Time of Presentation With CVT^

Presenting symptom	Prevalence (%)
Headache	87-89%
Seizure	24-40%
Focal Neurologic Deficits	18-48%
Depressed Level of Consciousness/encephalopathy	18-22%
Visual Loss	13-27%
Diplopia/other cranial neuropathies	11-14%

^This table summarizes the most common presenting symptoms from participants in the two largest prospective published series of symptomatic CVT but is not an exhaustive list of all potential presenting symptoms. (Duman et al. 2017; Ferro et al. 2004; Silvis et al. 2017)

FIGURE 1: Patient Characteristics, Risk Factors, and Conditions Associated with Cerebral Venous Thrombosis^^



Patient characteristics, risk factors and associated medical conditions associated with CVT, from less frequent to more frequent.

** Hereditary Thrombophilia includes, but is not limited to, Factor V Leiden Mutation, Prothrombin Gly20210Ala mutation Antithrombin Deficiency and Hereditary Protein C/S Deficiency.*

^^ Adapted from Silvis Nature Neurology 2017 (Silvis et al. 2017). Estimates of prevalence are based on data from ISCVT (Ferro et al. 2004), VENOST study (Duman et al. 2017) and other case control studies which examined particular risk factors.

Section 2 Acute Treatment of Symptomatic Cerebral Venous Thrombosis

2. Acute Treatment of Symptomatic CVT Recommendations 2024

Notes

These recommendations refer to initial acute management of CVT. Outpatient management of CVT in the post-acute phase is discussed in Section 3.

Anticoagulation treatment: Anticoagulation management for CVT can be categorized in 3 phases: ***(1) acute management***, which is immediately around the initial diagnosis; ***(2) "primary" management***, which is the period of time when a person is treated with therapeutic anticoagulation for their initial CVT; ***(3) "secondary prevention,"*** which is any further antithrombotic therapy after the primary phase aimed at preventing VTE recurrence (ASH Guideline 2020).(Ortel et al. 2020).

Symptomatic CVT - where the diagnosis is associated with neurological symptoms such as headache, focal neurological symptoms, seizure, or signs of increased intracranial pressure.

2.0 Stroke Unit Management

i. Individuals with a diagnosis of CVT requiring inpatient management should receive routine stroke unit care [Strong recommendation; High quality of evidence]. *Refer to CSBPR Acute Stroke Management module, Section 8 for additional information*.

ii. Individuals with CVT should receive supportive care with hydration, management of intracranial pressure, headache, nausea and vomiting, and seizures [Strong recommendations; Low quality of evidence]. Refer *to Section 3 for additional information on late seizures and epilepsy and post-acute headaches. Refer to CSBPR Acute Stroke Management module, Section 9 for additional information on post stroke complications and management*.

2.1 Antithrombotic Management

i. Therapeutic-dose subcutaneous low molecular weight heparin (LMWH) or intravenous unfractionated heparin (UFH) should be initiated as soon as possible following diagnosis of symptomatic CVT [Strong recommendation; Moderate quality of evidence].

   a. Subcutaneous LMWH is preferred over intravenous UFH infusion for most individuals with CVT due to more reliable and longer duration of anticoagulant effect, predictable pharmacokinetics enabling administration of fixed doses without laboratory monitoring, and lower risk of heparin-induced thrombocytopenia [Conditional recommendation; Moderate quality of evidence].

   b. Intravenous UFH is typically reserved for individuals with CVT who have severely impaired renal function or require a surgical or invasive procedure [Conditional recommendation; Low quality of evidence].

   c. If using intravenous UFH, it should be administered as a bolus followed by infusion and adjusted based on institutional protocols [Conditional recommendation; Low quality of evidence].

   d. Heparin should be avoided in individuals with CVT with a history of heparin-induced thrombocytopenia (HIT) [Strong recommendation; Moderate quality of evidence].

   e. For any individuals with CVT with a history of HIT consider consulting hematology to discuss anticoagulant management [Strong recommendation; Low quality of evidence].

ii. There is currently insufficient evidence to recommend the routine use of direct oral anticoagulants (DOACs) as the initial antithrombotic of choice (i.e., without parenteral lead-in

anticoagulation) in the acute management of CVT [Conditional recommendation; Low quality of evidence].

iii. The presence of intracranial or subarachnoid blood is not a contraindication to anticoagulation [Strong recommendation; Moderate quality of evidence].

iv. Systemic intravenous thrombolysis is ***not*** recommended in the acute treatment of CVT [Strong recommendation; Low quality of evidence].

Section 2.1 Clinical Considerations

1. There may be rare cases where there are concerns regarding the safety of anticoagulation (e.g. large or rapidly expanding intracranial hemorrhage, anticipated emergency surgical intervention, meningitis/encephalitis with cortical venous hemorrhage) that will require case-by-case collaborative decision-making by neurology, neurosurgery and hematology/thrombosis. The benefits of anticoagulation should be weighed against the risks of symptomatic hemorrhage and should be regularly re-evaluated based on clinical and neuroimaging reassessment. If experts are not available on site, arrangements should be in place to contact the nearest centre providing these services. *Refer to Section 2.7 on "Surgical Management, Clinical Consideration 2" for additional information.*
2. The presence of concurrent head or neck infection is not an absolute contraindication to anticoagulation.
3. There is insufficient evidence to support *routine* use of DOACs as first-line anticoagulation for CVT, although first-line DOAC may be considered on a case-by-case basis.

2.2 Inpatient Seizure Management

i. In individuals with CVT who have not had clinical seizures, use of prophylactic antiseizure medications is not recommended [Strong recommendation; Low quality of evidence].

ii. Acute symptomatic seizure(s) (occurring within 7 days of presentation) requires management with anti-seizure medications (ASM) per local protocols to prevent further acute symptomatic seizures [Strong recommendation; Low quality of evidence].

iii. Late seizures (occurring after 7 days of presentation), regardless of the presence or absence of acute symptomatic seizures, may require long-term management with anti-seizure medications [Strong recommendation; Moderate quality of evidence].

iv. Status epilepticus should be treated as per accepted local protocols [Strong recommendation; High quality of evidence].

v. Electroencephalography (EEG) should be considered for individuals with episodic or prolonged unexpected alterations in level of consciousness to rule out non-convulsive seizures or status epilepticus [Strong recommendation; Low quality of evidence].

Section 2.2 Clinical Considerations

1. The choice of antiseizure medications will be dependent on individual factors including co-morbidities and interactions with other treatments including anticoagulation. The duration of treatment with antiseizure medications will be person dependent. Long-term management with antiseizure medications (greater than 3 months) may not be required.

2.3 Acute Headache Management

Note, no evidence-based recommendations included for this section

Section 2.3 Clinical Considerations:

1. Headache from CVT is most commonly secondary to increased intracranial pressure or intracranial hemorrhage. Early treatment with anticoagulation to reduce venous hypertension may help with headache management.
2. It is reasonable to treat headache secondary to increased intracranial pressure with acetazolamide.
3. The use of prolonged nonsteroidal anti-inflammatory drugs (NSAIDs) for headache management while taking concurrent anticoagulation should be avoided given the risk of bleeding.

Refer to Section 3 for additional information on longer term management of chronic headaches.

2.4 Vision

Section 2.4 Vision

i. Individuals with visual symptoms or signs of increased intracranial pressure (ICP) on the initial treating physician's bedside examination should have an urgent ophthalmologic assessment, ideally within 24-48 hours of CVT diagnosis [Strong recommendation; Low quality of evidence].

Section 2.4 Clinical Considerations:

1. All individuals with a new diagnosis of CVT should have an initial ophthalmological assessment including fundus examination and assessment for papilledema, visual fields and enlarged blind spots at the time of their diagnosis.
    a. Individuals with evidence of visual abnormalities or severe papilledema should receive an urgent ophthalmology assessment and be started on acetazolamide.
2. Individuals without visual symptoms or signs of increased ICP should have an ophthalmologic assessment, ideally within 7 days of CVT diagnosis.
3. Individuals without ophthalmic abnormalities related to the CVT on initial assessment should have a subsequent ophthalmologic assessment to rule out development of later-onset papilledema (as outlined above).
4. The initial formal ophthalmological assessment should be performed by a neuro-ophthalmologist or ophthalmologist.
    a. If there are no ophthalmologists locally accessible, then an optometrist capable of performing a dilated fundus examination can perform the initial assessment with an ophthalmologist or neuro-ophthalmologist consulted remotely for advice.
5. Ophthalmologic assessment should include:
    a. Best-corrected visual acuity and color vision.
    b. Dilated fundus examination with stereoscopic viewing of the fundus.
    c. If papilledema is present, there should be automated threshold visual field testing with standard automated perimetry with white-on-white stimuli, which has the best evidence base for reliable, operator-independent longitudinal assessment of vision changes secondary to increased ICP. Papilledema can be graded using the modified Frisén scale for longitudinal follow-up.
6. In the case of ophthalmologic diagnostic uncertainty as to whether there is papilledema secondary to increased intracranial pressure (vs. drusen, crowded discs, hyperopia), lumbar puncture with opening pressure and cerebrospinal fluid analysis should only be undertaken to clarify the presence of increased intracranial pressure if the benefits are deemed to outweigh the potential risks related to herniation and/or disrupting anticoagulation.

7. Optimal timing for ophthalmologic reassessment is unclear; follow up can be considered at 4 weeks and 3-6 months following diagnosis to exclude later-onset papilledema or vision loss.

2.4.1 Management of Papilledema

i. Acetazolamide may be initiated with dose escalation depending on the response of the papilledema to therapy. The risks of acetazolamide therapy, including fluid loss, metabolic acidosis, and hypokalemia, should be monitored, and individuals with CVT should be counselled to be aware of paresthesia as a common side effect with higher doses [Strong recommendation; Low quality of evidence].

ii. If, despite optimal medical management with anticoagulation and acetazolamide, there are either (1) worsening of visual field deficits, acuity, or color vision; or (2) severe visual field loss or abnormal acuity; then surgical intervention should be considered. The optimal approach (i.e. optic nerve sheath fenestration or CSF diversion with shunting) can be considered as a shared decision with relevant experts (i.e. ophthalmologists, neurosurgeons) [Strong recommendation; Low quality of evidence].

Section 2.4.1 Clinical Considerations:

1. Individuals with papilledema or visual symptoms that could be attributed to increased intracranial pressure should be managed by a neuro-ophthalmologist or ophthalmologist.

2.5 Neurocritical Care Management For CVT

i. Individuals with CVT should be routinely and regularly monitored clinically for signs or symptoms of increased intracranial pressure [Strong recommendation; Low quality of evidence].

ii. Individuals with CVT identified to have elevated ICP should be treated emergently based on the severity of signs and symptoms using standard protocols [Strong recommendation; Low quality of evidence].

   a. Those who fail medical management for elevated ICP and are at risk of life-threatening increased ICP should be considered for surgical and/or endovascular management, as appropriate [Strong recommendation; Low quality of evidence]. *Please refer to Endovascular (Section 2.6) and Surgical management (Section 2.7) sections for additional information.*

Section 2.5 Clinical Considerations:

1. For signs and symptoms of ICP elevation, acetazolamide could be considered.
2. Appropriate referrals to critical care and neurosurgical services should be considered for management of worsening ICP.
3. Non-invasive or invasive ICP monitoring technologies can be considered in comatose patients.

2.6 Endovascular Management

i. Endovascular therapy should not be routinely used as first-line therapy for the acute treatment of cerebral venous thrombosis [Conditional recommendation; Moderate quality of evidence].

Section 2.6 Clinical Considerations

1. The optimal candidates for endovascular therapy (EVT) for CVT are not known.
2. The optimal technical approaches for endovascular therapy for CVT, if any, are not known, and the procedure should be performed by an experienced neurointerventionalist.
3. The optimal timing for EVT, if any, is not known.
    a. Endovascular therapy (EVT) may be considered for treatment of cerebral venous thrombosis in cases where there is clinical deterioration despite optimal medical therapy and mechanical recanalization is considered to be of potential benefit.
    b. In select cases where the treating physician and neurointerventionalist agree that the benefits of early intervention are highly likely to exceed potential risks, EVT may be considered alongside anticoagulation as first-line therapy for the acute treatment of CVT.
4. EVT should be considered as a complement, and not a substitute, to anticoagulation unless anticoagulation is otherwise contraindicated (e.g., active and uncontrolled bleeding).

2.7 Surgical Management

i. Decompressive hemicraniectomy should be considered in cases of life-threatening malignant mass effect due to venous infarction and/or hemorrhage [Strong recommendation; Moderate quality of evidence].

Section 2.7 Clinical Considerations:

1. Insertion of an external ventricular drain can be considered as a treatment and/or monitoring option for elevated ICP and/or hydrocephalus.
2. If anticoagulation must be disrupted for a neurosurgical procedure, the approach to restarting anticoagulation should be made on a case-by-case basis in discussion with a neurosurgeon and with review of repeat neuroimaging with relevant specialists involved (e.g., stroke neurology, hematology).
3. Long term management of chronically elevated ICP may require surgical management including insertion of a shunt (ventriculoperitoneal or lumboperitoneal); or optic nerve sheath fenestration.

Rationale

In the acute phase of CVT, potential causes of clinical deterioration and death include thrombus extension, venous edema or intracranial hemorrhage causing mass effect, status epilepticus, and other post-stroke complications including pulmonary embolism and sepsis. Therefore, early therapeutic interventions to address these issues are critical to ensure the best opportunity for a good outcome. Anticoagulation using subcutaneous low molecular weight heparin (LMWH), or intravenous unfractionated heparin (UFH) is the mainstay of acute treatment for CVT, with the aims of preventing clot extension, facilitating recanalization and treating the systemic hypercoagulable state. The incidence of early seizure associated with CVT is high (24-40%) (Duman et al. 2017; Ferro et al. 2004). Intracranial hypertension (IH) is a potential complication of CVT, which can cause both headache and vision loss, due to altered venous drainage. The incidence of IH in one small study was estimated to be 10% within a 6-month follow-up period, with a higher risk in patients who did not recanalize (Geisbüsch et al. 2021).

The use of endovascular thrombectomy (EVT) for the treatment of patients with CVT has been studied in one randomized trial. The recent TO-ACT trial was halted after the first interim analysis for reasons of futility (Coutinho et al. 2020). There were no significant differences between EVT or medical management groups in either 6-month or one-year mortality. Issues persist regarding patient selection, imaging, technique and lack of devices specific to treatment of the cerebral venous system (Goyal et al. 2022).

Hemicraniectomy is a life-saving measure that is performed in cases of CVT complicated by malignant mass effect. DECOMPRESS-2, the largest prospective study to date of over 180 CVT patients

receiving hemicraniectomy, is not yet published. Results presented at the European Stroke Organization Conference 2021 suggested that rates of death and functional dependence were higher that what was reported in previous retrospective series (Alimohammadi et al. 2022).

People with lived experience (PWLE) highlighted the importance of person-centred care, being actively involved in their treatment plan, and ongoing communication with their healthcare team. They emphasized the value of receiving specific information on what CVT is, how their brain was affected, the impact the stroke may have on their everyday tasks and functions, and CVT risk factors and risk of recurrence. Individuals with CVT also valued receiving information and feedback following tests, assessments and screenings. Doing so contributed towards an early understanding of CVT and the residual impairments that may be experienced. Information on early or late-onset seizures was also highly valued by PWLE.

System Implications

To ensure people experiencing CVT receive timely assessments, interventions and management, interdisciplinary teams need to have the infrastructure and resources required. These may include the following components established at a systems level.

1. Organized systems of stroke care including stroke units with a critical mass of trained staff (interdisciplinary team). Availability of Health Human Resources to appropriately staff stroke units and provide recommended best practice service (e.g., 7 days/week) and promote optimal outcomes.
2. Comprehensive and advanced stroke care centres with leadership roles within their geographic regions, to ensure specialized stroke care access is available to individuals with CVT who may first appear at general healthcare facilities (usually remote or rural centres) and facilities with basic stroke services only.
3. Protocols and mechanisms to enable the rapid transfer of individuals with CVT requiring admission from the emergency department to a specialized stroke unit as soon as possible after arrival in hospital.
4. Standardized evidence-based protocols instituted for optimal inpatient care of all individuals with CVT, regardless of where they are treated in the healthcare facility (stroke unit or other ward), and across the regional stroke system of care.
5. Efforts to facilitate building and maintaining of stroke expertise among staff to provide appropriate and evidence-based best practice care to individuals with CVT. The interprofessional healthcare team members should have stroke-specific knowledge, skills, and expertise, and access regular education to maintain competency.
6. Referral systems to ensure rapid access to specialty care such as ophthalmology and hematology.
7. Telestroke service infrastructure and utilization optimized to ensure access to specialized stroke care across the continuum to meet individual needs (including access to rehabilitation and stroke specialists) including the needs of northern, rural, and remote residents in Canada.
8. Information on geographic location of stroke units, rehabilitation, and home care services, and other specialized stroke care models available to community service providers, to facilitate navigation to appropriate resources and to strengthen relationships between each sector along the stroke continuum of care.
9. Ongoing professional development and educational opportunities for all healthcare professionals who care for individuals with CVT.

Performance Measures

System Indicators:

1. Median length of stay for during acute phase of care for all individuals with acute symptomatic CVT admitted to hospital (core).
2. Proportion of individuals with acute symptomatic CVT who experience prolonged length of stay beyond expected length of stay as a result of experiencing one or more complications.

Process Indicators:

3. Number of individuals with symptomatic CVT who are admitted to hospital and treated on a specialized stroke unit at any time during their inpatient hospital stay for CVT (numerator) as a percentage of total number of individuals with acute symptomatic CVT admitted to hospital.
4. Median length of stay, stratified by complication type, during acute phase of care for all individuals with CVT admitted to hospital who experience one or more complications during hospitalization (core).
5. Proportion of individuals discharged with CVT who are readmitted within 30 days (or 90 days) for any cause.

Patient-oriented outcome and experience indicators:

6. Proportion of individuals admitted to hospital with a diagnosis of acute symptomatic CVT who experience one or more complications during hospitalization (e.g., deep venous thrombosis, pulmonary embolus, secondary intracranial hemorrhage, gastrointestinal bleeding, pressure ulcers, UTI, pneumonia, seizures) during inpatient stay.
7. Proportion of individuals who have experienced multiple visits to acute medical care prior to having a definitive diagnosis of CVT.
8. Proportion of individuals with CVT who experience neuroradiological worsening (new or worsening edema or ICH, or new/extension of venous thrombus).
9. Quality of life rating at 30 and 90 days for people who experience complications during acute inpatient admission following CVT, using a validated tool.
10. In-hospital mortality rates (overall, 7 and 30-day) for patients with CVT.

Measurement Notes

a. ***For Indicator #1:*** CVT with deficits or stroke/ich should definitely be on a stroke unit. Uncomplicated CVT may reasonably be under neurology or medicine, and traumatic CVT under trauma so at the local level clarify which subpopulation to apply this to as denominator.

b. ***For Indicator #3:*** 'Expected length of stay' refers to the standard length of stay based on Canadian Institute for Health Information algorithms.

c. ***For Indicator #5:*** Due to the smaller incidence rates of CVT compared to other stroke types, numerators and denominators may become very small when looking at multiple sub-categories of complications and stratifying by age and sex. Larger grouping variables may be required.

Implementation Resources and Knowledge Transfer Tools

Resources and tools listed below that are external to Heart & Stroke and the Canadian Stroke Best Practice Recommendations may be useful resources for stroke care. However, their inclusion is not an actual or implied endorsement by the Canadian Stroke Best Practices team or Heart & Stroke. The reader is encouraged to review these resources and tools critically and implement them into practice at their discretion.

Healthcare Provider Information

- Heart & Stroke: Signs of Stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke

- CVT Consortium: https://cerebralvenousthrombosis.com/professionals/
- Heart & Stroke FAST Signs of Stroke... what are the other signs?: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Virtual Stroke Care Implementation Toolkit: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/csbpr-virtual-stroke-toolkit-final.pdf?rev=e545b3d0a8394ca18586090a74cdcf49
- Heart & Stroke: Taking Action for Optimal Community and Long-Term Stroke Care (TACLS) A Resource for Healthcare Providers: https://www.strokebestpractices.ca/resources/professional-resources/tacls
- Thrombosis Canada: Clinical Guidelines: https://thrombosiscanada.ca/clinicalguides/
- Canadian Association of Radiologists guidelines: https://car.ca/patient-care/practice-guidelines/

Information For Individuals With Lived Experience Of Stroke, Including Family, Friends And Caregivers

- Heart & Stroke: Cerebral Venous Thrombosis Infographic
- Heart & Stroke: FAST Signs of Stroke... what are the other signs?: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- CVT Consortium: https://cerebralvenousthrombosis.com/patients/patient-information-in-english/
- Heart & Stroke: Signs of Stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- Heart & Stroke: What is Stroke? https://www.heartandstroke.ca/stroke/what-is-stroke
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/pdf-files/canada/your-stroke-journey/en-your-stroke-journey-v20.pdf
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Enabling Self-management Following Stroke: A Checklist for Patients, Families and Caregivers: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbpr-enabling-self-management-following-stroke-checklist-jan2021-final.pdf?rev=03b045c41df04abfb7f4cb652869f031
- Heart & Stroke: A Family Guide to Pediatric Stroke: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/a-family-guide-to-pediatric-stroke-en.pdf?rev=ff206495b5a4479da4b1a1d7b54c7734
- Heart & Stroke: Stroke in Young Adults: A Resource for Patients and Families: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/stroke_young_final.pdf?rev=7338abd3dba746dc96180a057e244ce9
- Heart & Stroke: Secondary Prevention Infographic: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbpr7-infographic-secondaryprevention-final.pdf?rev=9f0dcf0ade22483ba9ae4113b2f0f3eb
- Heart & Stroke: Rehabilitation and Recovery Infographic: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/rehabilitation-nov2019/csbp-infographic-rehabilitation.pdf?rev=a2cff1fb27424c84bbd44b568d58d1b4

- Heart & Stroke: Transitions and Community Participation Infographic: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/transition-of-care-nov2019/csbp-infographic-transitions-and-participation.pdf?rev=595e990a17e14232aa3b1c731d983ce3
- Heart & Stroke: Virtual Healthcare Checklist: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbp-infographic-virtual-healthcare-checklist.pdf?rev=bf2f5b0e9e4a49cfbfc251208b6a15e2
- Heart & Stroke: Online and Peer Support: https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Stroke Engine: http://strokengine.ca/

Summary of the Evidence

Stroke unit management

Evidence summarizing the benefits of stroke unit care in a general post-stroke population can be found in the Canadian Best Practice Guidelines for Acute Stroke Management, 2022 Seventh Edition (Heran et al. 2022). The historical proportion of individuals with CVT comprising all patients admitted to stroke units is approximately 0.5-1%.

Systemic thrombolysis

A previous review of case reports and case series describing systemic thrombolysis for management of CVT (n=26 patients) reported high rates of intracranial (12%) and extracranial hemorrhage (19%), with an 8% rate of fatal hemorrhage. In those who survived, available information regarding rates of recanalization (n=16, 62%) and functional independence (n=26, 88%) were not out of keeping from other series of individuals with CVT with usual management (Duman et al. 2017; Ferro et al. 2004; Kim et al. 2023). Systemic thrombolysis is therefore not recommended.

Antithrombotic management

Anticoagulation is the mainstay of acute treatment for CVT, with the objectives of facilitating venous recanalization, preventing thrombus extension and treating the overall hypercoagulable state. Unlike with primary intracranial hemorrhage, the presence of intracranial bleeding in the context of CVT should not delay initiation of anticoagulation. Approximately 30-40% of individuals with CVT may have some type of intracranial bleeding on their initial scans (Afifi et al. 2020; Girot et al. 2007). A review of 260 patients from an international cohort found that 39% had hemorrhage at baseline, with 63% having intraparenchymal bleeding (29% with small juxtacortical hemorrhages) with subarachnoid blood and subdural blood in 24% and 11%, respectively. Approximately one-quarter had multiple hemorrhage types (Afifi et al. 2020). Approximately 5-10% of patients will go on to develop new intracranial bleeding (either expansion of pre-existing bleeding or a de novo hemorrhage in a separate anatomical location) following diagnosis (Busch et al. 2016; Girot et al. 2007). Baseline ICH is associated with a higher risk of delayed ICH (Busch et al. 2016); however, there is no evidence from the observational literature suggesting that anticoagulation increases the risk of delayed intracranial hemorrhage (Girot et al. 2007; Shakibajahromi et al. 2019). We note that the available literature in this regard is limited in defining symptomatic versus asymptomatic delayed ICH and may be biased by a lack of timed prospective follow-up early neuroimaging.

Despite its central role in the management of CVT, the quality of evidence comparing anticoagulation to placebo is based on small underpowered studies that are heterogenous with respect to populations, interventions and outcomes. Further, duration of follow-up is brief, with one randomized trial reporting outcomes at approximately one month and another at 13 weeks (Al Rawahi et al. 2018; Coutinho et al. 2011a).

The evidence supporting low-molecular weight heparin over unfractionated heparin as the initial therapy for CVT is based on observational and small randomized studies, that demonstrate non-significant trends in favour of LWMH for better functional outcomes and less intracranial bleeding (Al Rawahi et al. 2018) and reduced mortality (Al Rawahi et al. 2018; Coutinho et al. 2010). Comparisons between treatments in the non-randomized literature may be confounded by indication. The benefits of low molecular-weight heparin over unfractionated heparin for treatment of acute venous thromboembolism in general include more predictable pharmacokinetics without laboratory monitoring and more reliable anticoagulant effect in addition to lower rates of heparin-induced thrombocytopenia (HIT).

The overall rate of heparin-induced thrombocytopenia (HIT) is approximately 1 per 1500 hospitalizations in US-based data, with increased risks with major surgery and longer durations of heparin exposure (Dhakal et al. 2018; May et al. 2023). Indefinite avoidance of heparin anticoagulation is recommended in individuals with a history of HIT (Cuker et al. 2018; May et al. 2023). CVT secondary to HIT is a very rare occurrence, estimated to affect less than 2% of those with HIT (Aguiar de Sousa et al. 2022).

Clinical trials comparing DOACs to warfarin have mostly included participants who had an initial lead-in with parenteral anticoagulation. The RE-SPECT CVT trial, which compared dabigatran against vitamin K antagonist anticoagulation, required 5-15 days of lead-in parenteral anticoagulation prior to initiation of therapy (Ferro et al. 2019). The EINSTEIN-Jr pediatric thromboembolism trial, which included 117 children with CVT, also required 5-15 days of parenteral lead-in therapy (prior to randomization to rivaroxaban 20 mg daily equivalent dosing versus control (VKA or LWMH) (Connor et al. 2020). The SECRET trial, which compared rivaroxaban to standard-of-care anticoagulation (warfarin or ongoing LWMH) did not have any requirement for lead-in parenteral therapy. One of 26 participants randomized to rivaroxaban received no lead-in therapy, and the median time to initiation of rivaroxaban was 3 days (IQR 2 - 6), with 46% of patients initiated on rivaroxaban within 48 hours of diagnosis and 73% prior to day 5. There were no complications related to symptomatic intracranial bleeding or early (day 30) symptomatic extension of CVT or early recurrent VTE in either group (Field et al. 2023). There is insufficient evidence to support *routine* use of DOACs as first-line anticoagulation for CVT, although first-line DOAC may considered on a case-by-case basis (Carrion et al. 2024).

The role of anticoagulation for CVT secondary to head or neck infection is less well-characterized in the literature. A sub study of the prospective observational International Study on Cerebral Venous and Dural Sinus Thrombosis (ISCVT) had 57 (9%) participants with CVT secondary to head or neck infection. Of those, 83% were treated with therapeutic anticoagulation, without notable differences distinguishing those with versus without anticoagulation. Rates of new intracranial hemorrhage were high overall (6/23 in anticoagulated patients and 1/10 non-anticoagulated patients) but small numbers and low event rates precluded specific recommendations. In the CVT sub study of the EINSTEIN-Jr trial comparing rivaroxaban versus standard-of-care anticoagulation in a pediatric cohort of 117 children, 63% had infection-related CVT (80% otomastoiditis, 28% CNS infection 24% sinusitis, 12% upper respiratory tract infection and 39% with multiple infection sites. Anticoagulation was held for lumbar puncture (30%) and surgical interventions (55%). There were no major or clinically relevant nonmajor bleeding events in the surgical group. One patient in the standard treatment group with meningitis developed a subdural hemorrhage. No other patients had symptomatic intracranial bleeding, nor was there any bleeding on repeat neuroimaging performed in 69/74 by the three-month mark.

Seizure management

Rates of seizure complicating CVT are high. Over one-quarter will have seizures at the time of their presentation (Duman et al. 2017; Ferro et al. 2004). A recent study using retrospective and prospective data including 1,281 adults with CVT reported that one-third had a symptomatic seizure within 7 days of admission to hospital and 6% had status epilepticus. However, only 7% of patients with seizures post-admission did not have a seizure preceding their admission to hospital. Predictors of early seizures included presence of hemorrhagic or non-hemorrhagic parenchymal lesions or subarachnoid blood, cortical vein or sagittal sinus involvement, focal deficits and OCP- or pregnancy/puerperial CVT.

The authors concluded that prophylactic antiseizure therapy was not warranted in individuals presenting without seizure (Lindgren et al. 2020). In a substudy of the ISCVT (n=624), 39% presented with seizures. Of those who did not present with seizures, 3% had a new seizure within the first two weeks of diagnosis. Two-hundred and thirty-one were prescribed antiseizure medication, 75% of whom had seizures at presentation. Overall, use of anti-seizure medications (ASM) was associated with a reduced risk of seizure, but rates of new seizures in those without seizures at presentation were low.

Rates of later seizures (i.e. after one week following diagnosis)(Beghi et al. 2010) were 11% over a median follow-up of 2 years in a large cohort including retrospective and prospective data (n=1127). Median time to late seizure was 5 months. Predictors of late seizures included history of status epilepticus within the first week of admission, decompressive hemicraniectomy, subdural hematoma and intracerebral hemorrhage. Although 70% with late seizures experienced subsequent recurrence and 94% were initially prescribed antiseizure medication (Sánchez van Kammen et al. 2020), the study did not distinguish whether those with recurrences were still taking anti-seizure medications at the time. A recent meta-analysis including four studies also explored prevalence and risk factors for late seizures, although the previously discussed cohort of 1127 accounted for 86% of the 1309 patients in the analysis and findings were similar (Gasparini et al. 2022).

Headache management

Headache is a presenting feature in approximately 90% of individuals with CVT and is presumed to be due to increased intracranial pressure in most cases. Management principles of CVT-related headache include appropriate management with anticoagulation to facilitate recanalization, management of increased intracranial pressure, and appropriate analgesia. Beyond its role in the management of increased intracranial pressure, the role of acetazolamide in headache management for CVT is not known. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), which enrolled individuals with idiopathic intracranial hypertension, not CVT, found no reduction in headache-related disability, measured by the Headache Impact Test (HIT-6) at six months between individuals randomized to acetazolamide (maximum 4g/day) versus placebo (Wall et al. 2014).

Vision

Increased intracranial pressure can be associated with visual disturbances due to increased pressure transmitted along the optic nerve sheath, causing papilledema (swelling at the optic nerve head due to increased pressure). These visual changes can include transient visual obscurations and blurred vision as well as visual field deficits or enlarged blind spots. Other visual disturbances in CVT can include diplopia (usually secondary to increased pressure transmitted along the intradural portions of the sixth cranial nerves, or, in the case of cavernous venous thrombosis, direct disturbances of the intrasinus portions of the cranial nerves), and binocular vision loss (usually from focal parenchymal brain involvement) or positive visual phenomena (usually from seizure activity).

Individuals with papilledema, however, may not be aware of any visual disturbances, and it is important to assess for, and identify, papilledema as early as possible to facilitate timely, appropriate management to reduce the likelihood of any permanent visual loss. In addition to the initial bedside neurologic assessment, including fundoscopy, routine early involvement of healthcare professionals with dedicated expertise in ophthalmology is of importance for several reasons. First, papilledema is better detected on dilated fundoscopic exam than at the bedside. Second, appropriate assessments, including stereoscopic fundoscopic assessment with papilledema grading, and automated perimetry, can detect subclinical visual abnormalities, and can assess response to therapy over time.

There is minimal literature related specifically to management of papilledema in CVT. The literature for management of papilledema with mild visual loss secondary to idiopathic intracranial hypertension (IIH) demonstrates a benefit for use of acetazolamide for individuals with mild visual loss due to IIH. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) randomized adults with a diagnosis of IIH meeting modified Dandy criteria for diagnosis (Wall et al. 2014). Participants were randomized to acetazolamide and dietary intervention versus placebo and dietary intervention. The acetazolamide

treatment protocol was an initial dose of 500 mg bid, increasing by 250 mg every six days to a maximum tolerated dose of 2 g bid. The primary outcome was the perimetric mean deviation (PMD) in the worst affected eye at six-month follow-up. Eighty-six participants were randomized to active drug therapy, 44% of whom tolerated the maximum dose; 45% tolerated doses between 1 - 3.75 g/day. In the acetazolamide arm there was a modest statistically significant improvement in the primary outcome of average perimetric mean deviation in the more affected eye (0.71 light stimulus decibels [95% CI 0 to 1.43 dB; p=0.050). Although this did not meet the predetermined threshold for clinical significance (1.3 dB), treatment effects were greater in participants with higher-grade papilledema at baseline. There were also significant improvements in the acetazolamide arm compared to control for secondary outcomes including cerebrospinal fluid opening pressure, papilledema grade on fundus photography and optical coherence imaging, and quality of life in patients with mild visual field loss (Smith and Friedman 2017).

Interestingly, patients with CVT can also develop late intracranial hypertension/ papilledema, with or without venous recanalization, and for this reason it is important to have follow-up ophthalmological assessment, even if the initial evaluation is normal. In a retrospective cohort of 70 CVT patients with follow-up, 7 (10%) developed new (n=5) or worsening (n=2) symptomatic intracranial hypertension within a median follow-up of six months (Geisbüsch et al. 2021). Five of the 7 patients with late intracranial hypertension had achieved partial (n=3) or complete (n=2) recanalization. In the SECRET trial, 1/50 (2.5%) developed new persistent papilledema at 90 days despite complete recanalization. Anecdotal discussions with members of the International CVT Consortium also confirm a similar experience with late “idiopathic” intracranial hypertension in a minority of CVT patients who have achieved partial or complete recanalization. Although there is some overlap in predisposing features for CVT and IIH, including younger age, female sex, and increased body mass index, the mechanism for this phenomenon and associated risk factors are not currently known. The optimal timing for later reassessment is not known, but could be considered around the one-month mark (balancing timing at which some recanalization is expected to occur, (Aguiar de Sousa et al. 2020) but not waiting too long such that previously undetected papilledema would persist without management for a prolonged period of time) and again at the 3-6 month mark, to be reassessed alongside repeat vascular neuroimaging and usual clinical follow-up.

Endovascular management

The role of endovascular therapy (EVT) in the management of CVT is not well defined, and practices vary, including use of EVT as first-line versus rescue therapy, candidate selection, and approaches (Goyal et al. 2022). Assessment of the benefits of EVT in CVT may be further complicated by the challenges in defining an optimal outcome measure, as the modified Rankin Scale (mRS) may be insufficiently sensitive to measure outcomes after CVT, given high rates of functional independence amongst survivors.

The Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial randomized patients with CVT with one or more pre-defined risk factors for worse prognosis, including intracranial bleeding, GCS<9, “mental status disorder,” or deep venous involvement, to endovascular therapy as per local practices versus conservative therapy (Coutinho et al. 2020). Endovascular techniques included mechanical thrombectomy alone, intradural thrombolysis or both. The primary outcome was an mRS of 0-1 at 12 months. At enrollment, median GCS was 11 and median NIHSS was 12. The trial was stopped early for futility after 67 of a planned 164 patients were randomized. There was no difference between groups with respect to the primary outcome (67% vs. 68%, RR 0.99, 95% CI 0.71-1.38). One-quarter in the EVT group received intradural thrombolysis as part of therapy. Sinus perforation occurred in 3/33 in the EVT group.

Although systematic reviews of case series of CVT receiving EVT report high rates of favourable outcomes, (Goyal et al. 2022) studies comparing outcomes between patients undergoing EVT versus anticoagulation alone CVT report higher rates of mortality with EVT, likely suggesting that the procedure is being performed in participants with worse clinical presentations. One large single-centre prospective study of 546 CVT patients from India had 10% who went for EVT, most commonly for clinical deterioration. EVT was performed through retrograde venous access through the internal

jugular using a Fogarty balloon. The only complication reported was an intrasinus fracture of the Fogarty balloon retrieved with snare. There were no clinical incidences suspicious for pulmonary embolism. At 12-month follow-up, 67% in the EVT group had an mRS of 0-2. Outcomes for the non-EVT group were not described (Alwan et al. 2023). A recent systematic review and network meta-analysis of clinical trials and observational series of patients with CVT treated with anticoagulation or EVT (n=17 studies) found an increased odds of death (OR 1.83, 95% 1.04 - 3.21) in those treated with EVT (Naik et al. 2022). A recent review of cases of CVT undergoing mechanical thrombectomy (MT) between 2005 and 2018 in the US-based National Inpatient Sample identified use of MT in 1.56% of 85,370 CVT cases, with an upward trend of 0.13% per year (Wahood et al. 2023). Mortality was 16.7% in the MT group compared with 3.8% in those not receiving MT. Individuals who had MT had a higher proportion of markers in line with more severe presentations, including a higher prevalence of coma, ICH, and intubation.

Surgical management

Decompressive hemicraniectomy for CVT has been described in retrospective case series and systematic reviews. The results of the prospective DECOMPRESS-2 study were previously presented at the 2021 European Stroke Organization Conference but are not yet published (Aaron et al. 2021). In 118 individuals receiving decompressive hemicraniectomy for CVT, 58% were characterized as comatose prior to surgery, with 23% having unilaterally absent and 8% with bilaterally absent pupillary responses. Thirty-five percent had an mRS of 0-2 at 12 months, which is lower than what is reported in previous systematic reviews (Ferro et al. 2011).

Sex and gender considerations

No sex-specific concerns related to acute medical antithrombotic therapy have been identified outside of scenarios related to pregnancy or breastfeeding, where DOACs are contraindicated. Warfarin is contraindicated in pregnancy.

Acetazolamide has been identified as a potential teratogen in the context of animal studies, although a retrospective series of 50 women treated before 13 weeks of gestation with acetazolamide for IIH did not report an increase in spontaneous abortion above controls with IIH not taking acetazolamide, and no congenital anomalies were reported (Falardeau et al. 2013). In cases of individuals who are pregnant and being considered for treatment with acetazolamide, an obstetric opinion is recommended (Mollan et al. 2018; Thaller et al. 2022).

There are multiple considerations related to the use of ASM in women who are pregnant or breastfeeding which have been well-summarized in guidelines by the International League Against Epilepsy. https://www.ilae.org/patient-care/epilepsy-and-pregnancy

Special considerations related to acute treatment in pregnancy:

There is a previous Canadian Stroke Best Practice Consensus Statement related to management of acute stroke in pregnancy (Ladhani et al. 2018). As with other stroke types, acute treatment principles represent the confluence of two clinical considerations: (1) appropriate treatment if the patient were not pregnant and (2) appropriate treatment if the patient were not experiencing a stroke. Management decisions should thus be based on symptom severity, clinical condition of the patient and, when available, personal values and wishes of the patient and next of kin. A systematic review of management of CVT in pregnancy identified 66 cases, with a high prevalence of EVT, including thrombolysis alone (26%) or thrombectomy (8%) (Kashkoush et al. 2017). Five patients (8%) underwent hemicraniectomy. Those receiving EVT had a higher prevalence of coma at presentation. Overall, 94% in the series had an mRS of 0-2; 91% in the EVT group had an mRS of 0-2. It should be noted that the review was mostly composed of case reports and thus reporting bias towards successful cases, with an overrepresentation of EVT cases, is expected.

Evidence Table and Reference List: Cerebral Venous Thrombosis

Section 3 Post-acute Management of Cerebral Venous Thrombosis and Person-centered Care

3. Post-Acute Management of Cerebral Venous Thrombosis and Person-centered Care, Recommendations 2024

3.1 Factors Related to Clinical Decision-Making for Anticoagulation

i. Vitamin K antagonists (dose-adjusted to target INR 2.0-3.0) and/or DOACs are suitable options for oral anticoagulation for individuals with CVT [Strong recommendation; Moderate quality of evidence].

ii. Vitamin K antagonists are the preferred standard of care for individuals with a confirmed diagnosis of antiphospholipid antibody syndrome, and always for those with triple antiphospholipid antibody positivity [Strong recommendation; Moderate quality of evidence].

Section 3.1 Clinical Considerations

1. Unless there is a clear indication for ongoing parenteral anticoagulation (e.g. pregnancy), individuals with CVT should be transitioned to an oral anticoagulant for primary treatment once clinically stable.
2. Anticoagulation should be continued for a minimum of 3 months. The optimal duration of primary anticoagulation is not known. The net clinical benefit of long-term anticoagulation for secondary prevention for idiopathic CVT after initial 3 to 12 months of primary treatment is also not known.
3. In making decisions around duration of anticoagulation, individuals with CVT can be stratified according to the presence or absence of transient and chronic thrombotic risk factors, as well as other factors known to be associated with recurrent CVT and/or VTE (e.g., unprovoked event, male sex), which influence the risk of recurrence after discontinuation of anticoagulation.
    a. Individuals with CVT associated with a major transient risk factor (e.g. isolated oral contraceptive use, early post-partum period) should receive primary anticoagulation treatment for at least 3 to 6 months. *Refer to CVT and Pregnancy (Section 4) for additional information on thromboprophylaxis.*
    b. Individuals with a first episode of CVT without a prior history of VTE, or other identifiable risk factors, should receive primary anticoagulation treatment for 6 to 12 months. Decisions regarding further extension of anticoagulation for secondary prevention should be based on the estimated risk of recurrent CVT and/or VTE and bleeding, and with shared clinical decision-making in conjunction with the individual and with thrombosis expertise when necessary.
    c. Individuals with a major chronic thrombotic risk factor (e.g., active cancer), recurrent CVT, recurrent VTE, or high-risk thrombophilia (antiphospholipid antibody syndrome, homozygous factor V Leiden, homozygous prothrombin gene mutation, combination inherited thrombophilia, deficiencies of natural anticoagulants [protein C, protein S, antithrombin]) should be considered for indefinite anticoagulation, without disruption between the primary treatment and secondary prevention phases of therapy. Consider consultation with a clinician with thrombosis expertise for ongoing management.
4. Recommendations for ongoing antithrombotic therapy for secondary prevention and choice of agent should be made on a case-by-case basis based on the estimated risk of recurrent CVT and/or VTE and bleeding, and with shared clinical decision-making in conjunction with the individual with CVT and with thrombosis expertise when necessary.

3.1.1 CVT Workup: Cancer Screening and Hypercoagulability Testing

i. Individuals with CVT should be assessed for additional risk factors for CVT and managed as per usual care, including ensuring guideline-recommended age-appropriate cancer screening is up to date [Strong recommendation; Moderate quality of evidence].

3.1.2 Inherited Thrombophilia

Note, no evidence-based recommendations included for this section

Section 3.1.2 Clinical Considerations

1. Limited observational data suggest that inherited thrombophilia may increase the risk of VTE recurrence after CVT.
    a. Testing for inherited thrombophilia and the spectrum of thrombophilia workup is an area of ongoing controversy, as is decision-making around testing.
    b. Current guidelines from the International Society on Thrombosis and Hemostasis (ISTH) recommend testing for inherited thrombophilia in individuals with CVT who would otherwise not have an indication for indefinite anticoagulation.
2. Screening for inherited thrombophilia should include testing for antithrombin-3, protein C, and protein S deficiencies, factor V Leiden, and prothrombin gene mutation (G20210A) according to ISLH guidelines (Barbhaiya et al. 2023; Marlar et al. 2021).
    a. Levels of antithrombin, protein C and protein S can be affected by acute thrombosis, anticoagulation, and pregnancy/puerperium. Therefore, testing is not recommended in the acute setting (based on ISLH guidelines), and rather when making the decision as to if or when to transition to anticoagulation for secondary prevention (Barbhaiya et al. 2023; Marlar et al. 2021).
3. Consultation with hematology/thrombosis should be considered for guidance regarding the appropriateness, timing and interpretation of testing.

3.1.3 Antiphospholipid Antibody Syndrome (APS)

i. Individuals with CVT without a known history of antiphospholipid antibody syndrome should be tested for antiphospholipid antibodies as it may influence antithrombotic decision-making (choice of antithrombotic agent or duration of treatment) [Strong recommendation; Low quality of evidence]. *Refer to Appendix Four for testing considerations.*
    a. As per the 2023 American College of Rheumatology/European Alliance of Associations for Rheumaology (ACR/EULAR) criteria, an individual must meet required clinical and laboratory criteria for a diagnosis of APS. Testing includes measurement of non-specific inhibitor (lupus anticoagulant), anticardiolipin antibody, and anti-beta2 glycoprotein-I antibody according to guidelines (Baker et al. 2020; Barbhaiya et al. 2023; Devreese et al. 2014; Marlar et al. 2021; Tripodi et al. 2020) [Strong recommendation; Low quality of evidence].
    b. Testing for a non-specific inhibitor (lupus anticoagulant) should be conducted prior to initiation of anticoagulation, which interferes with the results of testing. Anticoagulation should not be delayed pending testing [Strong recommendation; Low quality of evidence].

3.2 Role of Routine Follow-up Vascular Neuroimaging

Section 3.2 Follow-Up Neurovascular Imaging

i. Routine follow-up vascular neuroimaging should be repeated within 3 to 6 months after initiating anticoagulation [Strong recommendation; Low quality of evidence].

Section 3.2 Clinical Considerations

1. The ideal timing of follow-up vascular neuroimaging is uncertain.
2. Although the role of late venous recanalization in predicting outcomes or guiding anticoagulation strategy is uncertain, repeat neuroimaging allows the treating clinician to visualize changes in thrombus burden over time and to establish a newer baseline if there are additional concerns about recurrent thrombosis in the future.
3. Ideally, repeat vascular neuroimaging should be performed with either CT or MRI contrast-enhanced vascular imaging.
4. Beyond six months of treatment, the role of routine subsequent vascular neuroimaging is uncertain but can be considered if it will change antithrombotic treatment considerations (i.e. duration of treatment).
5. In the clinically stable individual with CVT who has completed primary treatment with anticoagulation, with no recurrent symptoms and recanalization of a chronic stable thrombus, the role of ongoing surveillance with vascular neuroimaging is unlikely to be of benefit.
6. There is no indication for routine surveillance imaging after CVT in asymptomatic individuals to rule out development of dural arteriovenous fistula.
7. Choice of modality for repeat neuroimaging (i.e. CT vs MR), particularly in instances where there will be multiple follow-ups, should be considered in the context of resources (i.e. availability and wait-lists) as well as risks of repeat radiation exposure, particularly in younger individuals.

3.3 Management of Other Post-Acute Sequelae of Cerebral Venous Thrombosis

3.3.1 Post-CVT Management

Note, individuals with CVT tend to be younger than other individuals with lived experience of stroke. Their post-CVT care needs are unique, less studied and will vary depending on their individual work, school and home situations. Cognitive complaints, headaches and fatigue may be significantly disabling without radiologic evidence of residual CVT sequalae. Some basic principles do apply to all individuals post CVT.

i. All individuals with CVT should be assessed for mood, cognition, fatigue, functional impairments (including visual deficits), headache and rehabilitation needs at the time of their event and throughout their recovery [Strong recommendation; Low quality of evidence].

ii. All individuals with CVT with functional impairments and rehabilitation goals should undergo early rehabilitation as per Canadian Best Practice Stroke Guidelines Recommendations [Strong recommendation; Moderate quality of evidence]. *Refer to CSBPR Rehabilitation, Recovery and Community Participation Following Stroke for additional information.*

iii. Individuals with mood disturbance following CVT should be treated and referred to appropriate mental health support services [Strong recommendation; Moderate quality of evidence].

iv. Individuals with post-CVT fatigue should be assessed for reversible causes and be advised on pharmacologic and non-pharmacologic strategies for management [Strong recommendation; Low quality of evidence].

v. Individuals with CVT with cognitive concerns should be screened with validated screening tools [Strong recommendation; Low quality of evidence]. *Refer to CSBPR Vascular Cognitive Impairment module for additional information.*

a. Further neuropsychological evaluation is recommended if impairments are identified on screening, or the individual continues to have subjective cognitive complaints which are interfering with their daily functioning. This is especially important in individuals who are still working or in school, to establish the degree and severity of deficits, in order to inform return to work and school, and to determine what accommodations can be made [Strong recommendation; Low quality of evidence].

vi. Individuals with CVT should be assessed for return to work or school at follow-up and throughout transitions of care [Strong recommendation; Low quality of evidence]. *Refer to CSBPR Rehabilitation, Recovery and Community Participation Following Stroke for additional information.*

vii. Individuals with CVT with residual impairments and/or seizures should be assessed for return to driving when appropriate. Recommendations for return to driving should be guided by provincial licensing requirements [Strong recommendation; Low quality of evidence]. *Refer to CSBPR Rehabilitation, Recovery and Community Participation Following Stroke*

viii. Individuals with lived experience of CVT should be advised about what is known regarding the natural history of post-CVT sequalae and should be made aware of peer support groups [Strong recommendation; Low quality of evidence]. *Refer to CSBPR Transitions and Community Participation Following Stroke.*

3.3.2 Late Seizures and Epilepsy

i. Individuals with CVT who develop late seizures (>7 days post-diagnosis) should be treated with appropriate ASM per standard guidelines [Strong recommendation; Moderate quality of evidence].

ii. Most late post-CVT seizures will be associated with an elevated risk of recurrent seizures (epilepsy) related to chronic structural lesions (e.g. encephalomalacia). This will likely require long-term management with ASM, which is to be reviewed as part of routine clinical follow-up [Strong recommendation; Moderate quality of evidence].

Section 3.3 Clinical Considerations

Post-Acute Symptoms

1. Individuals with CVT with an adverse change in headache pattern, worsening seizures, new focal deficits, visual symptoms or pulsatile tinnitus following initial CVT should be evaluated clinically and with repeat parenchymal and vascular neuroimaging to exclude complications including CVT recurrence, intracranial hypertension or dural AV fistula.

2. After the acute phase, individuals with CVT who continue to experience headaches should be assessed and treated according to chronic headache management principles. If after standard management, the individual with CVT continues to have persistent and debilitating headaches, consider referral to a practitioner with expertise in treatment of headache.

Rationale

Most patients with CVT are transitioned to oral anticoagulation. Vitamin K antagonists (VKA) have traditionally been recommended by older guidelines (Ferro et al. 2017); however, a recent emerging body of evidence, including three small randomized trials (Connor et al. 2020; Ferro et al. 2019; Field et al. 2023) and a large retrospective observational study (Yaghi et al. 2022b) suggest that, in selected patients, DOACs may also be appropriate, which is also reflected in the updated AHA/ASA Scientific Statement on CVT (Saposnik et al. 2024). In those studies, markers of efficacy, including rates of recurrent CVT and peripheral VTE and venous recanalization are similar between patients treated with DOAC and VKA. Safety events including major extracranial and intracranial hemorrhage were low overall in the randomized trials; the large retrospective ACTION-CVT study found that rates of hemorrhage were

lower in patients treated with DOAC compared to VKA as part of their routine clinical care (Yaghi et al. 2022b).

DOACs are not the treatment of choice, however, for patients with known antiphospholipid antibody syndrome (APLAS). Multiple small trials examining DOAC versus warfarin for prevention of venous and arterial thromboembolic events in individuals with APLAS were stopped early due to safety concerns with an excess of thromboembolic events in the DOAC arm (Pengo et al. 2018; Woller et al. 2022), or were completed with similar findings (Ordi-Ros et al. 2019).

Rates of functional independence after CVT are high (85-90%). However, a number of studies have identified high rates of persisting issues with cognition, mood, fatigue and headache impacting quality of life. While retrospective studies report high rates of persisting symptoms months and years following CVT, (Hiltunen et al. 2016; Koopman et al. 2009) participants in the recent prospective SECRET trial found that these symptoms continued to improve on average over one year of follow-up (Field et al. 2023). Late seizures affect approximately 10% of patients with CVT (Sánchez van Kammen et al. 2020).

The needs, goals and experiences of people with lived experience of CVT are highly individualized. People with lived experience highlighted that approaches to ongoing management of CVT and other post-acute sequelae of CVT need to be person-centered and involve an interdisciplinary team as required. People with lived experience emphasized the importance of ongoing mental health support, as well as addressing “invisible” impairments such as cognitive impairment, visual changes, and headaches.

Throughout rehabilitation and recovery, people with lived experience highlighted the value of feedback from their healthcare provider on progress as well as areas in which progress may be slower or lacking. This is helpful to better understand their impairments and recovery post-stroke. They also emphasized the importance of ongoing follow-up, as rehabilitation and recovery needs and goals change over time. Peer support was identified as helpful for people with lived experience, in particular those who are at similar life stages and with other shared experiences. Person-centred support for return to work or school was very important among PWLE. Individuals with CVT also emphasized the importance of support and information for family members and caregivers.

System Implications

1. Health promotion efforts that contribute to the prevention of stroke and CVT in all communities (integrated with existing chronic disease prevention initiatives) must be established.
2. Improved communication and transition planning between all stages and settings of care and ensuring that primary care team members are fully informed on the goals of care, prevention therapies initiated by the healthcare providers during first assessments (e.g., in the emergency department), follow-up appointments for further investigations and long-term management.
3. Coordinated efforts among stakeholders such as the Heart and Stroke Foundation, public health agencies, ministries of health and care providers across the continuum to produce patient, family and caregiver education materials with consistent information and messages on risk factor management.
4. Coordinated processes for ensuring access to and awareness of educational materials, programs, activities, and other media related to risk factor management by healthcare professionals, patients and caregivers, including promotion of educational material and effective dissemination mechanisms.

Performance Measures

System Indicators:

1. Annual occurrence rates for CVT in each province and territory.
2. Number of individuals who experience CVT who are admitted to hospital annually.

Process Indicators:

3. Number of individuals who are readmitted to hospital within 30 days, 90 days and one year following initial admission for CVT, stratified by reason for readmission.
4. Number of visits to acute care post-discharge for individuals with CVT.
5. Number of follow-up investigations performed on individuals with CVT, stratified by age and sex (especially repeat CT/CTVs in young people) within first year following diagnosis.
6. Proportion of individuals with CVT who receive a referral for rehabilitation assessment at discharge and at one year.
7. Proportion of individuals with CVT who receive referrals to subspecialists, stratified by specialty (e.g., Ophthalmology, Hematology) in hospital and at 30 days following discharge.

Patient-oriented outcome and experience indicators:

8. CVT mortality rates across provinces and territories, including in-hospital or 30-day rate and one-year rate (KQI).
9. Quality of life rating at 30 and 90 days for individuals with CVT, using a validated tool.
10. Proportion of individuals with CVT unable to return to work or school following index event.
11. Proportion of individuals with CVT who experience adverse effects that impact daily living – e.g., changes in mood, fatigue, cognition, ongoing headaches at 30 and 90 days following diagnosis.

Measurement Notes

a. Validated tools should be used to measure quality of life, mood and cognitive changes and other impacts.
b. ***For Indicator #5:*** Due to the smaller incidence rates of CVT compared to other stroke types, numerators and denominators may become very small when looking at multiple sub-categories of complications and stratifying by age and sex. Larger grouping variables may be required.

Implementation Resources and Knowledge Transfer Tools

Resources and tools listed below that are external to Heart & Stroke and the Canadian Stroke Best Practice Recommendations may be useful resources for stroke care. However, their inclusion is not an actual or implied endorsement by the Canadian Stroke Best Practices team or Heart & Stroke. The reader is encouraged to review these resources and tools critically and implement them into practice at their discretion.

Healthcare Provider Information

- CSBPR Cerebral Venous Thrombosis Module: Appendix Four: Antiphospholipid Antibody Testing Flowsheet
- Heart & Stroke: Signs of Stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- CVT Consortium: https://cerebralvenousthrombosis.com/professionals/
- Heart & Stroke: FAST Signs of Stroke... what are the other signs?: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1

- Heart & Stroke: Virtual Stroke Care Implementation Toolkit: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/csbpr-virtual-stroke-toolkit-final.pdf?rev=e545b3d0a8394ca18586090a74cdcf49
- Heart & Stroke: Taking Action for Optimal Community and Long-Term Stroke Care (TACLS) A Resource for Healthcare Providers: https://www.strokebestpractices.ca/resources/professional-resources/tacls
- Stroke Engine: http://strokengine.ca/

Information For Individuals With Lived Experience of Stroke, Including Family, Friends and Caregivers

- Heart & Stroke: Cerebral Venous Thrombosis Infographic
- Heart & Stroke: Signs of Stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- CVT Consortium: https://cerebralvenousthrombosis.com/patients/patient-information-in-english/
- Heart & Stroke: FAST Signs of Stroke... what are the other signs?: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/pdf-files/canada/your-stroke-journey/en-your-stroke-journey-v20.pdf
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Enabling Self-management Following Stroke: A Checklist for Patients, Families and Caregivers: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbpr-enabling-self-management-following-stroke-checklist-jan2021-final.pdf?rev=03b045c41df04abfb7f4cb652869f031
- Heart & Stroke: A Family Guide to Pediatric Stroke: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/a-family-guide-to-pediatric-stroke-en.pdf?rev=ff206495b5a4479da4b1a1d7b54c7734
- Heart & Stroke: Stroke in Young Adults: A Resource for Patients and Families: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/stroke_young_final.pdf?rev=7338abd3dba746dc96180a057e244ce9
- Heart & Stroke: Secondary Prevention Infographic: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbpr7-infographic-secondaryprevention-final.pdf?rev=9f0dcf0ade22483ba9ae4113b2f0f3eb
- Heart & Stroke: Rehabilitation and Recovery Infographic: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/rehabilitation-nov2019/csbp-infographic-rehabilitation.pdf?rev=a2cff1fb27424c84bbd44b568d58d1b4
- Heart & Stroke: Transitions and Community Participation Infographic: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/transition-of-care-nov2019/csbp-infographic-transitions-and-participation.pdf?rev=595e990a17e14232aa3b1c731d983ce3
- Heart & Stroke: Virtual Healthcare Checklist: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbp-infographic-virtual-healthcare-checklist.pdf?rev=bf2f5b0e9e4a49cfbfc251208b6a15e2
- Heart & Stroke: Online and Peer Support: https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Stroke Engine: http://strokengine.ca/

Summary of the Evidence

Factors related to clinical decision-making for anticoagulation

Please see **section 2.1, "Antithrombotic management,"** for discussion of the evidence related to timing of transition from parenteral to oral anticoagulation.

Vitamin K antagonists have been the longstanding guideline-recommended treatment for secondary prevention after CVT (Ferro et al. 2017). Recently, multiple observational studies and small randomized trials have compared efficacy and safety of DOACs against warfarin for CVT. The RE-SPECT CVT trial randomized 120 individuals with CVT 1:1 to six months with dabigatran 150 mg bid, versus warfarin, target INR 2.0 - 3.0 (Ferro et al. 2019). There were no VTE recurrences in either group at 6 months. There were two major GI hemorrhages in the dabigatran group and one symptomatic intracranial hemorrhage in the warfarin group. There were no differences between groups with respect to recanalization. The pediatric EINSTEIN-Jr trial randomized 114 children with CVT 2:1 to three months of 20 mg equivalent dosing of rivaroxaban versus standard-of-care anticoagulation with either VKA, target INR 2.0 - 3.0, or low molecular-weight heparin (Connor et al. 2020). There was one recurrent VTE in the comparator group. Rates of recanalization were similar between groups. There were 5 clinically relevant non-major bleeding events in the rivaroxaban group and one symptomatic intracranial hemorrhage in the comparator group. The SECRET feasibility trial randomized 50 individuals with CVT 1:1 to a minimum of six months with rivaroxaban 20 mg daily versus standard-of-care anticoagulation with either warfarin, target INR 2.0 - 3.0, or low molecular-weight heparin (Field et al. 2023). At six months, there was one recurrent VTE in the rivaroxaban group. There was one symptomatic intracranial hemorrhage and two clinically relevant non-major bleeding events in the rivaroxaban group. There were no VTE recurrences, major or clinically relevant non-major bleeding events in the comparator group. There were no differences between groups with respect to recanalization. ACTION-CVT was a large retrospective international study comparing safety and efficacy of DOACs versus VKA prescribed to individuals with CVT as part of their routine clinical care (Yaghi et al. 2022b). Apixaban was the most commonly prescribed DOAC (67%), followed by rivaroxaban (18%) and dabigatran (14%), or other or multiple DOACs (3%). Rates of recurrent VTE did not differ between groups (aHR 0.94, 95% CI 0.15 - 1.73). There was a lower risk of major hemorrhage in the DOAC group (aHR 0.35, 95% CI 0.15 - 0.82), primarily driven by a lower risk of ICH. There were no differences in rates of partial or complete recanalization at a median of 345 days (IQR 140-720). A recent systematic review including three randomized trials and 16 observational studies comparing DOACs to VKAs found similar risks between groups with respect to VTE recurrence, major hemorrhage and complete recanalization (Yaghi et al. 2022a). Overall, the literature support using DOACs as an alternative to VKA in lower-risk individuals with CVT. DOACs are now included as an option for anticoagulation in CVT in the updated AHA/ASA guidelines (Saposnik et al. 2024).

Certain groups are excluded, or underrepresented, in studies to date comparing DOACs to warfarin. DOACs are contraindicated in pregnancy and breastfeeding and thus this population has been excluded by design. In addition to those who were pregnant, both RE-SPECT CVT and ACTION-CVT excluded individuals with malignancy, central nervous system infection, trauma and pregnancy. ACTION-CVT and SECRET excluded individuals with known antiphospholipid antibody syndrome. While malignancy-, infection- or trauma-associated CVT were not exclusion criteria for SECRET, these groups are not well-represented in the study. EINSTEIN-Jr had a large proportion of participants with CVT associated with head and neck infection (65%); less so major head trauma (7%) or active cancer (8%). No specific concerns related to use of DOACs were identified in these groups. The role of DOACs in malignancy-associated CVT remains an area of controversy, although randomized trials from the general (i.e. non-CVT) VTE literature suggest that DOAC is an acceptably safe and efficacious alternative to LMWH in malignancy-associated VTE (Agnelli et al. 2020; McBane et al. 2020; Raskob et al. 2018; Schrag et al. 2023; Young et al. 2018).

Clinical trials comparing DOACs to warfarin for prevention of venous and arterial events in antiphospholipid antibody syndrome (APLAS) have demonstrated an excess of thromboembolic events with DOAC. The TRAPS trial, which compared rivaroxaban to warfarin in 120 individuals with high-risk APLAS (triple-positive with a history of previous arterial or venous thromboembolism) was stopped early

due to an excess or arterial events in the rivaroxaban arm without any events in the warfarin arm (Pengo et al. 2018). A Spanish trial also examining rivaroxaban versus warfarin in 190 individuals with thrombotic APLAS found an excess of arterial thromboembolic events with rivaroxaban that was nearly double that of the warfarin group (Ordi-Ros et al. 2019). The ASTRO-APS trial, which was limited due to protocol modifications and slow recruitment, compared apixaban (initially 2.5 mg bid later changed to 5 mg bid) against dose-adjusted warfarin in 48 patients with definite (42%), likely (25%) or historical (33%) APLAS (Woller et al. 2022). There was a high rate of arterial thromboembolic events in the apixaban group compared to none in the warfarin group and the study was terminated having recruited one-quarter of its target sample size.

Duration of anticoagulation

In those without a permanent indication for anticoagulation following CVT, including antiphospholipid antibody syndrome, active malignancy, or major-risk hereditary thrombophilia, the optimal duration of anticoagulation for CVT is not known.

Previous AHA/ASA and European guidelines for the management of CVT recommend the initial use of parental heparin followed by transition to oral vitamin K antagonists (VKA) for 3-12 months in the context of transient risk factors, or indefinitely in the context of chronic major risk factors for thrombosis or recurrent VTE (Einhäupl et al. 2010; Ferro et al. 2017). Previous surveys of physician practices, and the recent Canadian SECRET randomized trial, suggest that most patients without an indication for permanent therapy are currently treated for 6-12 months (Coutinho et al. 2011b; Field et al. 2017).

This approach, however, diverges somewhat from current recommendations around management of DVT/PE from the general VTE literature. For DVT/PE, the first 3-6 months following VTE are considered as the “primary treatment” phase, with subsequent ongoing therapy termed “secondary prevention.” In the general VTE literature, events that are provoked in the context of a transient risk factor receive 3-6 months of primary treatment without secondary prevention. Events provoked by a chronic risk factor, however, may be indefinitely anticoagulated given the net clinical benefit of long-term versus short-term anticoagulation in this population, with decision-making based on a follow-up period of approximately 2 years. Overall, risk of bleeding is increased approximately two-fold, while relative rates of VTE recurrence and mortality are reduced by 20-30% and 75%, respectively.

How these results should be extrapolated to the CVT population, however, is unclear. The CVT population includes a high proportion of younger women with transient sex-specific provoking risk factors, including oral contraceptives and the puerperium. Outside of high-risk thrombophilias and those with a history of recurrent events, overall risks of recurrent CVT and other VTE appear to be low (Shu et al. 2022). However, certain groups, including those with unprovoked events, men, and heterozygotes for genetic thrombophilias such as Factor V Leiden and prothrombin gene mutation, (Palazzo et al. 2017; Pires et al. 2019) may have a higher risk. Estimated risks of recurrence are somewhat variable. A review of 4 observational studies from the American Society of Hematology estimated an overall rate of VTE recurrence of 38/1000 over the first year (Dentali et al. 2012a; Martinelli et al. 2010; Miranda et al. 2010; Palazzo et al. 2017). The recent retrospective ACTION-CVT study found a recurrence of 51 recurrent VTE (de novo recurrent CVT and peripheral VTE) per 1000 patient-years (Shu et al. 2022). There are additional inconsistencies in the literature around whether risk of recurrence is heightened in the first year as compared to subsequent years, (Shu et al. 2022) versus a more linear increase over subsequent years (Palazzo et al. 2017).

Additional information regarding duration of shorter versus longer durations of primary anticoagulation will be brought forth by the ongoing EXCOA trial comparing 3-6 months versus 12 months of anticoagulation (Miranda et al. 2018).

Refer to Section 3.2, “Role of Routine Follow-up Vascular Neuroimaging” around the role of repeat neuroimaging as it relates to duration of anticoagulation.

CVT workup: cancer screening

There is no strong evidence to date to suggest that individuals with CVT should receive enhanced cancer screening. A recent Danish population-based study with a median follow-up of 6.2 years found that overall, rate of incident cancer was not significantly higher in individuals with a diagnosis of CVT. Of 811 patients with CVT, 43 had an incident cancer diagnosis over time, rates that were similar to another recent Finnish population-based study (Sipilä et al. 2022). Risks of incident cancer compared to the general population were elevated over the first year following diagnosis, however, these high rates were driven by a small number of cases overall. The authors estimated that the number of patients to be screened in the six months after CVT to detect one additional incident cancer was 85.5 (95% CI 55.3 - 188.2) overall, 122.1 (95% CI, 71.7 - 411.2) in patients aged 18-54 years and 47.5 (26.2 - 258.8) in those aged $\geq$55 years (Skajaa et al. 2023). These numbers needed to screen are similar to those of DVT/PE.

Testing for Janus Kinase V617F mutations in people with CVT without signs or symptoms of myeloproliferative neoplasm (MPN) remains an area of controversy (Xavier et al. 2011). Larger cohorts of mostly unselected CVT patients from Italy, India and Israel report rates of 5.6-6.5% of the JAK2 V617F mutation (De et al. 2012; Lamy et al. 2017; Passamonti et al. 2012; Simaan et al. 2023). All series note that many diagnosed with the mutation at the time of their CVT did not meet criteria for MPN diagnosis.

CVT workup: hypercoagulability testing

Practices and recommendations around hypercoagulability testing following VTE continue to evolve. The recent guidelines from the American Society of Hematology for thrombophilia testing for management of venous thromboembolism included a conditional recommendation for patients with CVT where anticoagulation would otherwise be discontinued (Middeldorp et al. 2023). This recommendation was based on an estimate that, based on an annual recurrent risk of 38/1000/year (Dentali et al. 2012a; Martinelli et al. 2010; Miranda et al. 2010; Palazzo et al. 2017), that a strategy of testing for thrombophilia followed by indefinite anticoagulation in patients with thrombophilia, and stopping anticoagulation in patients without thrombophilia, would result in 18 (range 14-23)/1000 fewer recurrent VTE compared to a no-testing strategy.

Recommendations related to hypercoagulability testing for specific conditions have been published previously by the International Society on Thrombosis and Haemostasis and the International Society for Laboratory Hematology (Baker et al. 2020; Barbhaiya et al. 2023; Devreese et al. 2014; Marlar et al. 2021; Tripodi et al. 2020).

CVT workup: antiphospholipid antibody testing

Please see Section 3.1, ***Factors related to clinical decision-making for anticoagulation***, for a summary of the evidence related to warfarin versus DOACs in people who have a diagnosis of APLAS.

Given that a diagnosis of APLAS would affect decisions around choice of antithrombotic, it is reasonable to test for antiphospholipid antibodies in patients with CVT who do not have a previous diagnosis. In the absence of a history of APLAS or clinical suspicion of APLAS, however, it is reasonable to proceed with anticoagulation as if the patient did not have APLAS, without waiting for test results, and then altering the anticoagulant accordingly if testing is positive. The prevalence of APLAS-associated CVT is not known. A systematic review cited rates of 6-17% of positive antiphospholipid antibody testing in previous series, (Silvis et al. 2016) although definitions varied between studies and up to 5% of healthy individuals are noted to have antiphospholipid antibodies (Dabit et al. 2022).

Role of routine follow-up vascular neuroimaging

The literature comparing diagnostic accuracy of contrast-enhanced CT venography and contrast-enhanced MR venography to non-enhanced neuroimaging mainly relates to *diagnosis* of CVT, and not recanalization on follow-up imaging. One small study comparing contrast-enhanced versus time-of-flight MR venography in 6 patients with CVT undergoing follow-up imaging found that 10/15 venous segments

on contrast-enhanced MRV with peripheral enhancement and a central non-enhancing filling defect showed peripheral continuous channel morphology on time-of-flight MR venography. However, the study was cross-sectional and did not compare modalities with respect to assessing recanalization from baseline scans (Leach et al. 2007).

Whether degree of venous recanalization should inform duration of anticoagulation remains an area of uncertainty (Aguiar de Sousa et al. 2020; Aguiar de Sousa et al. 2018b; Ferro et al. 2022; Kim et al. 2023). Although a subset of clinicians will modify their duration of anticoagulation based on the degree of venous recanalization on repeat neuroimaging, (Field et al. 2017) it is unclear if this strategy is beneficial. An early prospective neuroimaging study found that 68% of patients experienced partial, and 4%, full recanalization, after one week of anticoagulation. By day 90, 95% of patients had partial (41%) or complete (54%) recanalization (Aguiar de Sousa et al. 2020). A substudy of the ACTION-CVT study found that 88.2% of patients had partial (48.5%) or complete (39.7%) recanalization. Of those patients who had complete recanalization, 59% were noted to be fully recanalized by three months, with 15.4% of additional patients achieving complete recanalization by 6 months and 16.7% by 12 months (Salehi Omran et al. 2023).

A recent prospective neuroimaging study noted that anticoagulated patients with a diagnosis of CVT who had at least partial recanalization within the first 8 days of treatment had fewer new non-hemorrhagic lesions and less extension of pre-existing non-hemorrhagic lesions. However, this was not associated with a reduction in headache or improved functional outcomes at day 90 (Aguiar de Sousa et al. 2020). Most recanalization literature focuses on later recanalization, past the three-month mark. A recent meta-analysis of observational data found that complete or partial venous recanalization was associated with an improved odds of a favourable functional outcome as compared with no recanalization as well as lower risk of recurrence and less presence of common headache (Aguiar de Sousa et al. 2018b). However, there was significant heterogeneity between studies, and the directionality of the association between recanalization and outcomes remains uncertain. The authors note that in meta-regression, the relationship between recanalization and functional outcomes was modified by sex. A prospective substudy of RESPECT-CVT found no association between recanalization and functional outcome (Ferro et al. 2022). Whether recanalization status is causally related to other post-CVT sequelae, including visual loss, cognition or development of dural arteriovenous fistulae (dAVF), is not known.

At present, there is no strong evidence to suggest routine follow-up neuroimaging to screen for dAVF after CVT. A substudy of the RE-SPECT CVT study found that out of 112 patients, none developed dAVF at six months on repeat MR venography (Ferro et al. 2020). A retrospective study from the international CVT consortium found that out of 1218 patients, 2.4% were found to develop dAVF on neuroimaging performed at a median of 6 months (IQR 5-12). Risk factors for dAVF included male sex, older age and late presentation with CVT (>30 days following symptom onset) (Lindgren et al. 2022).

Management of other post-acute sequelae of CVT

Although rates of functional independence after CVT are high, survivors are noted to have reduced quality of life, with a high prevalence of residual symptoms related to headache, depression, fatigue and cognitive impairment. In the Canadian SECRET trial, 72% of participants were functionally independent (modified Rankin 0 - 2) at the time of their diagnosis. However, mean baseline assessments were indicative of mild-moderate depression, substantial-severe impact of headache, substantial fatigue and impaired cognitive performance. On average, participants experienced improvements in all patient-centered metrics over time between baseline and day 180 and at day 365. Other retrospective studies suggest that reduced participation may persist in many survivors. A retrospective study from China including CVT patients who were employed or in school prior to their index event found that 42% had not returned at six months. Aphasia, cognitive impairment and recurrent CVT were independent predictors for an inability to return to previous activities (Liu et al. 2023).

The definition of “late seizures” in the CVT literature generally refers to those experiencing an event at seven days following presentation or later. A combined prospective and retrospective study from the International Cerebral Venous Thrombosis Consortium found that 11% of 1127 patients were noted to have late seizures, median time to onset being 5 months (IQR 1 - 16 months) (Sánchez van Kammen et

al. 2020). ASM was prescribed in 45% of patients prior to the first late seizure and in 94% following the first late seizure. Of those with late seizures, 70% were noted to have later recurrence, with a median time to recurrence of 1 month (IQR 0 - 8). However, the authors did not specify what proportion of those with later recurrence were no longer taking ASM. Independent risk factors for late seizures included acute seizures or status epilepticus at presentation, intracranial hemorrhage, subdural hematoma specifically, and decompressive hemicraniectomy. A meta-analysis including the aforementioned study and three smaller studies identified similar risk factors for late seizures (Gasparini et al. 2022).

Sex, gender and other equity-related considerations

Considerations related to choice of anticoagulant in women who are pregnant or breastfeeding are summarized in **Section 4.1, CVT and pregnancy**. Warfarin is a known teratogen and individuals with the potential to become pregnant should be counselled to use effective contraception while on this medication.

Determining duration of primary anticoagulation or strategies around secondary prevention anticoagulation may involve shared decision-making between patients and clinicians. Clinicians are encouraged to consider the potential for heavy menstrual bleeding in discussions with patients who menstruate and to take a thorough menstrual history as well as a complete blood count and ferritin at baseline. *Refer to section 4.1, clinical considerations, anticoagulation and heavy menstrual bleeding for further summary of the existing evidence around assessment and management of heavy menstrual bleeding.*

In a substudy of the ACTION-CVT study, Black race was an independent risk factor for recurrent VTE (HR 2.13, 95% CI 1.14-3.98), both overall in a sensitivity analysis examining events occurring off oral anticoagulation (HR 2.59, 95% CI 1.17-5.75). Provoking factors were not significantly different between individuals with Black race versus non-Black race, with lower rates of Factor V Leiden and prothrombin gene mutations in individuals with Black race. Black race was associated with lower rates of follow-up with INR checks in warfarin-treated patients. The authors concluded that, similar to what has been reported in the overall stroke literature, (Towfighi et al. 2023) that the increased risk associated with Black race was likely due to social determinants of health, including disparities in access to care, structural racism and socioeconomic inequities (Shu et al. 2022).

Evidence Table and Reference List: Cerebral Venous Thrombosis

Section 4 Special Considerations In The Longterm Management Of Individuals With Cerebral Venous Thrombosis

4. Special Considerations in the Longterm Management of Individuals with Cerebral Venous Thrombosis, Recommendations 2024

4.1 Cerebral Venous Thrombosis and Pregnancy

i. A history of CVT is not a contraindication to pregnancy [Strong recommendation; Moderate quality of evidence].

ii. Individuals with a history of CVT who are not receiving long-term anticoagulation, and, who become pregnant, should receive prophylactic low-dose thromboprophylaxis with low molecular weight heparin during their pregnancy and during the first six weeks post-partum, and should receive an assessment by a thrombosis specialist and/or obstetric medicine specialist [Strong recommendation; Moderate quality of evidence].

iii. Individuals who develop CVT during pregnancy should be anticoagulated with therapeutic Low Molecular Weight Heparin and receive follow-up by a Thrombosis and/or Obstetric Medicine specialist during their pregnancy [Strong recommendation; Moderate quality of evidence].

   a. A thrombosis specialist and/or obstetric medicine specialist should also be involved in anticoagulation management around the time of delivery [Conditional recommendation; Low quality of evidence].

iv. Direct oral anticoagulants (DOACs) and warfarin should not be used for anticoagulation in individuals who are pregnant [Strong recommendation; Low quality of evidence].

v. DOACs should not be used in individuals who are breastfeeding [Strong recommendation; Low quality of evidence].

Refer to CSBPR Acute Stroke Management during Pregnancy module for additional information.

Section 4.1 Clinical Considerations

4.1.1 Cerebral Venous Thrombosis and Pregnancy

1. There is uncertainty regarding the optimal mode of delivery in pregnant women with CVT. Discussion among the clinical team including neurology and obstetrics is recommended.

4.1.2 Anticoagulation and Heavy Menstrual Bleeding

1. Individuals who menstruate who are initiating anticoagulation should be counselled around the possibility of heavy menstrual bleeding on anticoagulation and should be referred to a thrombosis specialist if this issue arises.
2. Referral to gynecology should be made for definitive management of heavy menstrual bleeding or any post-menopausal vaginal bleeding on anticoagulation.
3. Use or continuation of OCP is acceptably safe if the individual is being concurrently anticoagulated. However, OCP should be discontinued if anticoagulation is discontinued.
4. Individuals with a history of CVT should be counselled to be vigilant for venous thromboembolism symptoms and should be assessed for thromboprophylaxis for venous thromboembolism during higher-risk scenarios (e.g. hospitalization, post-operative).

Rationale

CVT during pregnancy and puerperium is estimated to be 9 per 100,000 deliveries per year, accounting for approximately one-third of pregnancy-related stroke (Swartz et al. 2017). Among women who had sustained a prior CVT, the rate of recurrent CVT is much higher (9 per 1,000 pregnancies), which is approximately 80 times higher than would be expected in the general population (Aguiar de Sousa et al. 2016).

People with lived experienced emphasized the importance of receiving information about CVT and pregnancy that was relevant and tailored to their needs and life goals, as well as delivered at an appropriate time for the individual when they feel ready for such conversations. Information on the possibility of heavy menstrual bleeding on anticoagulation, and referrals to appropriate specialists should this occur, was also highly valued by individuals who menstruate and who were initiating anticoagulation. Individuals with CVT highlighted the importance of receiving information on risk associated with certain medications (e.g., OCP) and education on VTE symptoms for the general population.

System Implications

1. Systems in place to enable women who become pregnant or are planning pregnancy to access appropriate antenatal care.
2. Collaborative relationships established between obstetrical/maternal-fetal medicine, thrombosis experts, and stroke specialists to optimize access and management for women who experience CVT before, during or immediately after pregnancy.
3. Protocols to ensure rapid transfer of individuals with CVT who are pregnant to a centre with CVT and obstetrical services available.

Performance Measures

System Indicators:

1. Number of women who experience a CVT during pregnancy or within 6 weeks postpartum.
2. Proportion of women with a past history of CVT who experience a recurrent stroke (any subtype) during pregnancy or early postpartum.

Process Indicators:

3. Proportion of women with a history of CVT who are considering becoming pregnant or are pregnant who receive a referral to specialist care.
4. Proportion of women with a history of CVT who are prescribed anticoagulant prophylaxis with LMWH during a subsequent pregnancy.

Patient-oriented outcome and experience indicators:

5. Pregnancy-related maternal mortality and morbidity (venous thromboembolism, disability, postpartum hypertension) in women with a past history of CVT.
6. Proportion of women who experience CVT during pregnancy resulting in adverse fetal and neonatal outcomes (congenital anomalies, preterm delivery, perinatal and intrapartum fetal morbidity and mortality).
7. Descriptive statistics of CVT during pregnancy, including proportion of CVT occurring in each trimester, median gestational age at time of stroke, and maternal stroke severity as a result of CVT.

Measurement Notes

Implementation Resources and Knowledge Transfer Tools

Resources and tools listed below that are external to Heart & Stroke and the Canadian Stroke Best Practice Recommendations may be useful resources for stroke care. However, their inclusion is not an actual or implied endorsement by the Canadian Stroke Best Practices writing group. The reader is encouraged to review these resources and tools critically and implement them into practice at their discretion.

Healthcare Provider Information

- Canadian Stroke Best Practices Management of Acute Stroke during Pregnancy Consensus Statement
- CVT Consortium: https://cerebralvenousthrombosis.com/professionals/
- Stroke Engine: http://strokengine.ca/

Information For Individuals With Lived Experience of Stroke, Including Family, Friends and Caregivers

- Heart & Stroke: Cerebral Venous Thrombosis Infographic
- Heart & Stroke: Signs of Stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- CVT Consortium: https://cerebralvenousthrombosis.com/patients/patient-information-in-english/
- Heart & Stroke: FAST Signs of Stroke... what are the other signs?: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: What is Stroke? https://www.heartandstroke.ca/stroke/what-is-stroke
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/pdf-files/canada/your-stroke-journey/en-your-stroke-journey-v20.pdf
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Stroke in Young Adults: A Resource for Patients and Families: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/stroke_young_final.pdf?rev=7338abd3dba746dc96180a057e244ce9
- Heart & Stroke: Online and Peer Support: https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Stroke Engine: http://strokengine.ca/

Summary of the Evidence

Cerebral Venous Thrombosis and pregnancy

Rates of pregnancy-associated CVT are estimated to be 9/100,000 pregnancies. A meta-analysis of 13 studies found that after a pregnancy-associated CVT, risk of VTE recurrence during a subsequent pregnancy was 9/1,000 (95% CI 3-33) for CVT and 27/1,000 (95% CI 12-61) for peripheral VTE pregnancies. Rate of spontaneous abortion did not differ from that of the general population. The authors concluded that the absolute risk of pregnancy-associated VTE was low, but substantially higher (16-fold risk of CVT and 80-fold risk of VTE) compared to the general population (Aguiar de Sousa et al. 2016). An update to the meta-analysis found a trend towards lower rates of VTE in

patients receiving antithrombotic thromboprophylaxis with LMWH in both pregnancy and the puerperium (Aguiar de Sousa et al. 2018a).

Another study assessing recurrent VTE in pregnancy in women with a history of CVT interviewed 119 women who were pre-menopausal at the time of their CVT (10% pregnancy-associated CVT, 24% OCP-associated CVT) at a median of 14 years following their first event. There was 1 recurrent CVT among 82 pregnancies during follow-up (12 per 1,000 pregnancies; 95% CI, 2–66) in a woman during her first trimester with protein S deficiency receiving prophylaxis with LWMH. Two other women experienced non-cerebral VTE associated with pregnancy, both in the post-partum period (24 per 1,000 pregnancies; 95% CI, 7–85). One woman with recurrence had protein S deficiency and the event occurred on LMWH; the other had an event recovering from Caesarian section and was not on LMWH prophylaxis.

Prophylactic anticoagulation during pregnancy and the puerperium is indicated in women who experienced a CVT and are no longer on anticoagulation (Saposnik et al. 2024). The Highlow trial examined dosing regimens for prophylaxis during pregnancy (Bistervels et al. 2022). The trial recruited 1110 women with a history of venous thromboembolism who were currently pregnant and at a gestational age of 14 weeks or less. Participants were randomized 1:1 to weight-adjusted intermediate-dose vs. fixed low-dose low-molecular-weight heparin subcutaneously once daily until 6 weeks postpartum. The trial was powered for superiority and the primary efficacy outcome was confirmed VTE recurrence. The primary safety outcome was major bleeding in the antepartum, early post-partum (within 24 h after delivery), and late postpartum (24 h or longer after delivery until 6 weeks postpartum) periods. There were 11 (2%) VTE events (5 antepartum, 6 postpartum) in the intermediate-dose group and in 16 (3%, 5 antepartum, 11 postpartum) in the low-dose group (RR 0.69; 95% CI 0·32–1·47). On-treatment major bleeding (N=1045) occurred in 23 (4%) in the intermediate-dose group and in 20 (4%) of 525 in the low-dose group (RR 1·16; 95% CI 0·65–2·09). The authors concluded that fixed low-dose prophylaxis was appropriate given the lack of superiority of a higher-dose strategy. Co-management of pregnant patients with a history of CVT is recommended with thrombosis and maternal-fetal medicine experts.

Anticoagulation and heavy menstrual bleeding

Heavy menstrual bleeding (HMB) or abnormal uterine bleeding (which includes HMB and other differences in frequency, regularity or duration of bleeding) is estimated to occur in 70% of menstruating individuals who are on anticoagulation (De Crem et al. 2015; Micaily and Samuelson Bannow 2021). Underreporting and underascertainment, (Weyand and James 2021) as well as definitions for bleeding events in clinical trials, (Boonyawat et al. 2021) have been barriers in assessing prevalence of this issue with anticoagulation. Multiple definitions, including quantitative measures of blood loss, have been used but may be cumbersome for regular use (Zakherah et al. 2011). A more recent pragmatic definition used by international organizations is “excessive menstrual blood loss which interferes with physical emotional social and material quality of life, and which can occur alone or in combination with other symptoms”(Fraser et al. 2011).

HMB is associated with reduced quality of life (Lancastle et al. 2023) and can potentially worsen iron deficiency and anemia. One single-centre study identified an increased risk of VTE with HMB, likely due to associated issues with adherence to anticoagulation (Bryk et al. 2016). Importantly, HMB in patients on anticoagulation is treatable (DeLoughery and Bannow 2022). Collaborative management with gynecology and thrombosis medicine is encouraged. Options can include reinitiation or continuation of hormonal therapy while patients are anticoagulated, which is not associated with increased risk of recurrent VTE and reduces risk of bleeding, or procedural management, including endometrial ablation (DeLoughery and Bannow 2022). Evidence to support safety of continued use of oral contraception on anticoagulation after VTE comes from post-hoc analyses of DOAC trials for VTE. Use of oral contraception was not randomized. A sub analysis of 1888 women aged 60 and younger in the EINSTEIN-DVT and PE trials found that hormonal therapy was not associated with an increased risk of recurrent VTE in women receiving therapeutic anticoagulation (3.7% versus 4.7%, aHR 0.56, 95% CI 0.23 - 1.39) (Martinelli et al. 2016). A similar post-hoc analysis of the RE-COVER trial in 1264 women aged 18-50 found no association between hormonal contraception and VTE

recurrence during anticoagulation (OR 0.59, 95% CI 0.20 - 1.72) (Huisman et al. 2018). However, an international multicentre case-control study of VTE on oral contraceptives identified that the thrombogenic effect of estrogen-containing contraceptives persists within the three months following discontinuation (Venous thromboembolic disease and combined oral contraceptives: Results of international multicentre case-control study. World health organization collaborative study of cardiovascular disease and steroid hormone contraception 1995). Thus, timing of cessation may need to be considered in patients who continue oral contraceptives while on temporary treatment with anticoagulation (Schulman 2016). The safety and efficacy of other strategies used in clinical practice or in individuals with HMB without a history of VTE, including antifibrinolytics, (Hamulyák et al. 2021) and modification of anticoagulation (temporary lower dosing or interruption of therapy), are under investigation (DeLoughery and Bannow 2022).

Factor Xa inhibitors, but not dabigatran, a direct thrombin inhibitor, have been reported to have higher rates of abnormal uterine bleeding compared to VKA (Brekelmans et al. 2017; Hamulyák et al. 2021; Huisman et al. 2018; Martinelli et al. 2016; Scheres et al. 2018). The ongoing MEDEA trial is randomizing menstruating individuals on Factor Xa inhibitors 1:1:1 to a switch to dabigatran versus current therapy with tranexamic acid 1000 mg tid for four days starting on the first day of the menstrual period, versus current anticoagulant therapy alone. The primary outcome is the difference on the pictorial blood loss assessment chart (PBAC), a validated semi-quantitative score for menstrual product used pre- versus post-intervention.

Evidence Table and Reference List: Cerebral Venous Thrombosis

Section 5 Considerations related to Cerebral Venous Thrombosis in Special Circumstances

5. Considerations Related to Cerebral Venous Thrombosis in Special Circumstances

5.1 Trauma-Associated CVT

Note, no evidence-based recommendations included for this section

Section 5.1 Clinical Considerations

1. The antithrombotic management of individuals with CVT in the context of major head trauma should be managed with multidisciplinary expertise on a case-by-case basis. Management decisions may evolve over time and should incorporate clinical reassessment, when possible, and repeat neuroimaging.
2. The need for anticoagulation should be assessed in the context of whether the CVT is clinically symptomatic, demonstrates extension on follow-up vascular neuroimaging, and/or is associated with signs of parenchymal changes independently attributable to the CVT (i.e. venous edema/infarction, venous hemorrhage), as opposed to from an evolving traumatic brain injury.
3. The benefits of anticoagulation and dosing should be weighed against risks of intracranial or extracranial hemorrhage related to the traumatic brain injury and/or other extracranial injuries.

5.2 Incidentally Diagnosed Cerebral Venous Thrombosis

Note, no evidence-based recommendations included for this section

Section 5.2 Clinical Considerations

1. The clinical relevance of incidentally detected CVT in the context of vascular neuroimaging performed for other indications is not known. Indications for hypercoagulable testing should be the same as in symptomatic CVT.
2. Individuals with incidentally diagnosed CVT should be referred for routine thrombosis and ophthalmology assessments.
3. Suitability for primary anticoagulation and secondary prevention should be considered on a case-by-case basis in clinical and radiologic context.
4. It should be noted that dural arteriovenous fistula is associated with CVT and definitive investigations and management are outside the scope of this guideline. Individuals with dural arteriovenous fistula without definite preceding history of CVT should be evaluated by a interdisciplinary team to determine if there is any clinical suspicion of preceding history of CVT which will guide further investigations and management.

5.3 COVID-19-associated Cerebral Venous Thrombosis

Note, no evidence-based recommendations included for this section

Section 5.3 Clinical Considerations

1. Severe acute respiratory syndrome coronavirus *2* (COVID-19) infection may be associated with an increased risk of CVT. CVT in the context of COVID-19 infection should not be

managed differently than other cases of CVT. All recommendations and consensus statements in this module should be applied where appropriate.

2. Testing for COVID-19 infection in the context of CVT should be performed as per local protocols.
3. For individuals with CVT who have an indication for ritonavir, the treating physician should be aware of a potential drug-drug interaction with DOACs with increased anticoagulant effect. An individualized approach should be considered in adjusting management.

5.4 Vaccinations and Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) - Associated CVT

Note, no evidence-based recommendations included for this section

Section 5.4 Clinical Considerations

1. A history of CVT is not a contraindication to receiving mRNA vaccinations against COVID-19 or vaccinations against other diseases. Anticoagulant therapy is not a contraindication to receiving vaccinations. Application of prolonged pressure at the injection site following vaccination is recommended to reduce bruising.
2. VITT as the cause of CVT is extremely rare. Cases should only be considered in the specific context of recent adenovirus vector-based COVID-19 vaccination (AstraZeneca/Oxford ChadOx1 nCov-19 or Janssen/Johnson & Johnson Ad26.COV2.S).
3. Diagnostic criteria for VITT have varied depending on timing of publication, concurrent state of knowledge and local clinical environment. Common elements of most diagnostic criteria include elevated D-dimer, reduced fibrinogen, positive anti-Platelet Factor 4-antibodies by ELISA testing, thrombocytopenia and onset of symptoms after 4 days of adenovirus vector-based COVID-19 vaccination. Diagnosis as per local protocols is advised.
4. Management of VITT-associated CVT is distinct from other types of CVT. Treatment guidelines have been published by several national and international societies and generally involve use of high-dose intravenous immunoglobulin (IVIG), use of non-heparin anticoagulation, and avoidance of platelet transfusions unless there is life-threatening bleeding or immediate major surgery is indicated.
5. In cases of CVT where VITT is a potential consideration, expert thrombosis consultation should be sought immediately and prior to the initiation of therapy. Transfer to an EVT-capable centre should also be considered.

Rationale

The management of CVT occurring in certain contexts may be different from typical approaches to managing acute symptomatic CVT. The optimal management of CVT associated with head trauma, and CVT found incidentally on scans performed for other indications, is not clear. Head trauma is a well-documented risk factor for CVT, although the prevalence is not well-characterized. A US-based health services study found that 11% of CVT cases were associated with trauma (Otite et al. 2020). Skull fractures involving a venous sinus are at higher risk (Bokhari et al. 2020). Regarding incidental CVT found on scans for other indications, one Canadian study estimated that 11% of CVT cases at a single centre were incidental findings (Zhou et al. 2022).

The management of CVT occurring in association with Vaccine-induced Thrombosis with Thrombocytopenia (VITT) is distinct from the management of non-VITT-associated CVT. VITT is a very rare autoimmune complication of adenovirus vector-based COVID vaccinations affecting 1/26500 to 1/1273000 individuals with first doses of the AstraZeneca vaccine (ChAdOx1 nCoV-19) administered (Pai 2022). CVT was a common complication seen with VITT; immunomodulation is a cornerstone of management.

Data from the earlier part of the COVID-19 pandemic suggest that there is a heightened risk of CVT associated with recent COVID infection. Management, however, does not differ from that of non-COVID-associated CVT.

System Implications

1. Integration of care across all disciplines for people with CVT to efficiently manage appointments and ensure coordination of care, especially during transition from inpatient to outpatient and community-based care.
2. Support for ongoing research into diagnosis and management for individuals with CVT from a range of causes.

Performance Measures

System Indicators:

1. Number of individuals who experience CVT who are admitted to hospital annually.
2. Proportion of people who experience a CVT related to major trauma or other primary diagnoses.

Process Indicators:

3. Proportion of incidentally-diagnosed CVT referred for hematology assessment.
4. Proportion of individuals with CVT who have follow-up with a stroke specialist.

Patient-oriented outcome and experience indicators:

5. Mortality rates for individuals with other health conditions (e.g., COVID-19, VITT) who experience a CVT related to that condition (stratified by comorbidity).

Measurement Notes

Implementation Resources and Knowledge Transfer Tools

Resources and tools listed below that are external to Heart & Stroke and the Canadian Stroke Best Practice Recommendations may be useful resources for stroke care. However, their inclusion is not an actual or implied endorsement by the Canadian Stroke Best Practices writing group. The reader is encouraged to review these resources and tools critically and implement them into practice at their discretion.

Healthcare Provider Information

- CVT Consortium: https://cerebralvenousthrombosis.com/professionals/
- Stroke Engine: http://strokengine.ca/

Information For Individuals With Lived Experience of Stroke, Including Family, Friends and Caregivers

- Heart & Stroke: Cerebral Venous Thrombosis Infographic
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/pdf-files/canada/your-stroke-journey/en-your-stroke-journey-v20.pdf
- CVT Consortium: https://cerebralvenousthrombosis.com/patients/patient-information-in-english/

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Online and Peer Support: https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Stroke Engine: http://strokengine.ca/

Summary of the Evidence

Trauma-associated CVT

Head trauma is a well-documented risk factor for CVT, although rates are challenging to ascertain from observational CVT cohorts, which may focus primarily on individuals presenting with a diagnosis of new symptomatic CVT. A recent Canadian single-center study found that one-quarter of 289 CVT cases identified over a 10-year period through discharge diagnosis coding and validated through chart review were associated with trauma (Zhou et al. 2022) and an US-based study using State Inpatient data from New York and Florida found that 11.3% of cases identified between 2006-2016 were associated with a comorbid code for trauma (Otite et al. 2020).

Estimates for rates of CVT complicating head trauma are evolving as use of routine vascular imaging continues to increase. One Chinese single-centre study of 240 consecutive patients with moderate-to-severe closed traumatic brain injury found a CVT on CT venography or MR venography in 16.7%. (Li et al. 2015). Injuries crossing a venous sinus, specifically skull fracture or epidural hematoma, were found to be independent risk factors for CVT. A meta-analysis focusing specifically on patients with skull fracture reported a pooled frequency of 26.2% (Bokhari et al. 2020).

The body of literature examining secondary injury attributable to CVT after head trauma is small, and with methodological limitations. Rates of venous infarction and edema reported in three studies including adults were highly variable (5-46%) (Netteland et al. 2022). One study reported rates of secondary ICH attributable to the CVT in 11% of 73 patients. Members of the writing group note that this high rate is at odds with our collective clinical experience (Netteland et al. 2020). The aforementioned systematic review examined the available evidence for use of anticoagulation or specific treatment regimens did not find specific comparative studies but noted that the majority of studies including adults included a subset of patients treated with anticoagulation, (Netteland et al. 2022) although the writing group notes that this includes patients treated with both prophylactic as well as therapeutic doses. In the absence of supportive evidence for a particular strategy, case-by-case collaborative management is recommended.

Incidentally diagnosed CVT

With increased use of routine vascular neuroimaging, incidental CVT may be diagnosed more frequently. A single-centre Canadian study found that 11% of CVT cases identified between 2008-2018 using administrative data and verified through chart review were new incidental diagnoses. In the general VTE literature, the majority of prognostic studies on incidental VTE focus on populations with cancer. One registry including a non-cancer population (n=68 incidental, 1501 symptomatic) found that 90-day VTE recurrence was similar after incidental versus symptomatic VTE (1.5% vs. 2.3%, HR 1.02, 95% CI 0.30-3.42) (Spirk et al. 2021). Thus, assessment for suitability for anticoagulation is warranted. Ophthalmological assessment should be considered given that patients may be unaware of visual deficits complicating CVT.

COVID-19-associated CVT

COVID-19 has been associated with increased risk of CVT in both community- and hospital-based cohorts. Community-based studies have cited incidence rates with SARS-CoV-2 infection that are substantially higher than baseline incidence rates, though estimates have varied widely. A study using US-based administrative data reported a rate of 42.8 (95% CI 28.5 - 64.2) per million within the first

two weeks of infection (Taquet et al. 2021); a Singapore-based study examining radiologically-confirmed CVT diagnosed within 6 weeks of SARS-CoV2 infection estimated an incidence rate of 83.3 (95% CI 30.6 - 181.2) per one hundred thousand person-years based on the total number of SARS-CoV2 infections reported in Singapore over the same time period (Tu et al. 2022). Estimates from hospitalized patients are also variable. One study using US hospital-based administrative data estimated an overall rate of 231 per million person-years in patients hospitalized with COVID-19 (95% CI 152 - 351) (McCullough-Hicks et al. 2022); a meta-analysis of case series estimated a rate of CVT in hospitalized patients with COVID-19 that was 0.08% (95% CI 0.01% - 0.5%) (Baldini et al. 2021). Mortality rates with COVID-19-associated CVT may be higher than with non-COVID-associated CVT, although reporting biases cannot be excluded and small numbers and limited details make it challenging to ascertain if heightened mortality is due to worse CVT severity versus other medical issues (Siegler et al. 2023).

Vaccination

A history of CVT is not a contraindication to receiving mRNA vaccinations against COVID-19 or vaccinations against other infections. One observational study of 62 patients with a history of CVT receiving COVID-19 vaccination (69% Pfizer, 11% Moderna, 11% AstraZeneca ChAdOx1 and 9% Janssen Ad26.COV2.S found no thrombotic recurrences within 30 days of vaccination (95% CI 0.0 - 5.8%) (Gil-Díaz et al. 2022). In the general population, most studies have not found an increase in the risk of CVT following mRNA COVID-19 vaccination (Cari et al. 2021; Houghton et al. 2022; Simpson et al. 2021); one UK population-based study identified a small increased risk of CVT associated with mRNA vaccination on the order of 1 per 500000 doses (Hippisley-Cox et al. 2021; Nicholson et al. 2022). One retrospective study from the Mayo Clinic Health system that also examined risk associated with 10 common non-COVID-19 vaccines (n=771805 doses) found no difference in risk of CVT in the 30 days pre- versus post-vaccination (Pawlowski et al. 2021).

VITT-associated CVT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) was first identified as an entity in 2021, occurring as a rare complication after adenovirus vector-based vaccination against COVID-19 (ChAdOx1 nCoV-19 [AstraZeneca-Oxford] and Ad26.COV2.S [Janssen/Johnson+Johnson]). Antibodies directed against platelet factor-4 (PF4) were soon identified in association with the disorder.

Early case series of patients who were later identified as having confirmed or suspected VITT included patients with thrombocytopenia and venous and arterial thromboembolic events, but with a preponderance of CVT in particular (Klok et al. 2022). An international cohort comparing VITT-associated CVT to non-VITT-associated CVT found that the former was associated with a more fulminant course at presentation than non-VITT CVT, with higher rates of mortality, intracerebral hemorrhage and use of EVT and hemicraniectomy (Sánchez van Kammen et al. 2021b).

Overall, VITT is extremely rare, although incidence rates have varied widely, ranging from 1/265,000 to 1/127,000 per first doses and 1/518,181 after second doses of ChAdOx1 nCoV-19 (AstraZeneca-Oxford) vaccination, respectively, and 1/263000 Ad26.COV2.S (Janssen/Johnson+Johnson). Variable rates have been attributed to a number of factors including demographic differences between cohorts and differences in reporting structure (Klok et al. 2022; Pai 2022). Diagnostic criteria for the syndrome have evolved, but the UK Expert Hematology Panel (Pavord) criteria have been used in the Cerebral Venous Sinus Thrombosis With Thrombocytopenia Syndrome Study Group, and include: onset of symptoms 5–30 days (5–42 days if isolated DVT or PE) after COVID-19 vaccination, presence of thrombosis, thrombocytopenia (platelet count <150 × 109 cells per L), D-dimer concentration of more than 4,000 FEU), and positive anti-PF4 ELISA assay (Pavord et al. 2021). Diagnosis of VITT is considered definite if all five criteria are present and probable if one is missing. Later studies have identified patients without demonstrable thrombosis who otherwise meet criteria.

Thrombocytopenia in non-VITT CVT is unusual, with a prevalence of 8% in a study of 865 patients from the International CVT Consortium (Sánchez van Kammen et al. 2021a). The mechanism of VITT

has been likened to heparin-induced thrombocytopenia, which similarly has antibodies directed against PF4, although typical HIT, unlike VITT, is less commonly complicated by CVT. A meta-analysis of HIT case series reported 1.6% with CVT from 1,220 patients with HIT (Aguiar de Sousa et al. 2022). Greinacher and colleagues, supported by a combination of biophysical imaging, mouse modelling and analysis of samples from VITT patients, proposed a two-step process where (1) vaccine components form complexes with PF4, leading to exposure of an epitope ("neoantigen") while stimulating a proinflammatory response that amplifies production of antibodies against the neoantigen. (2) After several days, there is a sufficient amount of anti-PF4 antibodies to activate platelets; granulocytes, mediated by the presence of PF4-activated platelets, are also activated to release procoagulant neutrophil extracellular traps (NETs) (Greinacher et al. 2021). The reasons why CVT and splanchnic vein thrombosis, another unusual site, were more commonly involved in VITT remains unknown. Selectively persistent procoagulant activity of NETs in central nervous system endothelial cells has been proposed, (Greinacher et al. 2021) as well as procoagulant platelet-derived microparticles (also expressed by PF4) expressing tissue factor, mediating thrombogenesis in the cerebral venous system in particular (Marchandot et al. 2021).

Most management recommendations by national and international bodies thus involved common tenets of (1) immunomodulation, with intravenous immunoglobulin recommended in particular due to selective inhibition of VITT-mediated platelet activation of the FcγRII receptor on PF4 (2) non-heparin-based anticoagulation including DOACs, fondaparinux, danaparoid or argatroban, due to the theoretical risk of worsening the HIT-like response with heparin or heparinoids, (3) supportive care, avoiding platelet transfusions when possible to reduce additional substrate for the autoimmune response (Klok et al. 2022). The prognosis of VITT has improved over time, likely due to a combination of improving awareness with associated earlier diagnosis and treatment, in addition to the establishment of management guidelines alongside evolving understanding of pathophysiology (Scutelnic et al. 2022).

High-risk scenarios

After CVT, it is not known whether targeted prophylaxis would also be suitable in other higher-risk contexts. The American Society of Hematology guidelines for management of venous thromboembolism prophylaxis issued a conditional recommendation with very low certainty for graduated compression stocking or prophylactic LMWH for individuals with a history of VTE embarking on long-distance travel >4 hours (Schünemann et al. 2018). The recommendation did not pertain specifically to individuals with a history of CVT.

Evidence Table and Reference List: Cerebral Venous Thrombosis

APPENDIX ONE: CEREBRAL VENOUS THROMBOSIS SCIENTIFIC WRITING GROUP AND AUTHORS 2024

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Thalia S. Field, MD, MHSc, FRCPC **Co-Chair**	Associate Professor, Sauder Family/Heart and Stroke Professor of Stroke Research, Division of Neurology, University of British Columbia, Stroke Neurologist, Vancouver Stroke Program	Vancouver, British Columbia	Sauder Family/Heart and Stroke Professorship of Stroke Research, UBC for Protected time; Professional Investigator Awards from Bayer Canada, Heart and Stroke Foundation, CIHR, Health Research BC (Michael Smith); In-kind study medication (Bayer) for CIHR Project; research grants from the Heart and Stroke Foundation of Canada and Health Research BC; Educational events, personal fees from HLS Therapeutics; Expert witness - personal fees from AstraZeneca, Bayer Canada, Roche, HLS Therapeutics; Board member, DESTINE Canada and DESTINE Canada Stock options.
Jennifer Mandzia, MD, PhD, FRCPC **Co-Chair**	Associate Professor, Department of Clinical Neurological Sciences, Western University, Medical Director Southwestern Ontario Stroke Network and LHSC Stroke Program	London, Ontario	Received Study specific payments for participating site in the SECRET study; Member of the SECRET Study Steering Committee.
Derek B. Debicki, MD, PhD FRCPC, CSCN (EEG)	Assistant Professor, Neurocritical Care & Epilepsy, Department of Clinical Neurological Sciences, Western University, London Health Sciences Centre	London, Ontario	Member of speakers' bureau for UCB Canada.
Jonathan Gorman MD, FRCPC	Clinical Assistant Professor, Division of Neurology, University of British Columbia; Stroke Neurologist, Vancouver Stroke Program	Vancouver, British Columbia	Received honoraria from Astra Zeneca; Principal Investigator for the OCEANIC-Stroke study with Bayer; support for attending investigator meetings from Bayer.
Manraj (Raju) K.S. Heran, MD, FRCPC	Associate Professor, Division of Neuroradiology, Department of Radiology, University of British Columbia and Vancouver General Hospital; Section of Pediatric Interventional	Vancouver, British Columbia	None to declare

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
	Radiology, BC Children's Hospital.		
Leonard A. Levin, MD, PhD, FCAHS	Distinguished James McGill Professor and Chair of Ophthalmology and Visual Sciences, McGill University	Montreal, Quebec	Received grant finding from CIHR, US Department of Defense, NIH, Canada Research Chairs, Canadian Foundation for Innovation; Royalties from Elsevier for books unrelated to manuscript; Consulting fees from Dompe, Perfuse, Quark, Santen, Neuroptika, Annexon, Roche, Galimedix, Eyevensys, UNITY, Janssen, LifeBiosciences, Prilenia. Honoraria at various non-profit universities and scientific conferences unrelated to manuscript; Advisory board member for Gilbert Family Foundation and National Eye Institute; Former chair of Ophthalmology and Visual Sciences at McGill.
Mahendra Moharir MD	Professor, Dept. of Pediatrics, Temerty Faculty of Medicine, University of Toronto; Clinical Director, Children's Stroke Program, Division of Neurology, The Hospital for Sick Children	Toronto, Ontario	None to declare
Lissa Peeling, MD, FRCSC	Associate Professor, Department of Surgery, Division of Neurosurgery, University of Saskatchewan	Saskatoon, Saskatchewan	Serves as DSMB/CEC member for 2 trials with Styker Neurovascular.
Kanjana S Perera MD, FRCPC	Associate Professor Medicine (Neurology), McMaster University	Hamilton, Ontario	Received an education grant from Bayer AG; Clinical trial investigator for NAVIGATE-ESUS, Y-ESUS, CATIS-ICAD, AXIOMATIC, SECRET, TIMELESS, ACT.
Deborah Siegal, MD, MSc, FRCPC	Associate Professor and Scientist, Ottawa Hospital Research Institute, University of Ottawa Hematologist, Department of Medicine, The Ottawa Hospital	Ottawa, Ontario	Received consulting fees from Astra Zeneca (paid indirectly to institution); honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astra Zeneca, BMS-Pfizer, Roche, Servier; board member for Thrombosis Canada, Anticoagulation Forum, Hemostasis and Thrombosis Research Society.

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Steve Verreault, MD, FRCPC	Clinical professor Université Laval, Department of Medecine (Neurology); Stroke Neurologist, Head of Neurology, Hôpital Enfant-Jésus, CHU de Québec .	Quebec City, Quebec	None to declare
Wein, Theodore MD, FRCPC, FAHA	Assistant Professor of Neurology and Neurosurgery, McGill University		Holds grants from CIHR, Ipsen, AbbVie; receives consulting fees from AbbVie, Servier, Ipsen; honoraria for lectures from Ipsen, Servier, AbbVie; support for attending meetings from Ipsen; advisory board member for Pacers, Sunrise, Revance.
Smith, Eric E. MD, MPH, FRCPC, FAHA	Professor of Neurology, Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary; Neurologist, Calgary Stroke Program, Foothills Medical Centre	Calgary, Alberta	Nothing to declare
Mountain, Anita MD, FRCPC	Assistant Professor Division of Physical Medicine & Rehabilitation, Department of Medicine, Dalhousie University; Medical Lead, Acquired Brain Injury Program, Queen Elizabeth II Health Sciences Centre.	Halifax, Nova Scotia	Received grants from CIHR, Brain Canada, Heart and Stroke Foundation, Canadian Partnership for Stroke Recovery Governors of the University of Calgary Drs. Miriam and Adelson Medical Research Foundationship for Stroke Recovery; Site QI for Multi-centre studies FLOW: FLuoxetine to Open the critical time period Window to improve motor recovery after stroke, CAMAROS:The CAnadian Maraviroc Randomized controlled trial to Augment Rehabilitation Outcomesafter Stroke, MODEX: MODafinil and EXercise for PostStroke Fatigue; Rehab Co-Lead for Canadian Stroke Best Practice Advisory Committee, Heart and Stroke (no remuneration).

APPENDIX TWO: CEREBRAL VENOUS THROMBOSIS EXTERNAL REVIEWERS 2024

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Diana Aguiar de Sousa, MD, PhD	Assistant Professor, University of Lisbon, Faculdade de Medicina, Universidade de Lisboa; Consultant Neurologist, Lisbon Central University Hospital and Faculty of Medicine.	Lisbon, Portugal	Investigator or national coordinator: (ELAN) for DISTAL trial, LIBREXIA STROKE, ELAN trial, BIA-2093- 213. Received personal fees for AstraZeneca and Organon advisory board participation, travel support from Boehringer Ingelheim, DSMB participation for the SECRET trial (University of British Columbia) and speaking fees from Bayer and Bial. Speaker bureau for Bayer and Bial
Lana A. Castellucci, MD, MSc	Associate Professor, University of Ottawa, Department of Medicine; Scientist, Ottawa Hospital Research Institute.	Ottawa, Ontario	National New Investigator Award from the Heart and Stroke Foundation of Canada. Grant or honorarium: LEO Pharma
Luciana Catanese, MD	Associate Professor of Medicine, Division of Neurology, McMaster University; Director, Hamilton General Hospital Stroke Unit and McMaster Stroke Fellowship Program.	Hamilton, Ontario	Speaker and consultant fees from ROCHE and Servier Inc.
Johnathon Coutinho, MD, PhD	Associate Professor, Amsterdam University Medical Centers, University of Amsterdam; Stroke Neurologist.	Amsterdam, Netherlands	Co-founder and shareholder for TrianecT BV. Received grant support from Boehringer Ingelheim, Bayer, Astra Zeneca
Laura Gioia, MD, MSc	Stroke Neurologist Clinical Assistant Professor, Neurosciences, Centre Hospitalier de l'Université de Montréal	Montréal, Quebec	Advisory Board Honoraria/Speaker fees: AstraZeneca, Bayer, BMS Pfizer. Grant in Aid from Heart and Stroke Foundation of Canada. Currently participating, or have participated within the past two years, in a clinical trial: ENRICH-AF, COVASC-ich, FASTEST (Site Principal Investigator)
Brett Graham, MD, FRCPC	Assistant Professor, University of Saskatchewan; Medical Director, Stroke Prevention Clinic, Royal University Hospital.	Saskatoon, SK	Member of Saskatchewan chapter of the Heart and Stroke Foundation of Canada. Received grant or honorarium from HLS Therapeutics, member of a National Stroke Neurologist Expert Panel for icosapent ethyl. Local PI for Study of Rivaroxaban for CeREbral Venous Thrombosis (SECRET)

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Sherry Hu, MD, FRCPC, FCSC	Assistant Professor, Dalhousie University	Halifax, Nova Scotia	Site PI for OCEANICS. Sub-I for ENRICH AF, ESCAPE MEVO, ESCAPE NEXT, ACT, ANNEXA, and TEMPO-2. Received $200 honorarium for writing a stroke book chapter for Canadian Pharmacists Association.
Sylvain Lanthier, MD OD, CSPQ	Associate professor, University of Montreal, Faculty of Medicine, Department of Neurosciences; Stroke Neurologist, Hôpital du Sacré-Coeur de Montréal.	Montreal, Quebec	Steering Committee for Bayer, Brain AF. Speaker for BMS-Pfizer, Servier. Grant or honorarium from BMS-Pfizer, Servier, Ad Board member.
Neshika Samarasekera, PhD, MRCP	Honorary Clinical Senior Lecturer, University of Edinburgh; Consultant Neurologis.	Edinburgh, Scotland	Grant or honorarium from UK Stroke Association.
Arturo J. Tamayo, MD, FAHA, MSc, FAAN	Assistant Professor of Neurology, University of Manitoba; Consultant, HSC Winnipeg Stroke Clinic; Director, Brandon Stroke Prevention Clinic.	Winnipeg, Manitoba	Principal Investigator from ARCADIA and ENRICH AF.
Katie White, B.Sc.PT, M.Sc.	Director, Health Systems, Heart and Stroke Foundation of Canada; Previously, Lead, Provincial Clinical Initiatives and Innovation, Stroke Services BC.	Port Moody, British Columbia	Nothing to declare

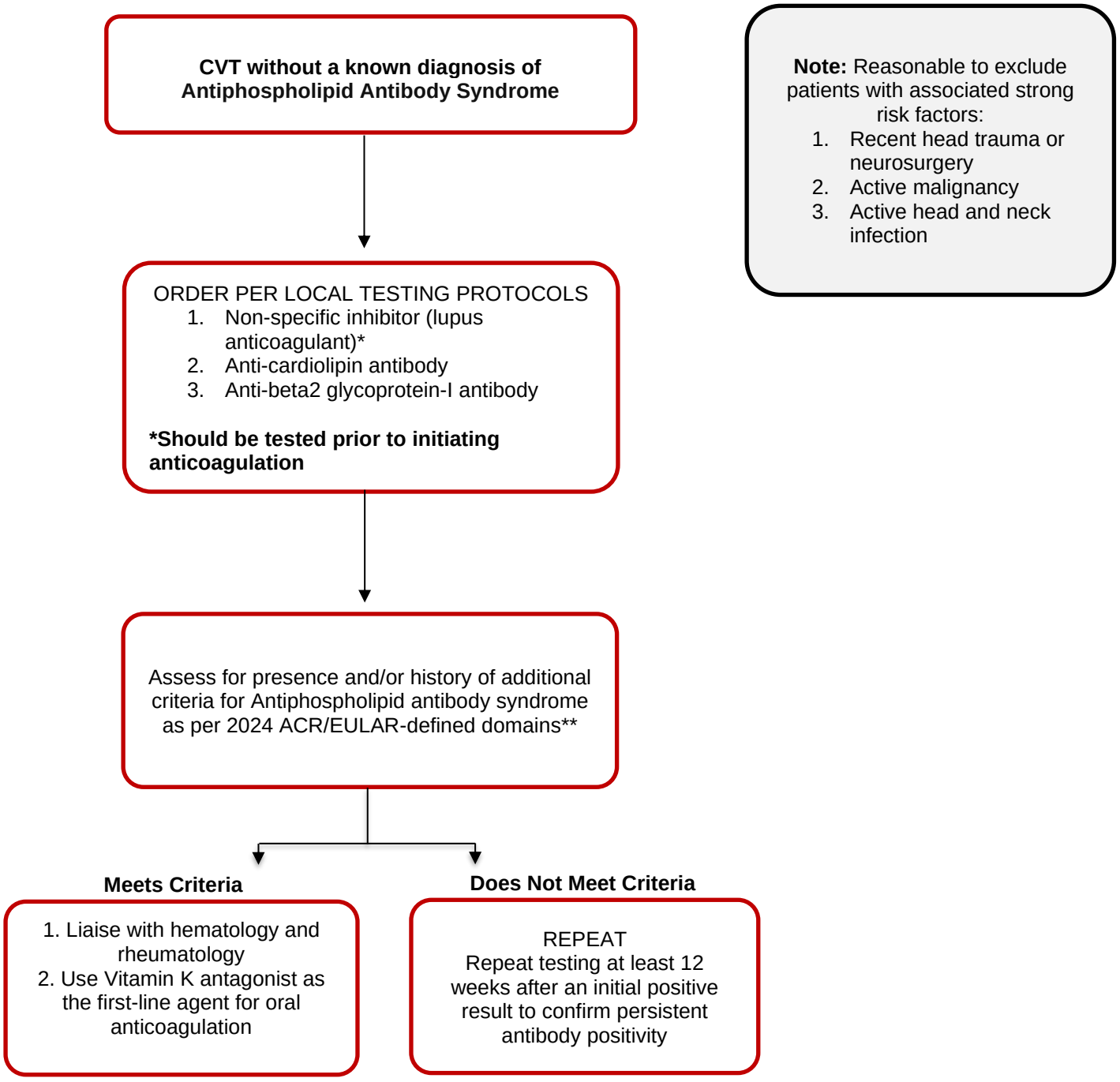
APPENDIX THREE: RECOMMENDED LABORATORY INVESTIGATIONS FOR INDIVIDUALS WITH CEREBRAL VENOUS THROMBOSIS

Recommended Laboratory Investigations for Individuals with acute presentation of cerebral venous thrombosis		
*Note: This list presents the recommended **initial** laboratory tests for individuals with CVT. Individual presentation, clinical judgment, and local protocols should be considered in selecting appropriate laboratory investigations and the timing of completion.*		
Complete blood count (CBC)	International Normalized Ratio (INR)	Partial thromboplastin time (aPTT)
Electrolytes	Creatinine and glomerular filtration rate (eGFR)	Liver enzymes (e.g., AST, ALT)
Random glucose	TSH	Pregnancy test (if applicable)
In individuals with CVT without a known APLAS diagnosis: Anticardiolipin antibodies, Beta-2-glycoprotein, Lupus anticoagulant (draw prior to initiating anticoagulation)		

Additional Laboratory Investigations for Consideration in Specific Circumstances		
*Note: Some individuals with CVT may require additional investigations to fully understand their clinical situation. The investigations noted below may be considered in **selected** individuals with CVT in the context of an appropriate clinical presentation and medical history.*		
ESR or CRP	Blood cultures	ANA and other connective tissue markers
Malignancy workup, JAK-2 mutation testing (*see Section 3.1, "Cancer screening"*)		
Lumbar puncture – in the specific context of concerns related to central nervous system infection/inflammation or leptomeningeal carcinomatosis, and not while on therapeutic anticoagulation (*see Section 1.2.2, diagnosis)*		

Recommended Laboratory Investigations at the time of completion of primary anticoagulation		
Venous hypercoagulability screen: For individuals without an indication for permanent anticoagulation		
Protein S	Protein C	Factor V Leiden
Prothrombin gene mutation	Antithrombin III	

APPENDIX FOUR: ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS) TESTING FLOWSHEET



**The 2024 ACR/EULAR Criteria for antiphospholipid antibody syndrome use a weighted scoring system using criteria within 6 clinical domains - macrovascular (venous thromboembolism), macrovascular (arterial thrombosis), microvascular, obstetric, cardiac valve and hematology - in addition to laboratory criteria. Please refer to: Barbhaiya M, et al. Ann Rheum Dis 2023;82:1258–1270. doi:10.1136/ard-2023-224609

APPENDIX FIVE: REFERENCES

Aaron S, Van Kammen M, Conforto A, Arauz A, Carvalho M, and Masjuan J. Decompressive neurosurgery for patients with severe cerebral venous thrombosis: Final results of the decompress 2 study. *Eur Stroke J.* 2021. 6 (1S): 4.

Afifi K, Bellanger G, Buyck PJ, Zuurbier SM, Esperon CG, Barboza MA, et al. Features of intracranial hemorrhage in cerebral venous thrombosis. *J Neurol.* 2020. 267 (11): 3292-3298.

Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med.* 2020. 382 (17): 1599-1607.

Aguiar de Sousa D, Canhão P, and Ferro JM. Safety of pregnancy after cerebral venous thrombosis: A systematic review. *Stroke.* 2016. 47 (3): 713-8.

Aguiar de Sousa D, Canhão P, and Ferro JM. Safety of pregnancy after cerebral venous thrombosis: Systematic review update. *J Neurol.* 2018a. 265 (1): 211-212.

Aguiar de Sousa D, Lucas Neto L, Arauz A, Sousa AL, Gabriel D, Correia M, et al. Early recanalization in patients with cerebral venous thrombosis treated with anticoagulation. *Stroke.* 2020. 51 (4): 1174-1181.

Aguiar de Sousa D, Lucas Neto L, Canhão P, and Ferro JM. Recanalization in cerebral venous thrombosis. *Stroke.* 2018b. 49 (8): 1828-1835.

Aguiar de Sousa D, Romoli M, Sánchez Van Kammen M, Heldner MR, Zini A, Coutinho JM, et al. Cerebral venous thrombosis in patients with heparin-induced thrombocytopenia a systematic review. *Stroke.* 2022. 53 (6): 1892-1903.

Al Rawahi B, Almegren M, and Carrier M. The efficacy and safety of anticoagulation in cerebral vein thrombosis: A systematic review and meta-analysis. *Thromb Res.* 2018. 169: 135-139.

Alimohammadi A, Kim DJ, and Field TS. Updates in cerebral venous thrombosis. *Curr Cardiol Rep.* 2022. 24 (1): 43-50.

Altinkaya N, Demir S, Alkan O, and Tan M. Diagnostic value of t2*-weighted gradient-echo mri for segmental evaluation in cerebral venous sinus thrombosis. *Clin Imaging.* 2015. 39 (1): 15-9.

Alwan A, Miraclin AT, Bal D, Moses V, Mannam P, Ahmed M, et al. Management of severe cerebral venous sinus thrombosis using mechanical balloon assisted thrombectomy. *Stroke: Vascular and Interventional Neurology.* 2023. 3 (1): e000574.

Amoozegar F, Ronksley PE, Sauve R, and Menon BK. Hormonal contraceptives and cerebral venous thrombosis risk: A systematic review and meta-analysis. *Front Neurol.* 2015. 6: 7.

Baduro Y, and Ferro JM. Cerebral venous thrombosis in sub-saharan africa: A systematic review. *J Stroke Cerebrovasc Dis.* 2021. 30 (6): 105712.

Baker P, Platton S, Gibson C, Gray E, Jennings I, Murphy P, et al. Guidelines on the laboratory aspects of assays used in haemostasis and thrombosis. *Br J Haematol.* 2020. 191 (3): 347-362.

Bakradze E, Shu L, Henninger N, Prabhakaran S, Siegler JE, De Marchis GM, et al. Delayed diagnosis in cerebral venous thrombosis: Associated factors and clinical outcomes. *J Am Heart Assoc.* 2023. 12 (19): e030421.

Baldini T, Asioli GM, Romoli M, Carvalho Dias M, Schulte EC, Hauer L, et al. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: A systematic review and meta-analysis. *Eur J Neurol.* 2021. 28 (10): 3478-3490.

Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023 acr/eular antiphospholipid syndrome classification criteria. *Arthritis Rheumatol.* 2023. 75 (10): 1687-1702.

Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia.* 2010. 51 (4): 671-5.

Bistervels IM, Buchmüller A, Wiegers HMG, F NÁ, Tardy B, Donnelly J, et al. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (highlow study): An open-label, multicentre, randomised, controlled trial. *Lancet.* 2022. 400 (10365): 1777-1787.

Bokhari R, You E, Bakhaidar M, Bajunaid K, Lasry O, Zeiler FA, et al. Dural venous sinus thrombosis in patients presenting with blunt traumatic brain injuries and skull fractures: A systematic review and meta-analysis. *World Neurosurg.* 2020. 142: 495-505.e3.

Boonyawat K, Lensing AWA, Prins MH, Beyer-Westendorf J, Prandoni P, Martinelli I, et al. Heavy menstrual bleeding in women on anticoagulant treatment for venous thromboembolism: Comparison of high- and low-dose rivaroxaban with aspirin. *Res Pract Thromb Haemost.* 2021. 5 (2): 308-313.

Bousser MG, and Ferro JM. Cerebral venous thrombosis: An update. *Lancet Neurol.* 2007. 6 (2): 162-70.

Brekelmans MP, Scheres LJ, Bleker SM, Hutten BA, Timmermans A, Büller HR, et al. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin. *Thromb Haemost.* 2017. 117 (4): 809-815.

Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Agree ii: Advancing guideline development, reporting and evaluation in health care. *Cmaj.* 2010. 182 (18): E839-42.

Bryk AH, Piróg M, Plens K, and Undas A. Heavy menstrual bleeding in women treated with rivaroxaban and vitamin k antagonists and the risk of recurrent venous thromboembolism. *Vascul Pharmacol.* 2016. 87: 242-247.

Busch MA, Hoffmann O, Einhäupl KM, and Masuhr F. Outcome of heparin-treated patients with acute cerebral venous sinus thrombosis: Influence of the temporal pattern of intracerebral haemorrhage. *Eur J Neurol.* 2016. 23 (9): 1387-92.

Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* 2014. 45 (5): 1545-88.

Cari L, Fiore P, Naghavi Alhosseini M, Sava G, and Nocentini G. Blood clots and bleeding events following bnt162b2 and chadox1 ncov-19 vaccine: An analysis of european data. *J Autoimmun.* 2021. 122: 102685.

Carrion AN, Allison TA, and Samuel S. Is a minimum duration of 5 days of unfractionated heparin infusion necessary before transition to oral anticoagulation in cerebral venous thrombosis? A retrospective chart review. *J Thromb Thrombolysis.* 2024. 57 (4): 691-698.

Connor P, Sánchez van Kammen M, Lensing AWA, Chalmers E, Kállay K, Hege K, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (einstein-jr cvt). *Blood Adv.* 2020. 4 (24): 6250-6258.

Coutinho J, de Bruijn SF, Deveber G, and Stam J. Anticoagulation for cerebral venous sinus thrombosis. *Cochrane Database Syst Rev.* 2011a. 2011 (8): Cd002005.

Coutinho JM, Ferro JM, Canhão P, Barinagarrementeria F, Bousser MG, and Stam J. Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. *Stroke.* 2010. 41 (11): 2575-80.

Coutinho JM, Seelig R, Bousser MG, Canhão P, Ferro JM, and Stam J. Treatment variations in cerebral venous thrombosis: An international survey. *Cerebrovasc Dis.* 2011b. 32 (3): 298-300.

Coutinho JM, Stam J, Canhão P, Barinagarrementeria F, Bousser MG, and Ferro JM. Cerebral venous thrombosis in the absence of headache. *Stroke.* 2015. 46 (1): 245-7.

Coutinho JM, Zuurbier SM, Aramideh M, and Stam J. The incidence of cerebral venous thrombosis: A cross-sectional study. *Stroke.* 2012. 43 (12): 3375-7.

Coutinho JM, Zuurbier SM, Bousser MG, Ji X, Canhão P, Roos YB, et al. Effect of endovascular treatment with medical management vs standard care on severe cerebral venous thrombosis: The to-act randomized clinical trial. *JAMA Neurol.* 2020. 77 (8): 966-973.

Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, et al. American Society of hematology 2018 guidelines for management of venous thromboembolism: Heparin-induced thrombocytopenia. *Blood Adv.* 2018. 2 (22): 3360-3392.

Dabit JY, Valenzuela-Almada MO, Vallejo-Ramos S, and Duarte-García A. Epidemiology of antiphospholipid syndrome in the general population. *Curr Rheumatol Rep.* 2022. 23 (12): 85.

De Crem N, Peerlinck K, Vanassche T, Vanheule K, Debaveye B, Middeldorp S, et al. Abnormal uterine bleeding in vte patients treated with rivaroxaban compared to vitamin k antagonists. *Thromb Res.* 2015. 136 (4): 749-53.

De T, Prabhakar P, Nagaraja D, and Christopher R. Janus kinase (jak) 2 v617f mutation in asian indians with cerebral venous thrombosis and without overt myeloproliferative disorders. *J Neurol Sci.* 2012. 323 (1-2): 178-82.

DeLoughery E, and Bannow BS. Anticoagulant therapy for women: Implications for menstruation, pregnancy, and lactation. *Hematology Am Soc Hematol Educ Program.* 2022. 2022 (1): 467-473.

Dentali F, Poli D, Scoditti U, Di Minno MN, De Stefano V, Siragusa S, et al. Long-term outcomes of patients with cerebral vein thrombosis: A multicenter study. *J Thromb Haemost.* 2012a. 10 (7): 1297-302.

Dentali F, Squizzato A, Marchesi C, Bonzini M, Ferro JM, and Ageno W. D-dimer testing in the diagnosis of cerebral vein thrombosis: A systematic review and a meta-analysis of the literature. *J Thromb Haemost.* 2012b. 10 (4): 582-9.

Devasagayam S, Wyatt B, Leyden J, and Kleinig T. Cerebral venous sinus thrombosis incidence is higher than previously thought: A retrospective population-based study. *Stroke.* 2016. 47 (9): 2180-2.

Devreese KM, Pierangeli SS, de Laat B, Tripodi A, Atsumi T, and Ortel TL. Testing for antiphospholipid antibodies with solid phase assays: Guidance from the ssc of the isth. *J Thromb Haemost.* 2014. 12 (5): 792-5.

Dhakal B, Kreuziger LB, Rein L, Kleman A, Fraser R, Aster RH, et al. Disease burden, complication rates, and health-care costs of heparin-induced thrombocytopenia in the USA: A population-based study. *Lancet Haematol.* 2018. 5 (5): e220-e231.

Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, and Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *Int J Gynaecol Obstet.* 2018. 141 (3): 287-294.

Duman T, Uluduz D, Midi I, Bektas H, Kablan Y, Goksel BK, et al. A multicenter study of 1144 patients with cerebral venous thrombosis: The venost study. *J Stroke Cerebrovasc Dis.* 2017. 26 (8): 1848-1857.

Einhäupl K, Stam J, Bousser MG, De Bruijn SF, Ferro JM, Martinelli I, et al. Efns guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. *Eur J Neurol.* 2010. 17 (10): 1229-35.

Falardeau J, Lobb BM, Golden S, Maxfield SD, and Tanne E. The use of acetazolamide during pregnancy in intracranial hypertension patients. *J Neuroophthalmol.* 2013. 33 (1): 9-12.

Ferro JM, Bendszus M, Jansen O, Coutinho JM, Dentali F, Kobayashi A, et al. Recanalization after cerebral venous thrombosis. A randomized controlled trial of the safety and efficacy of dabigatran etexilate versus dose-adjusted warfarin in patients with cerebral venous and dural sinus thrombosis. *Int J Stroke.* 2022. 17 (2): 189-197.

Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, et al. European stroke organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the european academy of neurology. *Eur J Neurol.* 2017. 24 (10): 1203-1213.

Ferro JM, Canhão P, Stam J, Bousser MG, and Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: Results of the international study on cerebral vein and dural sinus thrombosis (iscvt). *Stroke.* 2004. 35 (3): 664-70.

Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, Massaro A, et al. Delay in the diagnosis of cerebral vein and dural sinus thrombosis: Influence on outcome. *Stroke.* 2009. 40 (9): 3133-8.

Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhão P, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. *JAMA Neurol.* 2019. 76 (12): 1457-1465.

Ferro JM, Coutinho JM, Jansen O, Bendszus M, Dentali F, Kobayashi A, et al. Dural arteriovenous fistulae after cerebral venous thrombosis. *Stroke.* 2020. 51 (11): 3344-3347.

Ferro JM, Crassard I, Coutinho JM, Canhão P, Barinagarrementeria F, Cucchiara B, et al. Decompressive surgery in cerebrovenous thrombosis: A multicenter registry and a systematic review of individual patient data. *Stroke.* 2011. 42 (10): 2825-31.

Field TS, Camden MC, Al-Shimemeri S, Lui G, and Lee AY. Antithrombotic strategy in cerebral venous thrombosis: Differences between neurologist and hematologist respondents in a canadian survey. *Can J Neurol Sci.* 2017. 44 (1): 116-119.

Field TS, Dizonno V, Almekhlafi MA, Bala F, Alhabli I, Wong H, et al. Study of rivaroxaban for cerebral venous thrombosis: A randomized controlled feasibility trial comparing anticoagulation with rivaroxaban to standard-of-care in symptomatic cerebral venous thrombosis. *Stroke.* 2023. 54 (11): 2724-2736.

Fraser IS, Critchley HO, Broder M, and Munro MG. The figo recommendations on terminologies and definitions for normal and abnormal uterine bleeding. *Semin Reprod Med.* 2011. 29 (5): 383-90.

Frederick IO, Qiu C, Enquobahrie DA, Aurora SK, Peterlin BL, Gelaye B, et al. Lifetime prevalence and correlates of migraine among women in a pacific northwest pregnancy cohort study. *Headache.* 2014. 54 (4): 675-85.

Gasparini S, Neri S, Brigo F, Cianci V, Mammì A, Pascarella A, et al. Late epileptic seizures following cerebral venous thrombosis: A systematic review and meta-analysis. *Neurol Sci.* 2022. 43 (9): 5229-5236.

Geisbüsch C, Herweh C, Gumbinger C, Ringleb PA, Möhlenbruch MA, and Nagel S. Chronic intracranial hypertension after cerebral venous and sinus thrombosis - frequency and risk factors. *Neurol Res Pract.* 2021. 3 (1): 28.

Gil-Díaz A, Gil-Hernández A, Lozano-Jiménez AI, Benítez-Peña J, and Conde-Martel A. Safety of covid-19 vaccination in patients with previous cerebral venous sinus thrombosis. *Thromb Res.* 2022. 209: 84-85.

Girot M, Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, et al. Predictors of outcome in patients with cerebral venous thrombosis and intracerebral hemorrhage. *Stroke.* 2007. 38 (2): 337-42.

Goldhaber SZ. Race and venous thromboembolism: Nature or nurture? *Circulation.* 2014. 129 (14): 1463-5.

Goyal M, Fladt J, Coutinho JM, McDonough R, and Ospel J. Endovascular treatment for cerebral venous thrombosis: Current status, challenges, and opportunities. *J Neurointerv Surg.* 2022. 14 (8): 788-793.

Green M, Styles T, Russell T, Sada C, Jallow E, Stewart J, et al. Non-genetic and genetic risk factors for adult cerebral venous thrombosis. *Thromb Res.* 2018. 169: 15-22.

Greinacher A, Selleng K, Palankar R, Wesche J, Handtke S, Wolff M, et al. Insights in chadox1 ncov-19 vaccine-induced immune thrombotic thrombocytopenia. *Blood.* 2021. 138 (22): 2256-2268.

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. Grade guidelines: 1. Introduction-grade evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011. 64 (4): 383-94.

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, and Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? *Bmj.* 2008a. 336 (7651): 995-8.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. Grade: An emerging consensus on rating quality of evidence and strength of recommendations. *Bmj.* 2008b. 336 (7650): 924-6.

Hamulyák EN, Wiegers HMG, Scheres LJJ, Hutten BA, de Lange ME, Timmermans A, et al. Heavy menstrual bleeding on direct factor xa inhibitors: Rationale and design of the medea study. *Res Pract Thromb Haemost.* 2021. 5 (1): 223-230.

Heldner MR, Zuurbier SM, Li B, Von Martial R, Meijers JCM, Zimmermann R, et al. Prediction of cerebral venous thrombosis with a new clinical score and d-dimer levels. *Neurology.* 2020. 95 (7): e898-e909.

Heran M, Lindsay P, Gubitz G, Yu A, Ganesh A, Lund R, et al. Canadian stroke best practice recommendations: Acute stroke management, 7(th) edition practice guidelines update, 2022. *Can J Neurol Sci.* 2022. 1-94.

Hiltunen S, Putaala J, Haapaniemi E, and Tatlisumak T. Long-term outcome after cerebral venous thrombosis: Analysis of functional and vocational outcome, residual symptoms, and adverse events in 161 patients. *J Neurol.* 2016. 263 (3): 477-84.

Hippisley-Cox J, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and sars-cov-2 positive testing: Self-controlled case series study. *Bmj.* 2021. 374: n1931.

Houghton DE, Wysokinski W, Casanegra AI, Padrnos LJ, Shah S, Wysokinska E, et al. Risk of venous thromboembolism after covid-19 vaccination. *J Thromb Haemost.* 2022. 20 (7): 1638-1644.

Huisman MV, Ferreira M, Feuring M, Fraessdorf M, and Klok FA. Less abnormal uterine bleeding with dabigatran than warfarin in women treated for acute venous thromboembolism. *J Thromb Haemost.* 2018. 16 (9): 1775-1778.

Idbaih A, Boukobza M, Crassard I, Porcher R, Bousser MG, and Chabriat H. Mri of clot in cerebral venous thrombosis: High diagnostic value of susceptibility-weighted images. *Stroke.* 2006. 37 (4): 991-5.

Juli C, Amalia L, Gamayani U, and Atik N. D-dimer level associates with the incidence of focal neurological deficits in cerebral venous thrombosis patients. *J Blood Med.* 2020. 11: 449-455.

Kashkoush AI, Ma H, Agarwal N, Panczykowski D, Tonetti D, Weiner GM, et al. Cerebral venous sinus thrombosis in pregnancy and puerperium: A pooled, systematic review. *J Clin Neurosci.* 2017. 39: 9-15.

Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing G-J, Kyrle PA, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: Guidance from the ssc of isth. *Journal of Thrombosis and Haemostasis.* 2016. 14 (7): 1480-1483.

Ken-Dror G, Cotlarciuc I, Martinelli I, Grandone E, Hiltunen S, Lindgren E, et al. Genome-wide association study identifies first locus associated with susceptibility to cerebral venous thrombosis. *Ann Neurol.* 2021. 90 (5): 777-788.

Kim DJ, Honig A, Alimohammadi A, Sepehry AA, Zhou LW, and Field TS. Recanalization and outcomes after cerebral venous thrombosis: A systematic review and meta-analysis. *Res Pract Thromb Haemost.* 2023. 7 (3): 100143.

Klein P, Shu L, Nguyen TN, Siegler JE, Omran SS, Simpkins AN, et al. Outcome prediction in cerebral venous thrombosis: The in-revasc score. *J Stroke.* 2022. 24 (3): 404-416.

Klok FA, Pai M, Huisman MV, and Makris M. Vaccine-induced immune thrombotic thrombocytopenia. *Lancet Haematol.* 2022. 9 (1): e73-e80.

Koopman K, Uyttenboogaart M, Vroomen PC, van der Meer J, De Keyser J, and Luijckx GJ. Long-term sequelae after cerebral venous thrombosis in functionally independent patients. *J Stroke Cerebrovasc Dis.* 2009. 18 (3): 198-202.

Ladhani NNN, Swartz RH, Foley N, Nerenberg K, Smith EE, Gubitz G, et al. Canadian stroke best practice consensus statement: Acute stroke management during pregnancy. *Int J Stroke.* 2018. 13 (7): 743-758.

Lamy M, Palazzo P, Agius P, Chomel JC, Ciron J, Berthomet A, et al. Should we screen for janus kinase 2 v617f mutation in cerebral venous thrombosis? *Cerebrovasc Dis.* 2017. 44 (3-4): 97-104.

Lancastle D, Kopp Kallner H, Hale G, Wood B, Ashcroft L, and Driscoll H. Development of a brief menstrual quality of life measure for women with heavy menstrual bleeding. *BMC Womens Health.* 2023. 23 (1): 105.

Leach JL, Wolujewicz M, and Strub WM. Partially recanalized chronic dural sinus thrombosis: Findings on mr imaging, time-of-flight mr venography, and contrast-enhanced mr venography. *AJNR Am J Neuroradiol.* 2007. 28 (4): 782-9.

Li J, Wei L, Xu B, Zhang X, and Wang S. Risk factors and early diagnosis of cerebral venous sinus occlusion secondary to traumatic brain injury. *Neurol India.* 2015. 63 (6): 881-8.

Liberman AL, Bakradze E, McHugh DC, Esenwa CC, and Lipton RB. Assessing diagnostic error in cerebral venous thrombosis via detailed chart review. *Diagnosis (Berl).* 2019. 6 (4): 361-367.

Liberman AL, Gialdini G, Bakradze E, Chatterjee A, Kamel H, and Merkler AE. Misdiagnosis of cerebral vein thrombosis in the emergency department. *Stroke.* 2018. 49 (6): 1504-1506.

Lindgren E, Rentzos A, Hiltunen S, Serrano F, Heldner MR, Zuurbier SM, et al. Dural arteriovenous fistulas in cerebral venous thrombosis: Data from the international cerebral venous thrombosis consortium: Data from the international cerebral venous thrombosis consortium. *Eur J Neurol.* 2022. 29 (3): 761-770.

Lindgren E, Silvis SM, Hiltunen S, Heldner MR, Serrano F, de Scisco M, et al. Acute symptomatic seizures in cerebral venous thrombosis. *Neurology.* 2020. 95 (12): e1706-e1715.

Linn J, Michl S, Katja B, Pfefferkorn T, Wiesmann M, Hartz S, et al. Cortical vein thrombosis: The diagnostic value of different imaging modalities. *Neuroradiology.* 2010. 52 (10): 899-911.

Liu L, Jiang H, Wei H, Zhou Y, Wu Y, Zhang K, et al. Risk factors of impaired employability after cerebral venous thrombosis. *CNS Neurosci Ther.* 2023. 29 (4): 1086-1093.

Marchandot B, Carmona A, Trimaille A, Curtiaud A, and Morel O. Procoagulant microparticles: A possible link between vaccine-induced immune thrombocytopenia (vitt) and cerebral sinus venous thrombosis. *J Thromb Thrombolysis.* 2021. 52 (3): 689-691.

Marlar RA, Gausman JN, Tsuda H, Rollins-Raval MA, and Brinkman HJM. Recommendations for clinical laboratory testing for protein s deficiency: Communication from the ssc committee plasma coagulation inhibitors of the isth. *J Thromb Haemost.* 2021. 19 (1): 68-74.

Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, and Mannucci PM. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. *Circulation.* 2010. 121 (25): 2740-6.

Martinelli I, Lensing AW, Middeldorp S, Levi M, Beyer-Westendorf J, van Bellen B, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. *Blood.* 2016. 127 (11): 1417-25.

May J, Westbrook B, and Cuker A. Heparin-induced thrombocytopenia: An illustrated review. *Res Pract Thromb Haemost.* 2023. 7 (5): 100283.

McBane RD, 2nd, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The adam vte trial. *J Thromb Haemost.* 2020. 18 (2): 411-421.

McCullough-Hicks ME, Halterman DJ, Anderson D, Cohen K, and Lakshminarayan K. High incidence and unique features of cerebral venous sinus thrombosis in hospitalized patients with covid-19 infection. *Stroke.* 2022. 53 (9): e407-e410.

Micaily I, and Samuelson Bannow BT. Vte and anticoagulation in menstruating women. *Thrombosis Update.* 2021. 5: 100088.

Middeldorp S, Nieuwlaat R, Baumann Kreuziger L, Coppens M, Houghton D, James AH, et al. American Society of hematology 2023 guidelines for management of venous thromboembolism: Thrombophilia testing. *Blood Adv.* 2023. 7 (22): 7101-7138.

Miranda B, Aaron S, Arauz A, Barinagarrementeria F, Borhani-Haghighi A, Carvalho M, et al. The benefit of extending oral anticoagulation treatment (excoa) after acute cerebral vein thrombosis (cvt): Excoa-cvt cluster randomized trial protocol. *Int J Stroke.* 2018. 13 (7): 771-774.

Miranda B, Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, et al. Venous thromboembolic events after cerebral vein thrombosis. *Stroke.* 2010. 41 (9): 1901-6.

Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, et al. Idiopathic intracranial hypertension: Consensus guidelines on management. *J Neurol Neurosurg Psychiatry.* 2018. 89 (10): 1088-1100.

Naik A, Smith E, Dharnipragada R, Catapano JS, Cramer SW, Johnson R, et al. Endovascular and medical management of cerebral venous thrombosis: A systematic review and network meta-analysis. *World Neurosurg.* 2022. 165: e197-e205.

Nelson ML, Grudniewicz A, and Albadry S. Applying clinical practice guidelines to the complex patient: Insights for practice and policy from stroke rehabilitation. *Healthc Q.* 2016. 19 (2): 38-43.

Netteland DF, Mejlænder-Evjensvold M, Skaga NO, Sandset EC, Aarhus M, and Helseth E. Cerebral venous thrombosis in traumatic brain injury: A cause of secondary insults and added mortality. *J Neurosurg.* 2020. 134 (6): 1912-1920.

Netteland DF, Sandset EC, Mejlænder-Evjensvold M, Aarhus M, Jeppesen E, Aguiar de Sousa D, et al. Cerebral venous sinus thrombosis in traumatic brain injury: A systematic review of its complications, effect on mortality, diagnostic and therapeutic management, and follow-up. *Front Neurol.* 2022. 13: 1079579.

Newman-Toker DE, Moy E, Valente E, Coffey R, and Hines AL. Missed diagnosis of stroke in the emergency department: A cross-sectional analysis of a large population-based sample. *Diagnosis (Berl).* 2014. 1 (2): 155-166.

Nicholson M, Goubran H, Chan N, and Siegal D. No apparent association between mrna covid-19 vaccination and venous thromboembolism. *Blood Rev.* 2022. 56: 100970.

Oedingen C, Scholz S, and Razum O. Systematic review and meta-analysis of the association of combined oral contraceptives on the risk of venous thromboembolism: The role of the progestogen type and estrogen dose. *Thromb Res.* 2018. 165: 68-78.

Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, Vidal X, Riera-Mestre A, Castro-Salomó A, et al. Rivaroxaban versus vitamin k antagonist in antiphospholipid syndrome: A randomized noninferiority trial. *Ann Intern Med.* 2019. 171 (10): 685-694.

Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020. 4 (19): 4693-4738.

Otite FO, Patel S, Sharma R, Khandwala P, Desai D, Latorre JG, et al. Trends in incidence and epidemiologic characteristics of cerebral venous thrombosis in the united states. *Neurology.* 2020. 95 (16): e2200-e2213.

Pai M. Epidemiology of vitt. *Semin Hematol.* 2022. 59 (2): 72-75.

Palazzo P, Agius P, Ingrand P, Ciron J, Lamy M, Berthomet A, et al. Venous thrombotic recurrence after cerebral venous thrombosis: A long-term follow-up study. *Stroke.* 2017. 48 (2): 321-326.

Passamonti SM, Biguzzi E, Cazzola M, Franchi F, Gianniello F, Bucciarelli P, et al. The jak2 v617f mutation in patients with cerebral venous thrombosis. *J Thromb Haemost.* 2012. 10 (6): 998-1003.

Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, et al. Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. *N Engl J Med.* 2021. 385 (18): 1680-1689.

Pawlowski C, Rincón-Hekking J, Awasthi S, Pandey V, Lenehan P, Venkatakrishnan AJ, et al. Cerebral venous sinus thrombosis is not significantly linked to covid-19 vaccines or non-covid vaccines in a large multi-state health system. *J Stroke Cerebrovasc Dis.* 2021. 30 (10): 105923.

Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood.* 2018. 132 (13): 1365-1371.

Pires GS, Ribeiro DD, Oliveira JAQ, Freitas LC, Vaez R, Annichino-Bizzacchi JM, et al. Risk factors associated with recurrent venous thromboembolism after a first cerebral venous thrombosis event: A cohort study. *Thromb Res.* 2019. 178: 85-90.

Ranjan R, Ken-Dror G, Martinelli I, Grandone E, Hiltunen S, Lindgren E, et al. Age of onset of cerebral venous thrombosis: The beast study. *Eur Stroke J.* 2023. 8 (1): 344-350.

Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018. 378 (7): 615-624.

Salehi Omran S, Shu L, Chang A, Parikh NS, Zubair AS, Simpkins AN, et al. Timing and predictors of recanalization after anticoagulation in cerebral venous thrombosis. *J Stroke.* 2023. 25 (2): 291-298.

Sánchez van Kammen M, Aguiar de Sousa D, Poli S, Cordonnier C, Heldner MR, van de Munckhof A, et al. Characteristics and outcomes of patients with cerebral venous sinus thrombosis in sars-cov-2 vaccine-induced immune thrombotic thrombocytopenia. *JAMA Neurol.* 2021a. 78 (11): 1314-1323.

Sánchez van Kammen M, Heldner MR, Brodard J, Scutelnic A, Silvis S, Schroeder V, et al. Frequency of thrombocytopenia and platelet factor 4/heparin antibodies in patients with cerebral venous sinus thrombosis prior to the covid-19 pandemic. *Jama.* 2021b. 326 (4): 332-338.

Sánchez van Kammen M, Lindgren E, Silvis SM, Hiltunen S, Heldner MR, Serrano F, et al. Late seizures in cerebral venous thrombosis. *Neurology.* 2020. 95 (12): e1716-e1723.

Saposnik G, Bushnell C, Coutinho JM, Field TS, Furie KL, Galadanci N, et al. Diagnosis and management of cerebral venous thrombosis: A scientific statement from the american heart association. *Stroke.* 2024. 55 (3): e77-e90.

Scheres L, Brekelmans M, Ageno W, Ay C, Büller HR, Eichinger S, et al. Abnormal vaginal bleeding in women of reproductive age treated with edoxaban or warfarin for venous thromboembolism: A post hoc analysis of the hokusai-vte study. *Bjog.* 2018. 125 (12): 1581-1589.

Schrag D, Uno H, Rosovsky R, Rutherford C, Sanfilippo K, Villano JL, et al. Direct oral anticoagulants vs low-molecular-weight heparin and recurrent vte in patients with cancer: A randomized clinical trial. *Jama.* 2023. 329 (22): 1924-1933.

Schulman S. Less menorrhagia for women with vte. *Blood.* 2016. 127 (11): 1378-9.

Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of hematology 2018 guidelines for management of venous thromboembolism: Prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv.* 2018. 2 (22): 3198-3225.

Scutelnic A, Krzywicka K, Mbroh J, van de Munckhof A, van Kammen MS, de Sousa DA, et al. Management of cerebral venous thrombosis due to adenoviral covid-19 vaccination. *Ann Neurol.* 2022. 92 (4): 562-573.

Shakibajahromi B, Borhani-Haghighi A, Ghaedian M, Feiz F, Molavi Vardanjani H, Safari A, et al. Early, delayed, and expanded intracranial hemorrhage in cerebral venous thrombosis. *Acta Neurol Scand.* 2019. 140 (6): 435-442.

Shu L, Bakradze E, Omran SS, Giles J, Amar J, Henninger N, et al. Predictors of recurrent venous thrombosis after cerebral venous thrombosis: Analysis of the action-cvt study. *Neurology.* 2022. 99 (21): e2368-e2377.

Siegler JE, Dasgupta S, Abdalkader M, Penckofer M, Yaghi S, and Nguyen TN. Cerebrovascular disease in covid-19. *Viruses.* 2023. 15 (7).

Silvis SM, de Sousa DA, Ferro JM, and Coutinho JM. Cerebral venous thrombosis. *Nat Rev Neurol.* 2017. 13 (9): 555-565.

Silvis SM, Hiltunen S, Lindgren E, Jood K, Zuurbier SM, Middeldorp S, et al. Cancer and risk of cerebral venous thrombosis: A case-control study. *J Thromb Haemost.* 2018. 16 (1): 90-95.

Silvis SM, Lindgren E, Hiltunen S, Devasagayam S, Scheres LJ, Jood K, et al. Postpartum period is a risk factor for cerebral venous thrombosis. *Stroke.* 2019. 50 (2): 501-503.

Silvis SM, Middeldorp S, Zuurbier SM, Cannegieter SC, and Coutinho JM. Risk factors for cerebral venous thrombosis. *Semin Thromb Hemost.* 2016. 42 (6): 622-31.

Simaan N, Molad J, Honig A, Filioglo A, Shbat F, Auriel E, et al. Characteristics of patients with cerebral sinus venous thrombosis and jak2 v617f mutation. *Acta Neurol Belg.* 2023. 123 (5): 1855-1859.

Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, et al. First-dose chadox1 and bnt162b2 covid-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in scotland. *Nat Med.* 2021. 27 (7): 1290-1297.

Sipilä JOT, Ruuskanen JO, Heervä E, Posti JP, Rautava P, and Kytö V. Cancer occurrence after a cerebral venous thrombosis: A nationwide registry study. *Stroke.* 2022. 53 (5): e189-e191.

Skajaa N, Farkas DK, Adelborg K, and Sørensen HT. Risk and prognosis of cancer in patients with cerebral venous thrombosis compared with the danish general population. *Stroke.* 2023. 54 (10): 2576-2582.

Smith SV, and Friedman DI. The idiopathic intracranial hypertension treatment trial: A review of the outcomes. *Headache.* 2017. 57 (8): 1303-1310.

Spirk D, Sebastian T, Barco S, Banyai M, Beer JH, Mazzolai L, et al. Clinical outcomes of incidental venous thromboembolism in cancer and noncancer patients: The swiss venous thromboembolism registry (swivter). *Thromb Haemost.* 2021. 121 (5): 641-649.

Stewart WF, Simon D, Shechter A, and Lipton RB. Population variation in migraine prevalence: A meta-analysis. *J Clin Epidemiol.* 1995. 48 (2): 269-80.

Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, et al. The incidence of pregnancy-related stroke: A systematic review and meta-analysis. *Int J Stroke.* 2017. 12 (7): 687-697.

Taquet M, Husain M, Geddes JR, Luciano S, and Harrison PJ. Cerebral venous thrombosis and portal vein thrombosis: A retrospective cohort study of 537,913 covid-19 cases. *EClinicalMedicine.* 2021. 39: 101061.

Thaller M, Wakerley BR, Abbott S, Tahrani AA, Mollan SP, and Sinclair AJ. Managing idiopathic intracranial hypertension in pregnancy: Practical advice. *Pract Neurol.* 2022. 22 (4): 295-300.

Towfighi A, Boden-Albala B, Cruz-Flores S, El Husseini N, Odonkor CA, Ovbiagele B, et al. Strategies to reduce racial and ethnic inequities in stroke preparedness, care, recovery, and risk factor control: A scientific statement from the american heart association. *Stroke.* 2023. 54 (7): e371-e388.

Tripodi A, Cohen H, and Devreese KMJ. Lupus anticoagulant detection in anticoagulated patients. Guidance from the scientific and standardization committee for lupus anticoagulant/antiphospholipid antibodies of the international Society on thrombosis and haemostasis. *J Thromb Haemost.* 2020. 18 (7): 1569-1575.

Tu TM, Yi SJ, Koh JS, Saffari SE, Hoe RHM, Chen GJ, et al. Incidence of cerebral venous thrombosis following sars-cov-2 infection vs mrna sars-cov-2 vaccination in singapore. *JAMA Netw Open.* 2022. 5 (3): e222940.

van Dam LF, van Walderveen MAA, Kroft LJM, Kruyt ND, Wermer MJH, van Osch MJP, et al. Current imaging modalities for diagnosing cerebral vein thrombosis - a critical review. *Thromb Res.* 2020. 189: 132-139.

Venous thromboembolic disease and combined oral contraceptives: Results of international multicentre case-control study. World health organization collaborative study of cardiovascular disease and steroid hormone contraception. *Lancet.* 1995. 346 (8990): 1575-82.

Wahood W, Rizvi AA, Patel V, Narain S, Cloft H, Rabinstein AA, et al. Trends in utilization and outcomes of mechanical thrombectomy for cerebral venous thrombosis: A national inpatient sample study. *Interv Neuroradiol.* 2023. 15910199231182454.

Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: The idiopathic intracranial hypertension treatment trial. *Jama.* 2014. 311 (16): 1641-51.

Wasay M, Kojan S, Dai AI, Bobustuc G, and Sheikh Z. Headache in cerebral venous thrombosis: Incidence, pattern and location in 200 consecutive patients. *J Headache Pain.* 2010. 11 (2): 137-9.

Weyand AC, and James PD. Sexism in the management of bleeding disorders. *Res Pract Thromb Haemost.* 2021. 5 (1): 51-54.

Woller SC, Stevens SM, Kaplan D, Wang TF, Branch DW, Groat D, et al. Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: A randomized trial. *Blood Adv.* 2022. 6 (6): 1661-1670.

Xavier SG, Gadelha T, Rezende SM, Zalcberg IR, and Spector N. Jak2v617f mutation in patients with thrombosis: To screen or not to screen? *Int J Lab Hematol.* 2011. 33 (2): 117-24.

Xu W, Gao L, Li T, Ramdoyal ND, Zhang J, and Shao A. The performance of ct versus mri in the differential diagnosis of cerebral venous thrombosis. *Thromb Haemost.* 2018. 118 (6): 1067-1077.

Yaghi S, Saldanha IJ, Misquith C, Zaidat B, Shah A, Joudi K, et al. Direct oral anticoagulants versus vitamin k antagonists in cerebral venous thrombosis: A systematic review and meta-analysis. *Stroke.* 2022a. 53 (10): 3014-3024.

Yaghi S, Shu L, Bakradze E, Salehi Omran S, Giles JA, Amar JY, et al. Direct oral anticoagulants versus warfarin in the treatment of cerebral venous thrombosis (action-cvt): A multicenter international study. *Stroke.* 2022b. 53 (3): 728-738.

Yang Q, Duan J, Fan Z, Qu X, Xie Y, Nguyen C, et al. Early detection and quantification of cerebral venous thrombosis by magnetic resonance black-blood thrombus imaging. *Stroke.* 2016. 47 (2): 404-9.

Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (select-d). *J Clin Oncol.* 2018. 36 (20): 2017-2023.

Yu AYX, Hill MD, Asdaghi N, Boulanger JM, Camden MC, Campbell BCV, et al. Sex differences in diagnosis and diagnostic revision of suspected minor cerebral ischemic events. *Neurology.* 2021. 96 (5): e732-e739.

Zakherah MS, Sayed GH, El-Nashar SA, and Shaaban MM. Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: Diagnostic accuracy compared to alkaline hematin. *Gynecol Obstet Invest.* 2011. 71 (4): 281-4.

Zhou LW, Yu AYX, Hall W, Hill MD, and Field TS. Validity of icd-10 codes for cerebral venous thrombosis depends on clinical context. *Can J Neurol Sci.* 2022. 49 (6): 813-816.

Zhou LW, Yu AYX, Ngo L, Hill MD, and Field TS. Incidence of cerebral venous thrombosis: A population-based study, systematic review, and meta-analysis. *Stroke.* 2023. 54 (1): 169-177.

Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MR, et al. Risk of cerebral venous thrombosis in obese women. *JAMA Neurol.* 2016. 73 (5): 579-84.