Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Management of *Cerebral Venous Thrombosis*

Evidence Tables

Seventh Edition, 2024

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on Behalf of the Canadian Stroke Best Practice Recommendations
Cerebral Venous Thrombosis Writing Group and in collaboration with the
Canadian Stroke Consortium

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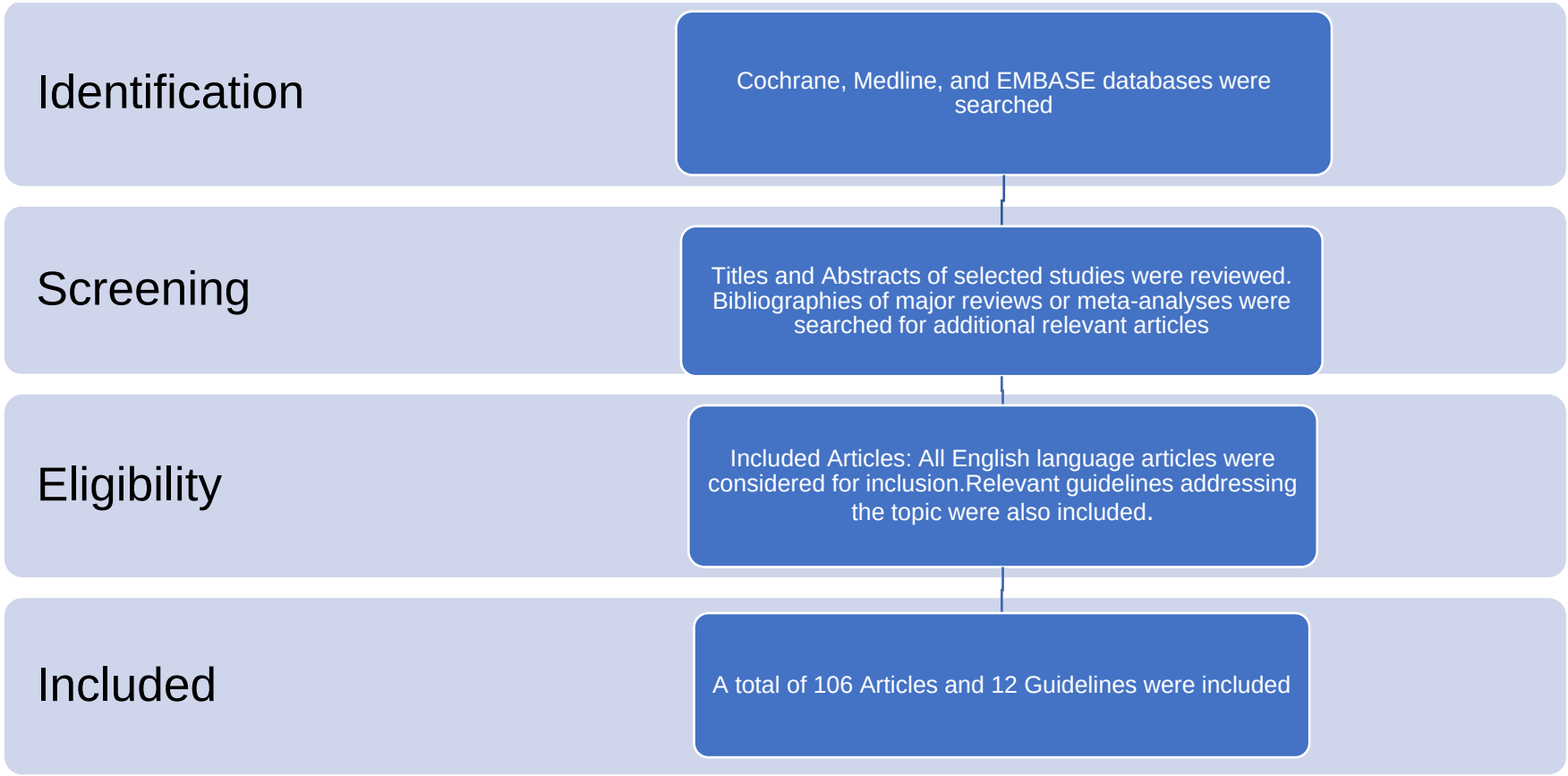
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms cerebral venous thrombosis OR cerebral venous sinus thrombosis. Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed for additional relevant articles. A total of 12 guidelines and 106 articles were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Saposnik G, Bushnell C, Coutinho JM, Field TS, Furie KL, Galadanci N et al; American Heart Association Stroke Council; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Cardiovascular and Stroke Nursing; and Council on Hypertension. **Diagnosis and Management of Cerebral Venous Thrombosis: A Scientific Statement from the American Heart Association.** ***Stroke.* 2024 Jan 29. doi: 10.1161/STR.0000000000000456.** **(selected)**	Key points for clinical practice • MRI/MRV is the recommended noninvasive study of the cerebral venous system to confirm the diagnosis. CT/CTV is a reasonable alternative in centers with limited resources or if the pretest probability is low. • Contrast-enhanced MRV, gradient-recalled echo, or susceptibility-weighted imaging sequences are the recommended techniques for the diagnosis of cortical venous thrombosis. (New) • The mainstream initial treatment of CVT includes parenteral heparin followed by transition to oral VKAs for 3 to 12 months, depending on the underlying cause, or indefinitely in the presence of thrombophilia or recurrent VTE. • DOACs appear to be a safe and effective alternative option to VKAs according to open-label retrospective and prospective randomized studies. (New) • The strategy of identifying venous recanalization in subsequent CTV or MRV to guide the duration of anticoagulation remains uncertain. (New) • Given the lack of controlled studies (and poorer outcomes in meta-analyses), endovascular therapies are reserved for patients with evidence of thrombus propagation, for individuals with neurological deterioration despite medical therapy, or for those with contraindications to anticoagulation. (New) • Despite the low level of evidence, decompressive surgery is a lifesaving procedure that may result in improved functional outcomes among patients with advanced clinical signs of herniation. (New) • For women with CVT during pregnancy, LMWH in full anticoagulant doses should be continued throughout pregnancy, and LMWH or VKA with a target international normalized ratio of 2.0 to 3.0 should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 3 months). • It is reasonable to advise women with a history of CVT that future pregnancy is not contraindicated. Prophylaxis with LMWH during future pregnancies and the postpartum period is usually recommended. • CVT in the pediatric population is more common in neonates than children, usually among those exposed to infections, dehydration, iron deficiency, anemia, or head trauma. Parenteral anticoagulation is also the first-line treatment, followed by LMWH, VKA, or rivaroxaban for at least 6 weeks. • VITT and CVT may occur (rarely) days or a few weeks after an individual receives adenovirus-based SARSCoV-2 vaccines, usually presenting with new onset of headaches and thrombocytopenia; it requires the expert management of a hematologist and multidisciplinary team. (New)

Guideline	Recommendations
Mead GE, Sposato LA, Silva GS, Yperzeele L, Wu S, Kutlubaev MA et al. **Systematic review and synthesis of global stroke guidelines for the World Stroke Organization.** ***Int J Stroke*. 2023 Feb 1:17474930231156753.**	A non-invasive venogram (CTV or MRV) should be performed in suspected CVST if the plain CT or MRI are inconclusive. (Strone recommendation) In patients with suspected or confirmed CVST, possible causative infections should be excluded (strong recommendation). Anticoagulation should be started immediately after the diagnosis of CVST, even if intracranial hemorrhage is present. IV heparin or subcutaneous LMWH can be used. (strong recommendation)
Ferro JM, Sousa DA, Coutinho JM, Martinelli I. **European stroke organization interim expert opinion on cerebral venous thrombosis occurring after SARS-CoV-2 vaccination.** ***Eur Stroke J* 2021 Jul 20:23969873211030842.** **(selected)**	*What antithrombotic medication should be used in the acute phase?* In patients with CVT and thrombocytopenia (<150 x10^9/L), in whom vaccine-induced immune thrombotic thrombocytopenia (VITT) is suspected or confirmed, heparin (unfractionated or low molecular weight) should be avoided. Use non-heparin anticoagulants such as argatroban, bivalirubin, danaparoid, fondaparinux, or direct oral anticoagulants, if platelets > 50 x 10^9 /L and there is no major or life-threatening systemic bleeding. *Should platelet transfusions be used or avoided?* In CVT with thrombocytopenia (<150 x 10^9 /L), until the diagnosis of VITT is not excluded or if the diagnosis of VITT is confirmed, platelet transfusions should be avoided, unless there is a major or life-threatening bleeding or the patient requires urgent surgery or an invasive diagnostic or therapeutic procedure, with high risk of bleeding. *Is immunotherapy necessary?* Based on indirect evidence from heparin-induced thrombocytopenia (HIT) and apparent efficacy in several of the previously reported cases of VITT, in CVT with thrombocytopenia (<150 x 10^9 /L), if the diagnosis of VITT is confirmed or likely, early intravenous immunoglobulin is recommended (1000 mg/kg daily for 2 days). If there is no response to intravenous immunoglobulin, steroids and/or plasmapheresis are reasonable alternatives. *What antithrombotic medication should be used in the postacute phase, in patients with diagnosis of VITT*? In CVT with confirmed VITT, vitamin K antagonists should only be started when the platelet count is stable and >150 x 10^9 /L). Direct oral anticoagulants are an alternative.
Ferro JM, Bousser M-G, Canhão P et al. **European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis – endorsed by the European Academy of Neurology.** ***Eur Stroke J* 2017; 24: 1203 – 13.** **(selected)**	*Topic: neuroimaging* PICO question 1: in patients suspected of CVT, should magnetic resonance (MR) venography versus digital subtraction angiography (DSA) be used to diagnose CVT? Recommendation: We suggest that MRV can be used as a reliable alternative to DSA for the confirmation of the diagnosis of CVT in patients with suspected CVT. Quality of evidence Very low; Strength of recommendation Weak. PICO question 2: in patients with suspected CVT, should computed tomographic (CT) venography versus DSA be used to diagnose CVT? Recommendation: We suggest that CTV can be used as a reliable alternative to DSA for the diagnosis of CVT in patients with suspected CVT. Quality of evidence Very low; Strength of recommendation Weak.

Guideline	Recommendations
	PICO question 3: in patients suspected of CVT, should CTV versus MRI and MRV be used to diagnose CVT? Recommendation: We suggest that CTV can be used as a reliable alternative to MRV for confirming the diagnosis of CVT in patients with suspected CVT. Quality of evidence Very low; Strength of recommendation Weak. *Topic: D-dimer* PICO question: in patients suspected of acute CVT, should D-dimer be measured before neuroimaging to diagnose CVT? Recommendation: We suggest measuring D-dimer before neuroimaging in patients with suspected CVT, except in those with isolated headache and in case of prolonged duration of symptoms (i.e. >1 week) before the test. Quality of evidence Low. Strength of recommendation Weak. *Topic: screening for thrombophilia* PICO question: in patients with CVT, does a policy of screening for thrombophilia prevent recurrent venous thrombosis, reduce death and improve functional outcome? Recommendation: We do not suggest thrombophilia screening to reduce death, improve functional outcome or prevent recurrent venous thrombosis in patients with CVT. Quality of evidence Very low. Strength of recommendation Weak. Good clinical practice point: Thrombophilia screening may be performed in patients with high pre-test probability of carrying severe thrombophilia (i.e. a personal and/or family history of venous thrombosis, young age at CVT, CVT without a transient or permanent risk factor) to prevent recurrent venous thrombotic events (VTEs). *Topic: malignancy screening* PICO question: in patients with CVT, does screening for an occult malignancy (including haematological malignancies) improve outcome? Recommendation: We suggest not performing routine screening for occult malignancy in patients with CVT to improve outcome. Quality of evidence Very low. Strength of recommendation Weak. *Topic: acute anticoagulant treatment* PICO question: in patients with acute CVT, does anticoagulation improve clinical outcome compared with no anticoagulation? Recommendation: We recommend treating adult patients with acute CVT with heparin at therapeutic dosage. This recommendation also applies to patients with an intracerebral haemorrhage at baseline. Quality of evidence Moderate. Strength of recommendation Strong. *Topic: type of heparin in acute CVT* PICO question: in patients with acute CVT, does LMWH improve clinical outcome compared with UFH? Recommendation: We suggest treating patients with acute CVT with LMWH instead of UFH. This recommendation does not apply to patients with a contraindication for LMWH (e.g. renal insufficiency) or situations where fast reversal of the anticoagulant effect is required (e.g. patients who have to undergo neurosurgical intervention). Quality of evidence Low. Strength of recommendation Weak.

Guideline	Recommendations
	Topic: thrombolysis and thrombectomy in acute CVT PICO question: does thrombolysis improve clinical outcome compared with anticoagulation in patients with acute CVT? Recommendation: We cannot provide a recommendation on thrombolysis for CVT. Quality of evidence Very low. Strength of recommendation Inconclusive. Good clinical practice point: We suggest not using thrombolysis in patients with acute CVT with a pretreatment low risk of poor outcome. *Topic: duration of anticoagulation* PICO question 1: for patients with CVT, does treatment with long-term anticoagulation (≥6 months) improve outcome compared with treatment with short term anticoagulation (n (<6 months)? PICO question 2: for patients with previous CVT, does treatment with long-term anticoagulation reduce recurrence of VTEs compared with treatment with short-term anticoagulation? Recommendation: We suggest using oral anticoagulants (vitamin K antagonists) for a variable period (3–12 months) after CVT to prevent recurrent CVT and other venous thromboembolic events. Quality of evidence Very low. Strength of recommendation Weak. Good clinical practice point: Patients with recurrent venous thrombosis or with an associated prothrombotic condition with a high thrombotic risk may need permanent anticoagulation. We suggest following specific recommendations for the prevention of recurrent venous thromboembolic events in those conditions. *Topic: new oral anticoagulants* PICO question: in patients with CVT, does treatment with direct oral anticoagulants improve clinical outcome, reduce major haemorrhagic complications and reduce thrombotic recurrences compared with conventional anticoagulation (heparin and vitamin K antagonists) Recommendation: We do not recommend using direct oral anticoagulants (factor Xa or thrombin inhibitors) for the treatment of CVT, especially during the acute phase. Quality of evidence Very low. Strength of recommendation Weak.
Saposnik, G, Barinagarrementeria, F, Brown, RD, Jr, Bushnell, CD, Cucchiara, B, Cushman, M, et al; American Heart Association Stroke Council and the Council on Epidemiology and Prevention. **Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke*. 2011;42:1158–1192.**	*Routine Blood Work* In patients with suspected CVT, routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed (Class I; Level of Evidence C). Screening for potential prothrombotic conditions that may predispose a person to CVT (eg, use of contraceptives, underlying inflammatory disease, infectious process) is recommended in the initial clinical assessment (specific recommendations for testing for thrombophilia are found in the long-term management section of this document) (Class I; Level of Evidence C). A normal D-dimer level according to a sensitive immunoassay or rapid enzyme-linked immunosorbent assay (ELISA) may be considered to help identify patients with low probability of CVT82,83 (Class IIb; Level of

Guideline	Recommendations
(selected)	Evidence B). If there is a strong clinical suspicion of CVT, a normal D-dimer level should not preclude further evaluation. *Imaging* 1. Although a plain CT or MRI is useful in the initial evaluation of patients with suspected CVT, a negative plain CT or MRI does not rule out CVT. A venographic study (either CTV or MRV) should be performed in suspected CVT if the plain CT or MRI is negative or to define the extent of CVT if the plain CT or MRI suggests CVT (Class I; Level of Evidence C). 2. An early follow-up CTV or MRV is recommended in CVT patients with persistent or evolving symptoms despite medical treatment or with symptoms suggestive of propagation of thrombus (Class I; Level of Evidence C). 3. In patients with previous CVT who present with recurrent symptoms suggestive of CVT, repeat CTV or MRV is recommended (Class I; Level of Evidence C). 4. Gradient echo T2 susceptibility-weighted images combined with magnetic resonance can be useful to improve the accuracy of CVT diagnosis70,129,151 (Class IIa; Level of Evidence B). 5. Catheter cerebral angiography can be useful in patients with inconclusive CTV or MRV in whom a clinical suspicion for CVT remains high (Class IIa; Level of Evidence C). 6. A follow-up CTV or MRV at 3 to 6 months after diagnosis is reasonable to assess for recanalization of the occluded cortical vein/sinuses in stable patients (Class IIa; Level of Evidence C). *Acute Management* 1. Patients with CVT and a suspected bacterial infection should receive appropriate antibiotics and surgical drainage of purulent collections of infectious sources associated with CVT when appropriate (Class I; Level of Evidence C). 2. In patients with CVT and increased intracranial pressure, monitoring for progressive visual loss is recommended, and when this is observed, increased intracranial pressure should be treated urgently (Class I; Level of Evidence C). 3. In patients with CVT and a single seizure with parenchymal lesions, early initiation of antiepileptic drugs for a defined duration is recommended to prevent further seizures (Class I; Level of Evidence B). 4. In patients with CVT and a single seizure without parenchymal lesions, early initiation of antiepileptic drugs for a defined duration is probably recommended to prevent further seizures (Class IIa; Level of Evidence C). 5. In the absence of seizures, the routine use of antiepileptic drugs in patients with CVT is not recommended (Class III; Level of Evidence C). 6. For patients with CVT, initial anticoagulation with adjusted-dose UFH or weight-based LMWH in full anticoagulant doses is reasonable, followed by vitamin K antagonists, regardless of the presence of ICH (Class IIa; Level of Evidence B). (For further details, refer to “Acute Management and Treatment of CVT: Initial Anticoagulation.”) 7. Admission to a stroke unit is reasonable for treatment and for prevention of clinical complications of patients with CVT (Class IIa; Level of Evidence C).

Guideline	Recommendations
	8. In patients with CVT and increased intracranial pressure, it is reasonable to initiate treatment with acetazolamide. Other therapies (lumbar puncture, optic nerve decompression, or shunts) can be effective if there is progressive visual loss. (Class IIa; Level of Evidence C). 9. Endovascular intervention may be considered if deterioration occurs despite intensive anticoagulation treatment (Class IIb; Level of Evidence C). 10. In patients with neurological deterioration due to severe mass effect or intracranial hemorrhage causing intractable intracranial hypertension, decompressive hemicraniectomy may be considered (Class IIb; Level of Evidence C). 11. For patients with CVT, steroid medications are not recommended, even in the presence of parenchymal brain lesions on CT/MRI, unless needed for another underlying disease (Class III; Level of Evidence B). *Long-term management and recurrence of CVT* 1. Testing for prothrombotic conditions, including protein C, protein S, antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A mutation, and factor V Leiden, can be beneficial for the management of patients with CVT. Testing for protein C, protein S, and antithrombin deficiency is generally indicated 2 to 4 weeks after completion of anticoagulation. There is a very limited value of testing in the acute setting or in patients taking warfarin. (Class IIa; Level of Evidence B). 2. In patients with provoked CVT (associated with a transient risk factor), vitamin K antagonists may be continued for 3 to 6 months, with a target INR of 2.0 to 3.0 (Class IIb; Level of Evidence C). 3. In patients with unprovoked CVT, vitamin K antagonists may be continued for 6 to 12 months, with a target INR of 2.0 to 3.0 (Class IIb; Level of Evidence C). 4. For patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia (ie, homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; or antiphospholipid syndrome), indefinite anticoagulation may be considered, with a target INR of 2.0 to 3.0 (Class IIb; Level of Evidence C). 5. Consultation with a physician with expertise in thrombosis may be considered to assist in the prothrombotic testing and care of patients with CVT (Class IIb; Level of Evidence C).
UFH Dosing	
Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, Svensson PJ, Veenstra DL, Crowther M, Guyatt GH. **Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.** ***Chest.* 2012 Feb;141(2 Suppl):e152S-e184S.**	6.1. For patients starting IV UFH, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or a fixed-dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C).
Clinical Laboratory Testing for Hereditary & Acquired Types of Thrombophilia	

Guideline	Recommendations
Marlar RA, Gausman JN, Tsuda H, Rollins-Raval MA, 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 Jan;19(1):68-74.**	1. Follow recommended guidelines/best practices for coagulation testing sampling. 2. Evaluate and defer testing for congenital protein S (PS) deficiency on patients with acquired conditions known to falsely alter plasma PS. 3. The initial assay for congenital PS deficiency should be the free PS antigen assay. 4. Total PS antigen assay can be performed to differentiate between type I and type III deficiency. 5. If no abnormality is identified during a thrombophilia workup, but clinical suspicion persists or in specific populations in which type II deficiencies are more common, PS activity assays in a patient with a normal free PS antigen may be useful. 6. Blood for all PS assays should be taken into standard coagulation blood draw tubes (3.2% sodium citrate anticoagulant) and maintained at room temperature. Plasma prepared using good laboratory practice. 7. Plasma can be tested fresh, within 4 hours of venipuncture, or must be frozen within the 4-hour window if testing is to be postponed. The 4-hour window can be extended for an assay if there is in-house validation. 8. Samples can be frozen below −20°C for up to 2 weeks (not in a self-defrosting freezer) or up to 18 months below −70°C. Frozen samples should be rapidly thawed in a water bath at 37°C, and thoroughly mixed by multiple, gentle inversions before testing. 9. The laboratory must know the limitations of all commercial activity and antigen assays and kits because they do not measure PS in the same manner and therefore can result in different PS values for the same patient. 10. The laboratory must validate or verify their RI based on age, sex, and ethic group to ensure the accuracy of the interpretation and therefore the diagnosis. 11. Under the age of 6 months, testing should be deferred if possible but comparison to an age-appropriate published RI may be informative but not definitive. 12. Abnormal values must be repeated after at least 4 weeks for confirmation. 13. Molecular PS testing is not readily available but can be sent out to selected research laboratories if molecular abnormality assessment is required. Suggest searching the literature for an appropriate research laboratory. 14. Assays for TFPIα cofactor activity of PS are not currently commercially available but could be in the future and/or sent to specialty laboratories when high clinical suspicion exists. Suggest searching the literature for an appropriate laboratory for performing this specialty testing.

Guideline	Recommendations
Devreese KMJ, de Groot PG, de Laat B, Erkan D, Favaloro EJ, Mackie I, Martinuzzo M, Ortel TL, Pengo V, Rand JH, Tripodi A, Wahl D, Cohen H. **Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis: Update of the guidelines for lupus anticoagulant detection and interpretation.** ***J Thromb Haemost*. 2020 Nov;18(11):2828-2839.**	*This guidance focuses on methodological aspects of lupus anticoagulant (LA) testing, as well as interpretation of results for clinicians. The main changes in how to test for LA compared with the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee 2009 guidelines, in the preanalytical phase are more detailed recommendations on how to handle testing in anticoagulated patients, and the timing of testing. Also, routine coagulation tests are advised to obtain more information on the coagulation background of the patient, and when necessary, anti-Xa activity measurement for heparins or specific assays for direct oral anticoagulants should be performed. The three-step procedure with two test systems (diluted Russell's viper venom time and activated partial thromboplastin time [aPTT]) is essentially not changed. Silica remains the preferable activator in the aPTT assays, but ellagic acid is not excluded. We advise simultaneous performance of the mixing and confirmatory step, in each sample with a prolonged screening test. The confirmatory step can also be performed on a mixture of patient plasma and normal pooled plasma. Cutoff values should be established in-house on at least 120 normals, with transference of the manufacturer's cutoffs as an alternative. Reporting of results has not been changed, although more attention is focused on what clinicians should know. Patient selection for LA testing has been expanded.*
Cooper PC, Pavlova A, Moore GW, Hickey KP, Marlar RA. **Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH.** ***J Thromb Haemost*. 2020 Feb;18(2):271-277.**	1. Blood should be processed according to CLSI H21-A5 guidelines and plasma frozen below −20°C if not tested within 4 hours of venipuncture. 2. Clinical details must be taken into account, and protein C (PC) should not be tested in patients taking VKA. Clotting-based PC assay should not be carried out in the presence of circulating direct thrombin or factor Xa inhibitors, or when heparin/low molecular weight heparin concentration exceeds the manufacturer’s validated limit. 3. Clotted or partially clotted samples must not be tested. 4. The chromogenic assay is recommended as screen for PC deficiency because it is highly specific and precise, but will miss the rare type 2b defects that require clotting-based PC assay. 5. The standard (calibrator) must be traceable to the International Standard and results (expressed as IU/mL or IU/dL) should be read directly from the calibration curve. 6. The patient’s age must be taken into account when interpreting PC level; adult reference ranges must not be applied to children and neonates. Reference ranges should be locally derived and the log-normal distribution of PC should be taken into account. 7. Clotting-based PC assay may be required if heritable thrombophilia is strongly suspected but chromogenic PC level is normal. Validity of the result should be confirmed by testing the specimen at three or more dilutions, especially if an interfering factor is thought to be present. If severe PC deficiency is suspected and chromogenic PC does not support the diagnosis, a clotting-based PC assay should be performed on patient and parents. 8. A prothrombin time and assay of other VK-dependent clotting factors can help interpret a low PC level, as can level of antithrombin and protein S. An isolated low PC level should be confirmed with a repeat specimen.

Guideline	Recommendations
	9. Genetic analysis cannot exclude heritable PC deficiency phenotype (thrombosis) but can define a genetic defect. Measurement of PC in parents, and if available, PROC analysis, is valuable for confirmation of severe protein C deficiency, including prenatal diagnosis. In case of negative results, a quantitative analysis for large heterozygous deletions/duplications with multiplex ligationdependent probe amplification should be performed.
Moore GW, Van Cott EM, Cutler JA, Mitchell MJ, Adcock DM; subcommittee on plasma coagulation inhibitors. **Recommendations for clinical laboratory testing of activated protein C resistance; communication from the SSC of the ISTH.** ***J Thromb Haemost.* 2019 Sep;17(9):1555-1561**	*Patient selection* Indiscriminate testing for activated protein C resistance (APC-R) is not recommended in unselected patients with venous thromboembolism (VTE). Targeted testing is recommended for those situations in which the results may give an indication of risk of recurrence and influence treatment, as is the case for any patient undergoing evaluation for thrombophilia involving VTE. Other topics discussed include analytic issues (including performance characteristics of available tests), post-analytic issues, recommendations for testing (algorithm), and genetic analysis.
Devreese KMJ, Ortel TL, Pengo V, de Laat B, for the Subcommittee on Lupus Anticoagulant/Antiphospholip ID Antibodies. **Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH.** ***J Thromb Haemost* 2018; 16: 809–13.**	1. Lupus anticoagulant (LAC) present in plasma detected according to the Scientific Standardization Subcommittee (SSC) on Lupus Anticoagulant/Phospholipid Antibodies recommendations 2. b2GPI-dependent anticardiolipin antibodies (aCL) of IgG/IgM isotype in plasma or serum, present at higher levels (> 99th percentile of normal controls), measured by solid phase assays (ELISA or automated systems), according to the SSC on Lupus Anticoagulant/Phospholipid Antibodies recommendations. 3. b2GPI-antibodies (ab2GPI) of IgG/IgM isotype in plasma or serum, present at higher levels (> 99th percentile), measured by solid phase assays (ELISA or automated systems), according to the SSC on Lupus Anticoagulant/Phospholipid Antibodies recommendations. 4. LAC, aCL and ab2GPI should be positive on two or more occasions at least 12 weeks apart. 5. Laboratory results need to be reviewed and interpreted in a collaboration between a clinical pathologist and a clinician who is skilled at interpreting the data. 6. Comprehensive aPL testing (LAC, aCL, and ab2GPI IgG and IgM) should be carried out as triple aPL-positive patients are at high risk of thrombosis or aPL-related pregnancy morbidity. 7. Other antiphospholipid antibody tests are not recommended yet.
Seizure Management (General)	
Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, Bare M, Bleck T, Dodson WE, Garrity L, Jagoda A, Lowenstein D, Pellock J, Riviello J, Sloan E, Treiman DM.	Treatment Algorithm Stabilization phase (0–5 minutes), which includes standard initial first aid for seizures. The initial therapy phase should begin when the seizure duration reaches 5 minutes and should conclude by the 20-minute mark when response (or lack of response) to initial therapy should be apparent. A benzodiazepine

Guideline	Recommendations
Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. ***Epilepsy Curr.* 2016 Jan-Feb;16(1):48-61.**	(specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety, and tolerability (level A, four class I RCTs). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy (level A, 1 class I RCT), its slower rate of administration, compared with the three recommended benzodiazepines above, positions it as an alternative initial therapy rather than a drug of first choice. For prehospital settings or where the three first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives (level B). Initial therapy should be administered as an adequate single full dose rather than broken into multiple smaller doses. Initial therapies should not be given twice except for IV lorazepam and diazepam that can be repeated at full doses once (level A, two class I, one class II RCT). Doses listed in the initial therapy phase are those used in class I trials. Note that some consensus guidelines list slightly different dosages; for example, phenobarbital is often recommended at 20 mg/kg. The second-therapy phase should begin when the seizure duration reaches 20 minutes and should conclude by the 40-minute mark when response (or lack of response) to the second therapy should be apparent. Reasonable options include fosphenytoin (level U), valproic acid (level B, one class II study) and levetiracetam (level U). There is no clear evidence that any one of these options is better than the others. The ongoing Established Status Epilepticus Treatment Trial (ESETT) should provide the answer in the next few years. Because of adverse events, IV phenobarbital is a reasonable second-therapy alternative (level B, one class II study) if none of the three recommended therapies are available. The third therapy phase should begin when the seizure duration reaches 40 minutes. There is no clear evidence to guide therapy in this phase (level U). Compared with initial therapy, second therapy is often less effective (adults—level A, one class I RCT; children—level C, two class III RCTs), and the third therapy is substantially less effective (adults—level A, one class I RCT; children—level U) than initial therapy. Thus, if second therapy fails to stop the seizures, treatment considerations should include repeating second-line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring). Depending on the etiology or severity of the seizure, patients may go through the phases faster or even skip the second phase and move rapidly to the third phase, especially in sick or intensive care unit patients. The evidence-based treatment of refractory status epilepticus is beyond the scope of this guideline, though others have addressed the issue

Evidence Tables

Incidence & Etiology

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Zhou et al. 2023 **Canada** **Retrospective study**	NA	554 persons in the province of BC, aged 18 or older with a hospital admission for first CVT between 2000 and 2017. Mean age was 50.9 years, 55.4% were women.	Incident CVT cases identified in administrative datasets were divided by BC census data to obtain annual CVT incidence. Differences in incidence rates were examined over 3 time periods (2000–2005, 2006–2011, 2012–2017). In addition, a systematic literature search was conducted to identify studies reporting the incidence of CVT by person-years, and the results were pooled.	**Primary outcome:** Incidence of CVT per 1,000,000	The overall annual incidence rate was 8.7 (95% CI 8.0–9.4) per million. The incidence was 5.2 per million in timeframe one, 7.1 per million in timeframe 2 and 12.95 per million in timeframe 3. The incidence increased among men over time, whereas it was increased in women from time 2 to time 3. Pooling data from 22 studies, identified from the systematic review, the annual incidence rate was 12.1 (95% CI 9.9–14.3) per million. Men were more likely to have cases associated with head trauma and head and neck infections.11% of women had CVT with the peripartum period (within 3 months of delivery).
Rezoagli et al. 2021 **Italy** **Retrospective study**	NA	1,147 adult patients admitted to hospitals in northwestern Italy between 2000 and 2012 with confirmed CVT. Median age was 44 years, 66.7% were women.	Rates of CVT and in-hospital mortality were estimated. Incidence rate time trends across the study period were compared by sex. Potential predictors of mortality were identified.	**Primary outcome:** CVT incidence (per 10^6 population) in-hospital case fatality rate (CFR)	The overall incidence rate of CVT across the study period was 11.6 per 10^6. Sex-specific incidence rates were 7.8 in men and 15.1 per 10^6 in women. Over the study period, rates of CVT increased significantly among women, but not men. 134 patients (7.8%) experienced an ICH. There were 52 deaths (3%). Increasing age, ≥4 comorbidities and ICH were independent predictors of in-hospital mortality. Median duration of hospital stay was 12 days.
Ruuskanen et al. 2021 **Finland**	NA	563 adult patients with CVT from 2005 to 2014, identified from 20 Finnish hospitals, serving all of mainland Finland. 56.6% were women. Women were younger	CVT rates were estimated.	**Primary outcome:** CVT incidence (per 100,000 population)	Overall incidence rate was 1.32 (95% CI, 1.21–1.43), with a 5.0% annual increase. In people <55 years of age, incidence was 0.92 (95% CI 0.76–1.10) for men and 1.65 (95% CI 1.43–1.89).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Retrospective study		than men (mean age 42.5 vs. 55 years).			In persons ≥ 55 years, incidence was 1.61 (95% CI 1.34–1.91) for men and 1.17 (95% CI 0.96–1.41) for women. In-hospital mortality was 2.1%. One-year mortality was 7.9%. Long-term mortality was higher in men and in older patients.
Otite et al. 2020 **USA** **Retrospective study**	NA	5,567 new adult cases of CVT retrieved from the in the State Inpatients Databases of New York and Florida from 2006–2016.	Administrative databases were used to retrieved new cases of hospitalizations for CVT, which were then combined with annual census data to compute incidence rates.	**Primary outcome:** Changes in annual age- and sex-standardized incidence of CVT	As a percentage of all strokes, the incidence of CVT rose over the study period from 0.47% in 2005 to 0.80% in 2016. The annual age and sex-standardized rate (per 10^6) rose from 13.9 (2005) to 20.3 (2016). The incidence over time was significantly higher in women, particularly in those aged 18-44 years, although the annualized percentage change (APC) was higher in men, across all age group (9.2%), compared with women aged 45 to 64 years (APC 7.8%, $p < 0.001$), and women ≥65 years of age (APC 7.4%, $p < 0.001$). Incidence in women 18 to 44 years of age remained unchanged over time. 57.4% of hospitalizations in men and 63.7% of hospitalizations in women had comorbid codes for at least 1 CVT risk factor. Pregnancy and puerperium (21.7%), cancer (11.8%), and inflammatory conditions (11.4%) were the most common associated conditions coded in women, while cancer (19.5%), CNS trauma (11.3%), and CNS infection (11.2%) were the most common conditions in hospitalizations in men. Rates were highest in African Americans, followed by non-Hispanic Whites, Hispanics, and Asians.
Devasagayam et al. 2016 **Australia**	NA	105 cases of CVT confirmed by coding and/or neuroimaging, from all Adelaide public hospitals from 2005 to 2011.	CVT incidence rate was calculated using population census (n= 953,390 adults)	**Primary outcome:** Incidence rate of CVT	The incidence rate was 15.7 million per year (95% CI 12.9–19.0).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Retrospective study		Median age was 49 years, 52% were women.			The risk of CVT was significantly higher in women of reproductive age, compared with men (RR=1.18, 95% CI 0.94–1.48).
Coutinho et al. 2012 **The Netherlands** **Retrospective study**	NA	94 adult patients with CVT, diagnosed between January 1, 2008, and December 31, 2010, from 19 hospitals located in 2 Dutch provinces serving 3.1 million persons. Median age was 41 years, 72% were women.	CVT incidence rate was calculated, using confirmed CVT cases and census data.	**Primary outcome:** Incidence rate of CVT	The incidence was 1.32 per 100 000 person-years (95% CI, 1.06–1.61) and was higher in women compared with men (1.86 vs. 0.75). Among women aged 31 to 50 years, the incidence was 2.78 (95% CI, 1.98–3.82) per 100 000 person-years. Mortality was 1% at discharge and 3% at follow-up.
Risk Factors					
Green et al. 2018 **UK** **Systematic review & meta-analysis**	NA	42 studies examining genetic and non genetic risk factors for CVT.	Pooled analysis was conducted for studies that examined non-genetic risk factors (n=9) and genetic risk factors (n=22). 11 studies examined both types of risk factors.	**Primary outcome:** CVT risk factors	*Non genetic risk factors OR (95% CI)* Glucocorticosteroid therapy: 18.3 (3.3–102.6) Alcohol consumption: 2.7 (1.8–3.9) Infection: 7.5 (2.6–21.6) Surgery: 9.6 (1.1–83.5) Hypercholesterolemia: 2.4 (1.3–4.4), Hyperhomocysteinaemia 3.1 (2.1–4.6) Antiphospholipid antibodies: 7.0 (2.1–23.6) Autoimmune diseases: 5.6 (2.3–13.6) Anemia: 4.0 (2.1–7.9) Malignancy: 3.2 (1.4–7.1) Pregnancy/puerperium: 11.4 (5.7–24.3) Smoking, hypertension and diabetes were not associated with increased CVT risk. Data were pooled from between 2 and 9 studies. *Genetic risk factors OR (95% CI)* Factor V Leiden (G1691A): 2.5 (1.9–3.3) Protein C deficiency: 10.7 (3.1–37.7) Protein S deficiency: 5.7 (1.4–22.4) Antithrombin deficiency: 3.8 (1.0–13.8) Prothrombin (G20210A): 5.5 (4.0–7.27) TAFI gene variant (C1040T): 1.6 (1.0–2.4) Data were pooled for 2-27 studies
Silvis et al. 2016	NA	-	-	**-**	An overview of risk factors for CVT is presented including female sex, infections, hereditary thrombophilia, systemic diseases (cancer,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
The Netherlands **Narrative review**					myeloproliferative neoplasms, thyroid disease, inflammatory bowel disease, systemic lupus erythematosus and antiphospholipid syndrome, Behçet Disease, nephrotic syndrome, sarcoidosis, Wegener granulomatosis), hematologic conditions other than cancer (anemia, paroxysmal nocturnal hemoglobinuria) and miscellaneous causes (obesity, head trauma, dural arteriovenous fistula, iatrogenic causes, spontaneous intracranial hypotension, dehydration)
Giladi et al. 2016 **Israel** **Retrospective study**	NA	90 consecutively admitted patients with acute CVT admitted to a tertiary care centre.	The percentage of patients with a head injury, sustained within the previous 30 days, was identified.	**Primary outcome:** Head injury	Trauma history was found in 13 (14%) patients. 6 patients had skull fractures; the others had blunt trauma. The overall standardized mortality ratio was 941 ($p<0.0001$). Results for men and women were 1,206 and 543, respectively.
Amoozegar et al. 2015 **Canada** **Systematic review & meta-analysis**	Study quality was moderate or high	11 studies including women aged 15-50 years taking hormonal contraceptives, who developed CVT (cases) and healthy controls, not taking hormonal contraceptives.	The risk of developing CVT among hormonal contraceptive users was estimated.	**Primary outcome:** Odds of CVT	The odds of developing CVT given oral contraceptive use were significantly higher compared with women not taking them (OR=7.59, 95% CI 3.82–15.09, n=9 studies).
SARS CoV-2					
Baldini et al. 2021 **Germany** **Systematic review & meta-analysis**	Study quality was generally low, assessed using the NOS	28 studies of 57 patients with SARS-CoV-2 infection, who had sustained a CVT. Most studies (n=21) were case reports. Mean age was 53.5 years, 50% were women.	Pooled analysis was conducted to estimate the percentage of patients with CVT among people hospitalized with SARS-CoV-2 infection.	**Primary outcome:** Frequency of CVT	Using data from 34,331 patients, the estimated frequency of CVT was 0.08% (95% CI 0.01–0.5). In a cohort of 406 inpatients with a cerebrovascular disorder, CVT accounted for 4.2% of individuals with COVID-19. In 4 cases, CVT diagnosis preceded the onset of COVID-19–related symptoms, whereas in all other reports, CVT signs, symptoms, and diagnosis followed the onset of COVID-19 with stroke onset ranging from day 1 to 47 following COVID-19 symptoms (mean of 13 days).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					11 patients (30.6%) had known CVT risk factors including 5 women who were taking oral contraceptives; one person who had a previous diagnosis of polycythemia, two individuals had solid tumors, one individual was a 3-year old child with concomitant tuberculous meningitis and another individual had concomitant traumatic occipital skull fracture. Full (n=9) or partial (n=12) recovery was reported in 21 cases. In-hospital mortality was 40%.
Abdalkader et al. 2021 **USA** **Case series and literature review**	NA	8 patients diagnosed with CVT and COVID-19 identified from 7 of 31 participating centres admitted from March 1, 2020 to November 8, 2020. Mean age was 63 years, 7 were women. An additional 33 cases were identified from the literature. In the combined series, mean age was 50 years, 54% were women.	Clinical presentations, risk factors, clinical management, and outcome were evaluated.	**Primary outcomes:** See methods	*Case series* Most frequent presenting symptoms were gastrointestinal (75%), headache and fever (50%), decreased consciousness (25%) and focal neurologic deficit (12.5%). The most common locations of CVT were the superior sagittal and transverse sinuses (75%). 87.5% of patients received therapeutic anticoagulation. One patient died in hospital. Five patients were discharged with mRS score ≤2. The median time to onset of CVT from initial COVID-19 diagnosis was 3 days. Median time from onset of COVID-19 symptoms to CVT radiologic diagnosis was 11 days. *Literature series* Most frequent presenting symptoms were headache (48.6%), decreased consciousness (25.7%) and focal neurologic deficit (31.4%). The most common locations of CVT were the transverse sinus (62.9%), and the superior sagittal sinus (37.1%). 48.5% of patients received therapeutic anticoagulation. Eight patients died in hospital. 15

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(45.5%) patients were discharged with mRS score ≤2. The median time to onset of CVT from initial COVID-19 diagnosis was 1 day.
Siegler et al. 2021 **USA (International)** **Retrospective study**	NA	14,483 patients with laboratory-confirmed SARS-CoV-2 evaluated in the emergency department and/or admitted to one of 31 hospitals in four countries, between February 1, 2020, and June 16, 2020).	Incidence rates of stroke and stroke types were estimated. (timing of evaluation for stroke not stated)	**Primary outcome:** Incidence rate of cerebrovascular events, including CVT	172 patients were diagnosed with an acute cerebrovascular event (1.13% of cohort; 1,130/100,000 patients). Of these, 156 had acute ischemic stroke (1.08%; 1,080/100,000), 28 had ICH (0.19%; 190/100,000 95%), and 3 had CVT (0.02%; 20/100,000).
Taquet et al. 2021 **UK** **Retrospective study**	NA	537,913 persons with confirmed Covid-19 who were/were not hospitalized between January 20, 2020 and March 25, 2021. Data from 59 healthcare organizations, primarily in the USA, were used. Mean age was 42. 1 years, 55% were women.	The absolute risk of CVT and portal vein thrombosis (PVT) were estimated in the two weeks following a diagnosis of COVID-19. In addition, 2 control cohorts, matched for age sex and race, were used to compare the risks of CVT and PVT: those with a diagnosis of influenza and those who received a first dose of the two COVID-19 vaccines.	**Primary outcome:** Frequency of CVT and PVT	23 people were diagnosed with a CVT in the two weeks following their diagnosis (42.8 per million people, 95% CI 28.5–64.2). Four patients also had a CVT diagnosed prior to their COVID-19 diagnosis. The two-week risk of being diagnosed with a CVT was significantly higher in the cohort diagnosed with COVID-19 compared to a matched cohort diagnosed with influenza (N=392,424 in each cohort; RR=3.83, 95% CI 1.56–9.41, P<0.001), or compared to a matched cohort receiving an mRNA vaccine (N=366,869 in each cohort; RR=6.67, 95% CI 1.98–22.43, P<0.001). 211 people were diagnosed with PVT in the two weeks following their diagnosis (392.3 per million people, 95% CI 342.8–448.9). 117 patients also had a PVT diagnosed prior to their COVID-19 diagnosis. The two-week risk of being diagnosed with a PVT was significantly higher in the cohort diagnosed with COVID-19 compared to a matched cohort diagnosed with influenza (RR=1.39, 95% CI 1.06–1.83, P=0.02) or compared to a matched cohort receiving an mRNA vaccine (RR=7.40, 95% CI 4.87– 11.24, P<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Shahjouei et al. 2020 **USA (International)** **Retrospective study**	Data from 25% of the centres were excluded from the meta-analysis due to high risk of bias.	17,799 adults admitted to 99 tertiary centres in 11 countries with SARS-CoV-2, with or without a subsequent stroke and hospitalized for >24 hours.	The risk of stroke was estimated, pooling data from selected centres.	**Primary outcome:** Risk of stroke	There were 156 cases of stroke, of which 123 (79%) presented with acute ischaemic stroke, 27 (17%) with ICH/SAH, and 6 (4%) with CVT. The mean age of persons with CVT was 50.3 years, 67% were women. The median onset of CVT from SARS-CoV-2 diagnosis was 4.5 days. In pooled analysis, the subsequent stroke risk was 0.5%, using data from all centres in all countries.
ChAdOx1 nCov-19 (AstraZeneca)Vaccination					
Schulz et al. 2021 **Germany** **Case series**	NA	45 CVT cases, admitted to hospital within one month from first dose of vaccination with BNT162b2 (BioNTech/Pfizer), ChAdOx1 (AstraZeneca), and mRNA-1273 (Moderna). Mean age was 44.3 years, 77.8% were women. Information is also presented on 9 patients admitted with primary ischemic strokes, 4 with primary intracerebral hemorrhages, and 4 with other neurological events. Total sample of 62 patients	The incidence of CVT was estimated using data obtained from a web-based questionnaire, sent to neurology departments in Germany. Responses received up to April 14, 2021, were included. The frequency of vaccine-induced immune thrombotic thrombocytopenia (VITT) as the underlying mechanism, was also estimated using a 4-point grading scale (a score of ≥2 was considered a high probability of VITT)	**Primary outcome:** Number of cases per 100,000 person-months	The response was 37 (93%) of neurology departments at university hospitals (tertiary centers) and 75 (30%) neurology departments of nonuniversity hospitals. All reported cases occurred after vaccination with either ChAdOx1 (85.5%) or BNT162b2 (14.5%). The median time interval from last administered vaccine shot to neurological symptoms was 9 days. 26 persons with CVTs (57.8%) had a VITT risk score > 2. After 7,126,434 first vaccine doses, the estimated rate of CVT incidence within 1 month from first dose administration was 0.55 (95% CI 0.38–0.78) per 100,000 person-months. Incidence rates by vaccine type were 1.52 (95% CI 1.00–2.21) for ChAdOx1, 0.11 (95% CI 0.03–0.29) for BNT162b2, and 0.00 (95% CI 0.00–1.48) per 100,000 person-months for mRNA-1273. The authors estimated the background incidence rate of CVT to be about 0.22 to 1.75 per 100.00 person-years (0.02–0.15 per 100,000 person months).
Perry et al. 2021	NA	95 patients recruited from 43 hospitals across the UK	The incidence and outcomes of persons with	**Primary outcome:**	100% of VITT patients were given the AstraZeneca vaccine compared with 84% of non VITT patients.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
CVT After Immunisation Against COVID-19 (CAIAC) collaborators **UK** **Prospective study**		admitted between April 1 and May 20, 2021 with CVT following vaccination with COVID-19, regardless of type or timing.	CVT-associated vaccine-induced immune thrombotic thrombocytopenia (VITT, n=70) were compared with persons non VITT CVT (n=25). VITT was identified in persons in whom the lowest platelet count recorded during admission was <150×10⁹ per L and, if the D-dimer was measured, the highest value recorded was > 2,000 µg/L.	Death or dependency (mRS ≥3) at hospital discharge	The median age of VITT patients was significantly lower (47 vs. 57 years, p=0.0045). VITT patients were more likely to be women (56% vs. 44%), had more intracranial veins thrombosed (median 3 vs 2, p=0·041), and had an increased likelihood of concurrent extracranial thrombosis (44% vs 4%; p=0·0003). The median time interval between vaccination and symptom onset was 9 days in patients with VITT and 11 days in those without VITT. The primary outcome occurred significantly more frequently in patients with VITT-associated CVT (33 [47%] vs 4 [16%], p=0·0061). The primary outcome occurred significantly less frequently among VITT patients who received non-heparin anticoagulants (18/50 [36%] vs.15/20 [75%]; p=0·0031), and in those who received intravenous immunoglobulin (22/55 [40%] vs. 11/15 [73%]; p=0·022).
Greinacher et al. 2021 **Germany** **Case series**	NA	11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 n Cov-19, between 5 and 16 days, previously. Median age was 36 years, 6 patients were women.	Clinical characteristics and outcomes, are described.	**Primary outcome:** Patient outcomes	Thrombotic events included CVT (n= 9 patients), splanchnic vein thrombosis (n= 3 patients), pulmonary embolism (n= 3 patients), and other types of thrombi (n= 4 patients). Five of 10 patients had more than one thrombotic event. One patient presented with fatal cerebral hemorrhage. The outcomes of the other 10 patients at the time of publication included death (n=5) or recovery (n=4). The outcome of one patient is unknown. 4 patients were treated with heparin, one was treated with LMWH. 9 patients tested positive on the PF4-dependent platelet activation assay. The results of the 2 other patients are unknown.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Platelet nadir ranged from 8,000 to 107,000 per mm^3
Scully et al. 2021 **UK** **Case series**	NA	23 previously healthy patients who presented with thrombosis and thrombocytopenia 6 to 24 days after receiving the first dose of the ChAdOx1 CoV-19 vaccine. Median age was 46 years, 61% were women.	Laboratory results, clinical characteristics and outcomes, are described.	**Primary outcome:** Patient outcomes	Patients presented with CVT (n=13), MCA infarcts, intracerebral hemorrhage or SAH (n=6), DVT or PE (n=5), and portal vein thrombosis (n=2). 7 patients (30%) died. 13 patients had low fibrinogen levels (range, 0.3 to 4.5 g per liter; normal range, 1.5 to 4.0) and elevated d-dimer levels (median, 31,301 fibrinogen-equivalent units [FEU]; range, 5000 to 80,000). 22 patients tested positive for antibodies to platelet factor 4 (PF4), with one equivocal result. One patient was negative. A summary of recommendations for testing and treatment, based on the current understanding of the syndrome, is presented.
Risk factors for thrombotic recurrence					
Pires et al. 2019 **Brazil** **Prospective study**	NA	203 patients ≥18 years with CVT admitted to 4 centres between April 1, 2000 and June 30, 2014. Median age was 30.8 years, 86.2% were women. 65.4% of women developed CVT while using oral contraceptives and 13 (8.0%) during puerperium. CVT was unprovoked in 54 (26.6%) patients.	A standardized questionnaire was used to collect data at admission and at follow-up visits, or by telephone, if required. The follow-up period started after discontinuing anticoagulation therapy and ended at the time of recurrence, last appointment, or last contact.	**Primary outcome:** symptomatic VTE recurrence	Median duration of follow-up was 3.0 years. 185 (91.1%) patients were treated with VKA after CVT diagnosis. The median duration of anticoagulant therapy was 9.9 months. 14 patients were lost to follow-up. Thirteen patients (6.9%) developed VTE recurrence after a first CVT, including 2 CVTs, 3 PEs, and 8 DVTs. Male sex and factor V Leiden mutation were independent predictors of recurrent VTE.
Palazzo et al. 2017 **France**	NA	187 patients admitted consecutively to one of 4 stroke centres, with CVT. Mean age was 46 years, 67% were	After discharge, follow-up visits were performed at 6 months, including neuroimaging follow-up, at 12 months, and yearly thereafter at outpatient	**Primary outcome:** Cerebral or extracranial venous thrombotic (VT) recurrence, independent	Mean duration of follow-up was 80 months. Patients received oral anticoagulant treatment for an average of 14 months. Overall mortality was 17%.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Prospective study		women. 98% had an admission GCS score between 9 and 15.	evaluation that included neurological examination. All patients received anticoagulation therapy with target INR 2:3.	predictors of VT recurrence	74% of patients had a mRS score of 0 or one at hospital discharge, 8% had mRS score of 2 and 16 had mRS score of 3-5. During follow-up, there were 30 new venous thrombotic events in 25 patients. CVT reoccurred in 6 patients, 19 subjects had new extracranial venous thrombotic events (DVT in 12 patients, PE in 5 patients, and portal vein thrombosis in 2 patients). Mortality in 2 patients was attributed to these events. Independent predictors of VT recurrence were previous VT, presence of cancer or malignant hemopathy, and unknown CVT cause.
Dentali et al. 2012 **Italy** **Retrospective study**	NA	706 patients with CVT, admitted to 27 centres in Italy, Czech Republic and the USA, who were followed for at least 6 months or who had a primary outcome within 6 months. Mean age was 40 years, 73.7% women.	The long-term frequencies of mortality, residual disability and recurrent venous thromboembolism (VTE) are described.	**Primary outcomes:** Disability (complete recovery: mRS 0-1, independent: mRS 2), mortality, recurrence of CVT and occurrence of VTE	Median duration of follow-up was 40 months. 89.1% of patients had a complete recovery, and 3.8% were independent. There were 20 deaths (2.8%). The most cause of death was malignancy related (n = 12). 75 patients (10.6%) had a recurrent, non-fatal VTE, of which 31 (4.4%) was a recurrent CVT. The overall incidence of recurrent VTE was 23.6 per 1,000 patient-years (95% CI 17.8– 28.7). Most events occurred after anticoagulation had been discontinued. In this group, the incidence of recurrent VTE was higher (35.1 events per 1,000 patient-years (95% CI, 27.7- 44.4). The only independent factor for recurrent CVT or VTE in other sites was a history of VTE (HR= 2.7, 95% CI 1.25–5.83).
Narayan et al. 2012 **India**	NA	428 consecutively admitted patients with CVT to a single institution. Mean age was 31.3 years, 53.7% were men.	Risk factors, outcomes and complications are described.	**Primary outcome:** In-hospital mortality, dependence at 90 days, long-term follow-up	Mean duration of hospital stay was 16.1 days. Headache, vomiting, and seizures were the most common clinical features found in 94.4%, 74.1% and 45.2% of patients, respectively. In terms of clinical presentation:

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Prospective study					Stroke like presentation 28.5% Presentation as isolated seizures 29.4% Benign intracranial hypertension 18.2% Encephalopathy 25.2% Psychosis 1.8% The most common risk factors were anemia (18.4%), hyperhomocysteinemia (18.2%), alcoholism (15.6%), protein S deficiency (12.3%), oral contraceptive pill use (11.4%), postpartum state (9.8%), and anticardiolipin antibodies 7.2%). 92.5% of patients received unfractionated heparin for 7 days overlapping with oral anticoagulants for 3 days which was continued for a minimum of 6 months. In-hospital mortality was 7.7%. At 90 days, 52.8% patients were independent (mRS 0-1), 10.9% of patients were functionally independent (mRS = 2), and the remaining 25.7% of patients remained dependent (mRS 3-5). Independent predictors of poor outcome were fever, DVT, seizures, focal neurological deficit and unconsciousness. Follow-up ranging from 6 months to 5 years was available for 60.2% of patients with a mean follow-up of 33 months. Recurrence of CVT was seen in 22 patients (5.1%). All the recurrences occurred after 6 months and occurred up to 4.5 years after the initial episode.
Martinelli et al. 2010 **Italy** **Prospective study**	NA	145 patients with first-ever CVT who were referred for thrombophilia screening at an outpatient thrombosis clinic. Median age at time of event was 33 years, 73% were women. Most cases were related to the	Following discontinuation of anticoagulation therapy, patients were followed for a median of 6 years, to determine the frequency, timing and predictors of outcome events. Median	**Primary outcome:** Recurrent CVT or another venous thromboembolism, including deep vein thrombosis (DVT) and	15 patients (10%) developed a second episode of nonfatal venous thrombosis (CVT in 5 cases, 8 cases of DVT and 2 cases of isolated PE). The rate of any venous thromboembolism was 2.03 per 100 person-years and 0.53 per 100 person-years for CVT.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		use of oral contraceptives, pregnancy or the puerperium.	duration of anticoagulation use was 12 months.	pulmonary embolism (PE).	The incidence of recurrent venous thromboembolism was higher i) in the first year of follow-up after discontinuation of anticoagulant treatment compared with years 3 and 10 (5.03/100 person years vs. 2.63 and 1.74, respectively, ii) in men (4.95/100 person years vs. 0.65/100 person years in women), and iii) in patients with severe thrombophilia than in those without or with mild thrombophilia (6.50/100 person years vs. 1.35 and 1.01, respectively). The risk of recurrent venous thromboembolism was significantly higher in men (adjusted for age, BMI, presence of thrombophilia, and duration of anticoagulant treatment; HR=9.66, 95% CI, 2.86 to 32.7).
Miranda et al. 2010 **Portugal** **Prospective study** ***The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)***	NA	624 adults with CVT included in the study from 89 centers in 21 countries. Mean age was 39.1 years, 74.5% were women.	Patients were followed up at 6 months, 12 months, and yearly thereafter, to determine the timing and frequency of the primary outcomes.	**Primary outcomes:** New venous thromboembolic events (VTEs), including recurrent CVT	Median duration of follow-up was 13.9 months. 36 (5.8%) patients had at least 1 VTE. The cumulative probability of venous thrombotic recurrence was 1.7% at 3 months, 2.6% at 6 months, 4.0% at 12 months, 6.5% at 2 years, and 12.8% at 3 years. The venous thromboembolic recurrence rate was 4.1 per 100 person-years. Independent predictors of VTEs were male sex (HR=2.6; 95% CI 1.4 to 5.1) and polycythemia/thrombocythemia (HR=4.4; 95% CI, 1.6 to 12.7). 14 (2.2%) patients had an episode of recurrent CVT. The cumulative incidence of a recurrent CVT event after 3, 6, and 12 months was 0.2%, 0.9%, and 1.7%, respectively. The 2-year and 3-year cumulative incidences were 2.3% and 5.7%, respectively). 5 (35.7%) of the total CVT recurrences occurred in the first 6 months and 9 (64.3%) within the first year. The CVT recurrence rate was 1.5 per 100 person-years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Dentali et al. 2006 **Italy & Canada** **Systematic review**	NA	19 studies (12 retrospective, 5 prospective, 2 combination of pro/retrospective) including 1,488 patients who had experienced a CVT with follow-up of >3 months.	The frequencies of outcomes of interest were assembled an averaged, where possible.	**Primary outcomes:** Mortality, good outcome (mRS 0-2, or a Glasgow Outcome Scale of 1-2) **Secondary outcomes:** Recanalization, recurrence	Mean/median duration of follow-up ranged from 3 to 145 months. Mean mortality during first month was 5.6% (66/1,180). Mean mortality at the end of follow-up was 9.4% (122/1,303). At 3 to 6 months of follow-up, a mean of 87.2% of surviving patients had a good outcome and 8.7% had a poor outcome. At 12 months, a mean of 88.3% of patients had a good outcome, 9.7% had a poor outcome. Data on recanalization were available in 5 studies. At 3 to 6 months, 82.5% of patients (94/114) had complete or partial recanalization. At one year, 84.5% had complete or partial recanalization (93/110). The frequency of CVT recurrence was 2.8% (29/1,048).
Appenzeller et al. 2005 **Brazil** **Retrospective study**	NA	24 patients admitted to a single facility with CVT. Mean age was 29.5 years, 75% were women.	The clinical and imaging features, treatments and outcomes of patients are described.	**Primary outcome:** None stated	The most common presenting symptoms were headache, vomiting and impairment of consciousness. The probable etiology of CVT could be determined in 21 (88%) patients and included pregnancy/puerperium (25%), use of oral contraceptives (17%), head trauma (8%), nephrotic syndrome (4%) and mastoiditis (4%). Antiphospholipid syndrome was diagnosed in 3 patients. An inherited thrombophilia was identified in 4 patients (17%). CT images were abnormal in 15 (62.5%) patients. Parenchymal involvement was seen in 9 (37.5%) patients. MRI scans were performed in 17 patients, including all patients who had normal CT scans. All patients with normal CT had abnormal MRI. MRI

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					showed signs of sinus thrombosis in all 17 patients and parenchymal lesions in 9 patients. Patients received heparin for 3–5 days followed by oral anticoagulants for 6 months. Antiepileptic drugs were used in 6 patients with acute seizures. 13 patients had no neurological symptoms at hospital discharge, while 11 patients continued to suffer from various degrees of neurological impairment. Patients with CVT associated with pregnancy, puerperium or oral contraceptive use had better outcome than patients with inherited thrombophilia or systemic disease.
Stolz et al. 2000 **Germany** **Prospective study**	NA	25 patients admitted to a single centre with CVT. Mean age was 37.1 years, 76% were women.	Patients were screened for inherited coagulation disorders. The association between their presence and long-term outcome was also examined.	**Primary outcome:** Hereditary thrombophilic risk factors	Inherited thrombophilic risk factors were identified in 9 (36%) patients, of which 4 were positive for the heterozygous factor V Leiden mutation, 2 were heterozygous carriers of the prothrombin-G20210A-polymorphism, 1 had a familial plasminogen deficiency and 1 patient each had a protein S and C deficiency. At the time of presentation, 15 patients had no neurological abnormalities, 8 patients had minor neurological deficits, 1 patient was bedridden, and 1 patient suffered from seizures, requiring surgery. After an average follow-up of 4.8 years, a significantly lower percentage of patients with a coagulopathy had no neurological findings, compared with those with no coagulopathy (33% vs. 75%, p<0.05).

Diagnosis & Initial Clinical Assessment

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Imaging					

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hedderich et al. 2019 **Germany** **Cost-effectiveness analysis**	NA	Age in the base case was 37 years.	A decision model based on Markov simulations was used to estimated lifetime costs and quality-adjusted life years (QALY) associated with the following imaging strategies: non-contrast CT (NCCT), NCCT plus CT venography (CTV), routine MRI without vascular imaging (R-MRI), and MRI with venography (MRV).	**Primary outcome:** Cost and QALYs	The base-case analysis in the low pre-test probability setting of CVT at 1.6% showed that NCCT and NCCT plus CTV were dominant over R-MRI and R-MRI plus MRV. Imaging with NCCT plus CTV led to incremental lifetime QALYs compared with NCCT (23.385 QALYs vs. 23.374 QALYs) at slightly higher lifetime costs ($5,210 vs. $5,057). When the pre-test probability of CVT was set to 50%, diagnostic imaging with NCCT and NCCT plus CTV also dominated over MRV and R-MRI in the base-case analysis.
Xu et al. 2018 **China** **Systematic review & meta-analysis**	Most of the studies had low or indeterminate risk of bias, assessed using the QUADAS-2 tool.	24 articles (21 retrospective, 3 prospective) comprising 48 studies (4,595 cases) including those in which CT and/or MRI were used in the differential diagnosis of CVT or cerebral sinus thrombosis. Sample size ranged from 17 to 429.	The accuracy of CT and MRI in the differential diagnosis of CVT and cerebral venous sinus thrombosis (CVST) was examined using MR venography (MRV) and/or CTV and/or digital subtraction angiography (DSA) as the standard reference.	**Primary outcome:** Sensitivity/specificity	There were 15 articles including 2,822 cases, using CT evaluations. The pooled sensitivity for CT–CVT was 0.79 (95% CI 0.76- 0.82), and 0.81 (95% CI 0.78- 0.84) for CT–CVST. The pooled specificity for CT-CVT was 0.90 (95% CI 0.89- 0.91) and 0.89 (95% CI 0.88- 0.91) for CT-CVST. The area under the curve (AUC) of the summary receiver operating characteristic (ROC) for CT-CVT and CT-CVST were 0.9314 and 0.9161, respectively. There were 11 articles including 1,773 cases, using MRI evaluations. The pooled sensitivity for MRI–CVT was 0.82 (95% CI 0.78- 0.85), and 0.80 (95% CI 0.76- 0.83) for MRI–CVST. The pooled specificity for MRI-CVT was 0.92 (95% CI 0.91-0.94) and 0.91 (95% CI 0.89- 0.92) for MRI-CVST.

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					The AUC of the ROC for MRI-CVT and MRI-CVST were 0.9221 and 0.9314, respectively.
Duman et al. 2017 **Turkey** ***Cerebral Venous Thrombosis (VENOST) study***	NA	1,144 adult patients with acute CVT recruited from 35 stroke centres, from 2000-2015. Median age was 37 years, 67.9% were women. 47% of participants were aged18-36y, 33% were 37-50 years and 20% were >50 years.	Demographic, etiological, and clinical characteristics, outcomes (at months 1, 3, 6 and 12) of patients are described.	**Primary outcome:** Patient symptoms, etiologies and predictors of poor outcome	The most common symptom was headache (n = 997 cases; 87.2%), followed by nausea and vomiting (n = 317, 27.7%), visual field defects (n = 303, 26.5%), epileptic seizures (n = 271, 23.7%), focal neurological deficits (n = 208, 18.2%), altered consciousness (n = 204, 17.8%), and cranial nerve palsies (n = 128, 11.2%). The most frequent symptoms were headache (89.4%) and visual field defects (28.9%) in men, and headache (86.1%) and epileptic seizures (26.8%) in women. Gynecological causes comprised the largest group of risk factors (41.7%), including pregnancy/puerperium and oral contraceptive use. Prothrombotic conditions (26.4%), mainly methylenetetrahydrofolate reductase mutation (6.3%) and Factor V Leiden mutation (5.1%), were the most common hereditary etiologies. Independent predictors of poor outcome (mRS ≥ 3) were older age (>50 years) (OR = 3.55, 95% CI = 1.492-8.448), parenchymal involvement (OR = 6.50, 95% CI = 2.38- 17.691), and malignancy (OR = 3.23, 95% CI = 1.07-9.73).
Qu & Yang 2013 **China** **Retrospective study**	NA	62 patients with CVST diagnosed by magnetic resonance imaging (MRI) and/or digital subtraction angiography (DSA) at a single institution. Mean age was 30.6 years, 58% were women. 15 cases presented within 1 week, 36 cases were between 1 week and 1 month and 11 cases presented >1 month from onset.	Patients received CT, MRI and/ore DSA imaging. In 21 cases, patients received all 3 forms of imaging.	**Primary outcome:** Typical characteristics and/or location sites of lesions associated with each imaging type are described	On CT examination, 56 cases presented with direct or indirect signs of CVST. Among the 56 cases receiving both MRI and MRV examinations, 54 cases presented with adverse development or non-development of the venous sinus at lesion sites (96.4% positive). 32 patients received DSA imaging, of whom all were diagnosed with CVST.

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					Among the 21 cases that received all 3 forms of imaging, 20 were positive in both MRI and MRV examinations, while the DSA examination was positive in 19 cases. The authors suggest that MRI combined with MRV examination is the preferred means of diagnosing CVST.
Wong et al. 2011 **China** **Prospective study**	NA	109 consecutive patients <70 years of age with spontaneous nonhypertensive and/or lobar intracerebral hemorrhage who presented within 96 hours after the initial ictus. Mean age was 47.6 years, 67% were men.	The ability of computed tomography angiography and venography (CTAV) to detect an underlying structural vascular abnormality was compared with digital subtraction angiography (DSA). If both images were normal, then a second catheter angiography and/or MRI were arranged 6 to 12 weeks later.	**Primary outcomes:** Accuracy, positive predictive value (PPV), and negative predictive value (NPV)	DSA-positive pathologies causing hemorrhage were identified among 37 patients, which included cerebral arteriovenous malformation (22), cerebral aneurysm (2), sinus thrombosis (7), and brain tumor (2). All lesions were also identified via CTAV. There was one false positive whereby CTAV identified a case of a cerebral arteriovenous malformation, which turned out to be a venous angioma on DSA. The accuracy of CTVA was 99.1% (95% CI, 95.7%–100%). PPV and NPV were 97.3% (95% CI, 88.3%–99.9%) and 100% (95% CI, 95.9%–100%), respectively.
Khandelwal et al. 2006 **India** **Prospective study**	NA	50 patients with clinical suspicion of CVT. Median age was 32 years, 60% were women.	The ability of cerebral CT venography to detect CVT lesions was compared with MR venography (reference standard). Test characteristics were calculated for each involved vein or sinus.	**Primary outcomes:** Test characteristics including accuracy, sensitivity (SN), specificity (SP) positive predictive value (PPV), and negative predictive value (NPV)	30 patients were diagnosed as having CVT on both CT venography and MR venography. The involvement of various sinuses (on CT venography/MR venography) were: superior sagittal sinus (20/19), right transverse sinus (11/12), left transverse sinus (14/14), right sigmoid sinus (12/9), left sigmoid sinus (11/10), straight sinus (5/5), Galen's vein (4/4), right internal cerebral vein (2/2), and left internal cerebral vein (2/2). *Superior sagittal sinus* Accuracy: 90%, SN: 94.7%, SP: 81.8%, PPV: 90%, NPV: 90% *Right transverse Sinus*

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					Accuracy: 90%, SN: 83.8%, SP: 94.4%, PPV: 90.9%, NPV: 89.5%
Liang et al. 2001 **Japan** **Prospective study**	NA	35 consecutive patients (19 women and 16 men, ages 19 to 76 years; mean age, 49 years). 18 patients were examined for suspected dural sinus thrombosis, 6 had proved arteriovenous fistula and 11 patients had intraaxial tumors that were located far from the dural sinuses and served as a control group.	Patients underwent imaging with both 2D-TOF MR venography and 3D contrast-enhanced MP RAGE during the same scan session. All patients also underwent DSA within one week. ROC curves were created to assess the ability of MR venography to diagnose sinus thrombosis, using DSA as the reference standard.	**Primary outcome:** Sensitivity (SN), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV)	Dural sinus thrombosis was diagnosed at 26 sinus sites in 12 patients by intraarterial DSA. *3D contrast-enhanced MP-RAGE* SN: 83.3%, SP: 99.6%, PPV: 97.5%, NPV: 96.8% *2D-TOF MR venography* SN: 51.0%, SP: 92.5%, PPV: 56.8%, NPV: 91.0% *T1-weighted imaging* SN: 33.3%, SP: 84.3%, PPV: 31.2%, NPV: 87.0% *T2-weighted imaging* SN: 7.7%, SP: 92.4%, PPV: 14.8%, NPV: 84.2% *Contrast-enhanced T1-weighted imaging* SN: 14.7%, SP: 80.0%, PPV: 13.4%, NPV: 82.8%
Wetzel et al. 1999 **Switzerland** **Prospective study**	NA	25 patients consecutively admitted to a single centre who underwent both intraarterial DSA and CT venograph. Mean age was 54 years, 60% were women. The indications for DSA were suspicion of dural sinus thrombosis (n=4), evaluation of a tumor (n=11), and a vascular malformation (n=5) Arterial cerebrovascular disease was investigated in 5 patients.	The findings from patients who underwent both intraarterial DSA and CT venography (CT multiplanar reformatted [MPR] and maximum intensity projection [MIP] images were independently reviewed by blinded observers, to ascertain whether venous structures were present, partially present, or absent.	**Primary outcome:** Sensitivity and specificity (using DSA, as the references standard)	426 sinuses or veins were examined. Using DSA, 344 structures were identified as present, 28 as partial present, and 54 as absent. Using CT MPR images, 381 structures were identified as present, 16 as partial present, and 29 as absent. CT MIP images, 298 structures were identified as present, 29 as partial present, and 99 as absent. Overall, CT MPR images had a sensitivity of 95% and specificity of 19%. Overall, CT MIP images had a sensitivity of 80% and specificity of 44%. In a second evaluation, based on interobserver consensus, 415 venous structures were considered to be present as they were seen clearly on at least one of the imaging techniques.

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					The sensitivity/specificity was 95%/91% for MPR, 90%/ 100% for DSA, and 79%/91% for MIP images.
Lafitte et al. 1997 **France** **Prospective study**	NA	20 patients with CVT. Mean age was 37 years, 80% were women.	All patients underwent CT, MRI (with MRA for 15 patients) and digital subtraction angiography (DSA). 11 patients had follow-up after treatment with MRI, 9 with MRA, an average of 3 months after admission. The sensitivity of MRI/MRA in the diagnosis and follow-up is described.	**Primary outcome:** Sensitivity	The sensitivity of MRI to diagnose CVT was 90%. The sensitivity of MRI+MRA to diagnose CVT was 100%. When performed within 3 days of admission, CT results were normal in 5 patients. Direct and indirect imaging signs were present in the remaining patients. These signs were more evident on repeat imaging performed between days 3 and 15.
Ozsvath et al. 1997 **USA** **Retrospective study**	NA	24 patients from one centre who had received CT venography as well as technically successful MR venography within the previous 24 months. Mean age was 29 years. 14 patients were women.	Patients underwent both CT and MR venography of the intracranial venous circulation using a maximum-intensity-projection (MIP) algorithm. Without knowledge of the patients' case histories, 2 radiologists each evaluated the CT venogram and MR venogram and arrived at a consensus regarding the absence or presence of dural sinus thrombosis. In addition, the venograms were assessed for the presence of 12 different venous structures.	**Primary outcome:** Not stated	17 patients were examined for suspected dural sinus thrombosis. Using MR venography, 8 patients were diagnosed with dural sinus thrombosis. The same patients were also diagnosed using CT venography. Diagnosis of dural sinus thrombosis was confirmed by follow-up CT venography in 4 patients and by follow-up MR imaging in 2 patients. The comparison of imaging techniques showed that CT venography reliably revealed all cerebral veins and sinuses when seen with MR venography. CT venography more frequently visualized sinuses or smaller cerebral veins with low flow as compared with MR venography.
Vogl et al. 1994 **Germany** **Prospective study**	NA	42 patients with clinically suspected dural sinus thrombosis plus 10 healthy volunteers.	Patients and volunteers were imaged using venous MR angiography with spin echo MR imaging and conventional angiography, to identify direct and indirect signs. The results	**Primary outcome:** Not stated	In the first interpretation of the initial MR angiograms, 25 patients and all control subjects, were judged not to have dural sinus thrombosis, and 17 patients were judged to have dural sinus thrombosis, which was verified either by conventional angiography (cut-film on digital subtraction angiography, n = 9) or by MR

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			of MR angiography for patients were compared with results in 10 control subjects. Confirmation of the diagnosis of dural sinus thrombosis was based either on conventional angiographic findings or on the changes seen in follow-up examinations.		angiognaphic studies that showed clear improvement on follow-up examinations. In 7 patients who did not undergo conventional angiography, repeated MR angiographic examinations (3-8 times) showed clear improvements following therapy with heparin. Individual frames from two-dimensional fast low-angle shot sequences allowed direct visualization of thrombus. Limited spin-echo sequences provided inconsistent findings and were Insufficient for diagnosis.
Lumbar puncture					
Ferro et al. 2004 **Portugal** **Prospective study** ***The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)***	NA	624 adults with CVST included in the study from 89 centers in 21 countries. Mean age was 39.1 years, 74.5% were women.	Patients were treated at the discretion of the treating physician. The outcomes of patients were assessed at 6 months and then yearly thereafter. Independent predictors of death or dependency were identified.	**Primary outcome:** Death or dependence (mRS>2) at the end of follow-up	The diagnosis of CVT was established by MRI/MR venography in 71% of patients, by intra-arterial angiography in 12% of patients, by CT venography in 2% and by multiple imaging methods in 14% of patients. Median duration of follow-up was 16 months. 1.3% of patients were lost to follow-up after discharge. At the end of follow-up, 13.4% of patients were dead or dependent, 79.1% had an mRS score of 0 or 1. Independent predictors of the primary outcome were age>37 years, male sex, coma, mental status disorder, intracranial hemorrhage on admission, thrombosis of the deep cerebral venous system, central nervous system infection, and cancer. 2.2% of patients had a recurrent sinus thrombosis, while 4.3% had other thrombotic events,
Biousse et al. 1999 **France**	NA	160 consecutive patients with CVT admitted to a single institution between 1975 and 1998.	The characteristics of patients presenting only with isolated intracranial hypertension (ICH, n=59) were compared with those of patients presenting with	**Primary outcomes:** None stated	82% of patients presenting with other symptoms had increased intracranial pressure, 57% had seizures, 76% had focal signs, and 45% had altered consciousness. No patients with isolated ICH had seizures, focal signs or altered consciousness.

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Prospective study			other neurologic symptoms and signs (n=101).		The superior sagittal sinus was involved in 32 patients (54%) (isolated in 7) and lateral sinuses in 47 (80%) (isolated in 17) in isolated ICH patients compared with 62% (15 isolated) and 60% (12 isolated) in patients with other symptoms. The difference in proportions of lateral sinus involvement was significantly different between groups. A significantly higher percentage of patients with isolated ICH had a normal CT scan (54% vs. 16%, p<0.001). Lumbar puncture was performed in 44 patients with ICH and in 77 patients presenting with other factors. A significantly higher percentage of patients with isolated ICH had a normal result (75% vs. 41%, p<0.001). In terms of etiological factors, a significantly higher percentage of patients with isolated ICH had an inflammatory disease (30.5% vs. 12%, p<0.005). Significantly fewer isolated ICH patients were in a postpartum state (1.5% vs. 12%, p<0.05). A significantly higher percentage of isolated ICH patients had a complete recovery (93% vs. 67%, p<0.001). No isolated ICH patients had neurological sequelae compared with 26% of patients presenting with other factors (p<0.001). Anticoagulants were used in 41 of 59 patients (69.5%), steroids or acetazolamide in 26 (44%), therapeutic lumbar puncture in 44 (75%), and surgical shunt in 1. Three patients had optic atrophy with severe visual loss, 1 died from carcinomatous meningitis, and 55 (93%) had complete recovery.
D-dimer					

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Heldner et al. 2020 **Switzerland** **Prospective study**	NA	359 adult patients admitted to hospital with suspected acute CVT. Mean age was 40 years, 70% were women.	Patients underwent clinical examination, blood sampling for D-dimers, and MR/CT venography. A CVT score was developed based on the association with clinical variables independently associated with CVT in regression analysis, and weighted by regression coefficients. The predictive value of the newly developed scale was calculated. Patients were stratified as low, moderate, and high CVT probability. D-dimer levels were calculated within each probability group. CVT was predicted using only D-dimer levels and by using D-dimer levels + newly developed CVT score result.	**Primary outcomes:** Positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, accuracy, and ROC curve with area under the curve (AUC)	Median time from symptom onset to hospital presentation was 5 days. CVT was confirmed in 26.2% of patients by neuroimaging. The optimal estimate of clinical probability of CVT was based on 6 variables: seizure(s) at presentation (4 points), known thrombophilia (4 points), oral contraception (2 points), duration of symptoms >6 days (2 points), worst headache ever (1 point), and focal neurologic deficit at presentation (1 point), with an AUC of 0.889. Low probability scores were defined as 0-2, moderate probability was 3-5 points and high was 6-14. A score of ≥3 was associated with the best test characteristics (sensitivity 78.7%; specificity 83%/NPV 91.7%/PPV 62.2%; accuracy 80.5%). The predictive value of D-dimers alone for CVT was: >500 µg/L sensitivity 89.4%; specificity 66.4%; NPV 94.6%; PPV 48.6%; accuracy 72.4%. >675 µg/L sensitivity 77.7%; specificity 77%; NPV 90.7%; PPV 54.5%; accuracy 77.2%. At a cut-off of ≥6 points, the addition of D-dimer >500 µg/L resulted in the best CVT prediction score (sensitivity 83%/specificity 86.8%/NPV 93.5%/ accuracy 84.4%/AUC 0.937).
Meng et al. 2014 **USA** **Prospective study**	NA	233 adults <45 years, with suspected acute CVT, of which 34 cases had confirmed CVT and 199 served as mimic controls. 34 healthy age- and gender matched persons were included as controls. Mean age of cases was 28 years, 74%	D-dimer and fibrinogen levels of all patients and controls were measured before imaging and treatment and compared between groups for up to 180 days.	**Primary outcome:** Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of d-dimer and fibrinogen to predict CVT	At baseline, the mean D-dimer among CVT cases was significantly higher than in either mimic or controls (968·9 mg/l vs. 343·2 vs. 320.2 mg/l). At baseline, the mean fibrinogen level among CVT cases was significantly higher than in either mimic or controls (6.87 g/l vs. 3·2 vs. 2.9 g/l). Among CVT cases, 94·1% had d-dimer elevation, 73·5% had fibrinogen elevation, and 67·6% had

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		were women. Mean duration of symptoms was 4.5 days.			both d-dimer and fibrinogen elevation. In the mimics, 2·5% had d-dimer elevation, 16·1% had fibrinogen elevation, 1% had both d-dimer and fibrinogen elevation. The corresponding values in the controls were 8.8% and 0%. Among al CVT cases, the sensitivity of elevated d-Dimer to predict CVT was 94.1%, sensitivity was 97.5%. The sensitivity and specificity of elevated fibrinogen was 73.5% and 83.9%, respectively. Using both d-dimer and fibrinogen, the sensitivity and specificity was 67.6% and 98.9%. The PPV of d-dimer + fibrinogen was higher than when each value was used alone (92% vs. 86·5% vs. 43·9%). The highest NPV was for d-dimer (98·9%), compared with fibrinogen (94·9%) or the combination (94·7%). After the initiation of anticoagulation, d-dimer levels gradually decreased over 180 days, at which point, no CVT case had elevated levels. In contrast, while the percentage of patients with elevated fibrinogen levels fell over time, at 180 days, 33% still had elevated levels.
Dentali et al. 2012 **Italy** **Systematic review & meta-analysis**	Risk of bias was generally low	14 studies, including 1,134 patients with suspected or confirmed CVT.	The sensitivity of D-dimer to aid in the diagnosis of CVT was assessed, using CTV, MRI, MRV, or angiography as the reference standard.	**Primary outcome:** Weighted mean sensitivity (WMS)	*Studies including patients with suspected CVT* Mean prevalence was 17% using data from 5 studies. 7 studies included 155 patients in whom CVT was confirmed and 771 patients where CVT was ruled out. D-dimer was elevated in 145 patients with objectively confirmed CVT (bivariate WMS 93.9%; 95% CI 87.5–97.1), whereas D-dimer was normal in 692 patients in whom CVT was objectively ruled out (bivariate weighted mean specificity 89.7%; 95% CI 86.5– 92.2). Among 363 patients in whom CVT was confirmed, D-dimer was elevated in 325 cases (WMS of 89.1%, 95% CI 84.8–92.8). Sensitivities varied and were lower depending on duration of symptoms,

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					isolated headaches and in patients with only single sinus involvement.

Acute Treatment

i) *Antithrombotic Management*

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Al Rawahi et al. 2018 **Oman** **Systematic review & meta-analysis**	Risk of bias was rated as low to intermediate	4 RCTs including 189 persons with acute CVT.	Trials compared UHF vs. placebo (n=1), LMWH vs. placebo (n=2) and UHF vs. LMWH (n=2). Duration of treatment was ≤21 days	**Primary outcome:** Mortality **Secondary outcomes:** Severe disability (as defined by each study's authors), pulmonary embolus (PE)	In the 2 trials that compared any anticoagulant vs. placebo, the odds of mortality during follow-up were not reduced significantly with anticoagulant treatment (OR=0.31, 95% CI 0.07-1.45), nor were the odds of severe disability (OR=0.30, 95% CI 0.09-1.01). There were no cases of PE in either group. In the 2 trials that compared any LMWH vs. UHF, the odds of mortality were not reduced significantly with LMWH treatment (OR=0.21, 95% CI 0.02-2.44), nor were the odds of severe disability (OR=0.50, 95% CI 0.11-2.23). There were no cases of PE in either group.
Xu et al. 2018 **China** **Systematic review & network meta-analysis**	Risk of bias was rated as low to intermediate	14 studies (10 RCTs, 4 prospective studies) including 1,135 cases of acute CVT.	7 studies compared LMWH vs. UFH, 5 studies compared LMWH vs. placebo, and 2 studies compared UFH vs. placebo.	**Primary outcome:** Good recovery (defined using 4 grades, based on Barthel Index, mRS or NIHSS scores), mortality, bleeding complications	In both direct and indirect analyses, LMWH and UFH were associated with increased odds of good recovery, compared with placebo, while there was no significant difference between LMWH vs. UFH. In both direct and indirect analyses, LMWH and UFH were associated with decreased odds of death, compared with placebo, while there was no significant difference between LMWH vs. UFH. In both direct and indirect, the odds of bleeding complications were not increased significantly for the comparisons of LMWH vs. UFH, UFH vs. placebo or LMWH vs. placebo.

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Qureshi & Perera 2017 **UK** **Systematic review & meta-analysis**	Among the 2 RCTs, one was blinded and one was not. The 3rd study was a prospective cohort study	3 trials including patients with acute CVT (Afshari et al. 2015, Misra et al. 2012, [both described below] and Coutinho et al. 2010).	Trials compared LMWH (n=179) vs. UFH (n=352) in the immediate management of CVT.	**Primary outcomes:** Mortality, functional outcome and extra-cranial hemorrhage	The odds of mortality were non-significantly lower in persons taking LMWH (OR=0.51, 95% CI 0.23, 1.10, p=0.09, n=3 trials). There was no significant increase in the odds of good functional recovery associated with LMWH use (OR=0.79, 95% CI 0.49-1.26, n=2 trials). There was no significant increase in the odds of extracranial hemorrhage associated with LMWH use (OR=1.00, 95% CI 0.29-3.52, n=3 trials).
Afshari et al. 2015 **Iran** **RCT**	Concealed Allocation: ☒ Blinding: Patient ☑ Assessor ☑ ITT: ☒	52 patients admitted to a single hospital with CVT. Mean age was 37.3 years, 67% were women.	Patients were randomized (1:1) to receive LMWH (enoxaparin, 1 mg/kg subcutaneously 2x/day) or UFH (loading-dose of 80 units/ kg IV followed by 18 units/kg/hour by continuous IV infusion with dose adjustment to achieve a target activated partial-thromboplastin time of 60-85 seconds) for 7-10 days, followed by oral anticoagulation therapy for ≥6 months.	**Primary outcomes:** Hospital mortality, NIHSS at discharge and one month. **Secondary outcome:** mRS score at 30 days, hemorrhagic complications	8 patients in the UHF group were lost to follow-up. There was one death in each group. There was no significant difference between groups in mean NIHSS scores at discharge (1.04 vs. 4.41) or at one month (0.40 vs. 0.53). There was no significant difference between groups in mean mRS scores at one month (0.56 vs. 0.47). There were no cases of symptomatic intracerebral hemorrhage. Extra cranial hemorrhage occurred in 3 cases, of which one occurred in the LMWH group and one of them was in UFH. There was one case of DVT in the UFH group.
Selim et al. 2014 **USA** **Comment on a comment and opinion article**	NA	-	-	**-**	The author highlights some limitations associated with the argument raised by Dr. Cundiff, addressing the safety and efficacy of anticoagulation for all patients with CVT, citing his comment and opinion article (Stroke 2014;45:298-304).
Cundiff et al. 2014 **USA**	NA	-	A non-systematic review that evaluated the safety and efficacy of full-dose heparin (UFH or LMWH)	**-**	Mortality: Using data from studies published prior to 1999, the odds of death among patients fully anticoagulated during hospitalization were significantly lower compared to those who were

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Comment and opinion			during initial hospitalization and subsequent VKA treatment for CVT, using the results from 62 studies published from 1990 to 2013.		not anticoagulated (9.1% vs. 14.0%, OR=0.62; 95% CI, 0.47 to 0.82); however, when using studies published after 1999, there was a non-significant increase in mortality among those who were fully anticoagulated (9.7% vs. 8.8%, OR=1.11; 95% CI, 0.55 to 2.24). Major Bleeding During Full-Dose Heparin Treatment: 27% of patients who received full-dose heparin had major bleeding. A new ICH or an increased volume of ICH occurred in 2.6% of patients. Major systemic bleeding during full-dose heparin treatment occurred in 2.3% of patients. Heparin-Induced Thrombocytopenia: 1.3% of patients developed HIT. Deaths during post hospitalization follow-up: Among patients receiving VKAs, the odds of death were significantly lower compared with non-anticoagulated patients (1.6% vs. 7.0%; OR=0.22; 95% CI, 0.08–0.57). Venous thrombosis events: The overall rate was 0.22% patient recurrences per patient-month. The recurrence rate was significantly higher while patients were on VKAs compared with not taking VKAs (0.33%/month vs. 0.20%/ month; OR=1.60; 95% CI, 1.06–2.42). Major bleeding: While patients were taking VKAs during follow-up, the rate of major bleeding was 0.21%/ patient-month. The author suggests that due to selective reporting, the benefits of anticoagulation during initial hospitalization have been overstated and the harms, underestimated.
Misra et al. 2012	Concealed Allocation: ☒	56 consecutively admitted patients with CVT. Mean age was 34.5 years, 62% were	Patients were randomized to receive LMWH (n=34) 100 unit/kg subcutaneously	**Primary outcomes:** In-hospital mortality, 3-month functional	A significantly higher percentage of patients in the UFH group died (6 vs. 0, p= 0.01).

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India **RCT**	Blinding: Patient ☒ Assessor ☒ ITT: ☑	women. Mean Canadian Neurological Scale score was 4.2.	twice daily or UFH (n=32) 80 U/kg I.V bolus followed by 18 U/kg/h IV infusion for 14 days.	outcome, poor, partial or complete, based on modified Barthel Index scores	There was no significant difference between groups in functional outcome. At 3 months, 88.2% of patients in the LMWH group had a complete recover compared with 62.5% in the UFH group.
Coutinho et al. 2011 **The Netherlands** **Cochrane review**	Risk of bias was low in both trials.	2 trials (n=79) including patients with CVT. Trial 1: 20 patients. Mean age was 37 years, 55% were women. Trial 2: 59 patients. Mean age was 37 years, 85% were women.	Trials compared intravenous, adjusted dose unfractionated heparin vs. placebo and high dose, body weight adjusted, subcutaneous, low-molecular weight heparin vs. placebo. Duration of treatment was 12 weeks.	**Primary outcomes:** Death at the end of scheduled follow-up, death or dependency at the end of scheduled follow-up (3 months) **Secondary outcomes:** Pulmonary embolism (PE), symptomatic fatal or non-fatal intracranial hemorrhage (ICH) and major extracranial hemorrhage	Anticoagulant treatment was not associated with significantly reduced risks of death, or death or dependency (RR=0.33, 95% CI 0.08 to 1.21 and RR=0.46, 95% CI 0.16 to 1.31, respectively). There were no new ICHs in either trial. There were 2 cases of PE (both in the control group). There was a single case of major extracranial hemorrhage (gastrointestinal) in one patient in the intervention group.
Coutinho et al. 2010 **The Netherlands** **Prospective study**	NA	624 patients with CVT included in the International Study on Cerebral Vein and Dural Sinus Thrombosis. 75% were women.	The outcomes of 119 patients treated exclusively with LMWH (28%), and 302 patients (72%) treated with UFH, were compared. Models were adjusted for age, gender, thrombosis of the deep cerebral venous system, mental status disorder, coma, intracranial hemorrhage, infection of the CNS, malignancy, and focal neurological deficits (motor or sensory deficit, neglect, aphasia, or hemianopia).	**Primary outcome:** Functional independence (mRS 0-2) at 6 months **Secondary outcomes:** Complete recovery (mRS score 0 to 1), mortality, at 6 months and new intracranial hemorrhages	The median age of patients treated with LMWH was significantly lower (41 vs. 36 years, p=0.02). A significantly higher percentage of patients in the LMWH group were independent at 6 months (92% vs. 84%, adj OR=2.4, 95% CI 1.0–5.7). There were no significant differences between groups for the secondary outcomes of complete recovery (78% vs. 78%), mortality (6% vs. 8%) or new intracranial hemorrhages (10% vs. 16%). Among 270 patients who had an intracranial hemorrhage or infarct before treatment with heparin, a significantly higher percentage of patients in the LMWH group were independent at 6 months (9% vs. 78%, adj OR=3.0, 95% CI 1.1–8.3) and a significantly lower percentage had a new intracranial hemorrhage (11% vs. 21%, adj OR=0.19, 95% CI 0.04–0.99).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
de Bruijn et al. 1999 **The Netherlands** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	60 adult patients recruited from 14 hospitals with CVT. Patients with cerebral hemorrhage caused by sinus thrombosis were also included. Mean age was 37 years, 85% were women.	Patients were randomized to receive body weight–adjusted subcutaneous nadroparin (180 anti–factor Xa units/kg per day) or matching placebo for 3 weeks, followed by 3 months of oral anticoagulants for patients allocated to nadroparin, with target INR between 2.5 and 3.5.	**Primary outcome:** Poor outcome, defined as Barthel Index (BI) ≤15 or death at 3 weeks. **Secondary outcomes:** Death or dependence (Oxford Handicap Scale of 3-5) and BI score at 3 months. **Safety outcomes:** New symptomatic intracranial hemorrhage, DVT, PE and major bleeding	35 patients (59%) had an onset of symptoms within 10 days of randomization. 12 patients had isolated intracranial hypertension. There was no significant difference between groups in the percentage of patients with a poor outcome (20% nadroparin vs. 24% placebo; (risk difference=-4%; 95% CI, -25 to 17). There was no significant difference between groups in the percentage of patients who were dead or dependent at 3 months (13% nadroparin vs. 21% placebo; (risk difference=-7%; 95% CI, -26 to 12). At the end of 3 weeks, 67% pf patients treated with nadroparin had a BI score of 20 compared with 72% of patients in the placebo group. Corresponding percentages at 3 months were 90% and 79%. There were no new cases of symptomatic intracranial hemorrhage. One patient on nadroparin had a major gastrointestinal hemorrhage and 4 patients in each group had a minor extracranial hemorrhage. One patient on placebo died suddenly from suspected PE.

ii) Seizures

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lindgren et al. 2020, 2022 **Sweden**	NA	1,281 consecutive adult patients with CVT recruited from 12 hospitals, from 1990-2018. Median age was 40 years, 69% were women.	The characteristics, predictors, and outcomes of patients who developed acute (<7 days of diagnosis)	**Primary outcome:** Seizure incidence	441 patients (34%) had a symptomatic seizure. 93 (7% of all patients, 21% of patients with acute symptomatic seizures) had solely postdiagnosis seizures.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Prospective study			symptomatic seizures, are described		Independent predictors were intracerebral hemorrhage (adj OR- 4.1, 95% CI 3.0–5.5), cerebral edema/infarction without ICH (adj OR 2.8= 95% CI 2.0–4.0), cortical vein thrombosis (adj OR=2.1, 95% CI 1.5–2.9), superior sagittal sinus thrombosis (adj OR= 2.0, 95% CI 1.5–2.6), focal neurologic deficit (adj OR= 1.9, 95% CI 1.4–2.6), sulcal subarachnoid hemorrhage (adj OR=1.6, 95% CI 1.1–2.5), and female-specific risk factors (adj OR=1.5, 95% CI 1.1–2.1). In long-term follow-up (>3 months), the odds of death or poor outcome (mRS 2-6) were not increased significantly in persons with acute symptomatic seizures. *2022 Incidence of dural arteriovenous fistulas (dAVF)* During a median of 8 months of follow up, dAVF was confirmed in 29 (2.4%) patients. In univariate analysis persons who developed dAVF were significantly more likely to be men, were younger, had symptoms onset >30 days, were less likely to have parenchymal lesions at baseline and more likely to have a sigmoid sinus location. dAVF was diagnosed prior to the CVT in 8% of cases, simultaneously to CVT in 56% of cases and subsequently to the CVT in 36% of cases. Among patients with dAVF, 50% had multiple dAVFs. Fistulas most frequently involved the sigmoid sinus or the transverse sinus. Most patients were treated with endovascular intervention. After adjustment for age and sex, the presence of dAVF was not associated with poor clinical outcome at follow-up (mRS score 3–6, adj aOR= 1.0, 95% CI 0.4–2.5).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sánchez van Kammen et al. 2020 **Sweden** **Prospective study**	NA	1,127 consecutive adult patients with CVT recruited from 12 hospitals, from 1990-2018. Median age was 41 years, 70% were women.	The characteristics and predictors of patients who developed late (≥7 days of diagnosis) symptomatic seizures, are described.	**Primary outcome:** Seizure incidence	During a median follow-up of 2.0 years, 123 patients (11%) experienced ≥1 late seizure (incidence rate of 30 per 1,000 person-years, 95% CI 25–35). Median time to first seizure was 5 months. Baseline predictors were status epilepticus in the acute phase (HR= 7.0, 95% CI 3.9–12.6), decompressive hemicraniectomy (HR= 4.2, 95% CI 2.4–7.3), acute seizure(s) without status epilepticus (HR= 4.1, 95% CI 2.5–6.5), subdural hematoma (HR= 2.3, 95% CI 1.1–4.9), and intracerebral hemorrhage (HR= 1.9, 95% CI 1.1–3.1). 85 patients (70% of patients with first late seizure) experienced a recurrent seizure during follow-up, although 94% received AED treatment after the first late seizure.
Kalita et al. 2019 **India** **Retrospective study**	NA	153 patients with CVT admitted to a single institution, aged 3–76 years (median 29). 43.4% were women. Most patients had presentation between 3 and 30 days.	The outcomes of patients who had status epilepticus (SE), self-limiting seizures and no seizures during hospitalization were compared.	**Primary outcomes:** Hospital mortality, good functional outcome at 6 months (mRS 0-2)	90 (58.8%) patients had seizures, 28 of whom had SE and 62 had self-limiting seizure. 63 patients had no seizures. The only predictor of SE was supratentorial lesion (OR=5.65, 95% CI 1.11–28.76). 17 patients died in hospital (3 with SE, 9 with self-limiting seizures and 5 without seizures, p=0.51). The incidences of focal motor deficit and supratentorial lesions were higher in the SE group compared with the no-seizure group (71.4% vs. 33%, P=0.006 and 93% vs 55.5%, P=0.003, respectively). At 6 months, 128 (83.7%) patients had a good outcome. There was no significant difference in the proportion of patients who had a good outcome between groups (SE vs. self-limiting vs. no seizures)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Price et al. 2014 **UK** **Cochrane review**	NA	Participants who had experienced CVT, regardless of etiology.	Participants were randomized to receive treatment with ≥1 antiepileptic drugs or control group (receiving placebo or no drug).	**Primary outcome:** Clinical seizures during scheduled follow-up	No relevant studies were found.
Davoudi et al. 2014 **Iran** **Prospective study**	NA	94 patients with CVT admitted to a single institution. Mean age was 37.2 years, 83% were women. One case of CVT was recurrent.	Independent predictors of seizures (acute and remote) were identified, using demographic data, clinical and imaging factors between patients with or without acute and remote seizures.	**Primary outcome:** Independent predictors of early and remote seizures	75 patients were treated with anticonvulsant drugs during hospitalization. Phenytoin was the most widely used. 32 patients experienced at least one seizure. 18 patients had a presenting seizure before the diagnosis was confirmed, and 20 patients had early seizures. Six patients had recurrent early seizures after a presenting seizure. In univariate analysis, acute seizures were more common in patients with paresis, hemorrhagic lesions, supratentorial lesions, lesions in the frontal and parietal lobes, thrombophilia and a history of miscarriage. No independent predictors of early seizures were identified. 63 patients were followed up after discharge. 8 patients had a remote seizure. In univariate analysis, remote seizures were more common in patients with loss of consciousness at presentation, supratentorial lesions, lesions in the occipital, temporal and parietal lobes, thrombophilia, acute seizures (early or presenting seizure) and sigmoid sinus thrombosis. No independent predictors of early or remote seizure were identified.
Kalita et al. 2012 **India** **Retrospective study**	NA	90 patients admitted with CVT consecutively to a single institution. Median age was 30 years, 48 were women.	Independent predictors of seizures (acute and remote) were identified.	**Primary outcome:** Frequency of early and remote seizure, functional outcome at 6 months	42 patients had presenting seizure, and 4 had an early seizure. During the 12-month follow-up, 5 patients had recurrent seizures, of whom 4 patients had presenting seizure and one patient had an early seizure. There were no patients with remote seizures.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					6 patients died in hospital (4 with seizures, 2 without) Supratentorial parenchymal lesion on MRI was the only independent predictor of presenting seizure (OR=4.67, 95% CI 1.51–15.08). At 6 months, 10 patients had died, and 73 patients had complete recovery.
Ferro et al. 2008 **Portugal** **Prospective study** ***The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)***	NA	624 adults with CVST included in the study from 89 centers in 21 countries. Mean age was 39.1 years, 74.5% were women.	Independent predictors of presenting and early seizures (within 2 weeks) were identified.	**Primary outcome:** Independent predictors of presenting and early seizures	245 (39.3%) patients had presenting seizures. Independent predictors were supratentorial lesion (OR=4.05, 95% CI 2.74 to 5.95), cortical vein thrombosis (OR=2.31, 95% CI 1.44 to 3.73), sagittal sinus thrombosis (OR=2.18, 95% CI 1.50 to 3.18), and puerperal CVT (OR=2.06, 95% CI 1.19 to 3.55). 43 (6.9%) patients had an early seizure. Of these, 26 were recurrent seizures. Independent predictors were supratentorial lesion (OR=3.09, 95% CI 1.56 to 9.62) and presenting seizures (OR=1.74, 95% CI 0.90 to 3.37). Prophylactic AEDs were prescribed for 231 patients. AEDs were more often prescribed for patients with presenting seizures, those who were comatose, who had parenchymal lesions on admission CT/MR, who were aphasic and who had sagittal sinus or cortical vein thrombosis. The risk of early seizures in patients with supratentorial lesions and presenting seizures was significantly lower when AED prophylaxis was used (1 with seizures in 148 patients with AEDs vs 25 in 47 patients without AEDs; OR=0.006, 95% CI 0.001 to 0.05).

iii) Headache

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Dalgaard et al. 2020 **USA** **RCT** ***Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial***		18,201 patients with atrial fibrillation (AF) and at least 1 additional risk factor for stroke. Mean age was 70 years, 35% of participants was female. Approximately 19% of individuals assigned to each condition had a history of previous stroke or TIA.	The risk of bleeding in patients taking either apixaban (5 mg bid) or warfarin (dose adjusted to maintain INR 2-3) for atrial fibrillation with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), was examined. There were 832 patients who were using NSAIDs at baseline, 2,185 who were incident (new) users and 14,406 never users.	**Primary outcome:** Major bleeding, using the International Society on Thrombosis and Haemostasis definition **Secondary outcomes:** Clinically relevant nonmajor (CRNM) bleeding, gastrointestinal bleeding, stroke/systemic embolism, heart failure hospitalization, and all-cause death	Median duration of follow-up was 1.8 years. Those with NSAID use at baseline and incident NSAID use were more likely to have a history of bleeding than never users (24.5% vs. 21.0% vs. 15.6%, respectively). After excluding those taking NSAID at baseline, compared with never users, incident NSAID use was associated with an increased risk of major bleeding (HR=1.61, 95% CI, 1.11–2.33) and CRNM bleeding (HR=1.70, 95% CI, 1.16–2.48), but not gastrointestinal bleeding. There were no significant interactions observed between NSAID use and anticoagulant use for any outcome. *****This trial was included to highlight the risk of bleeding given NSAID use.
Ferro et al. 2008 **Portugal** **Review**	NA	-	-	**-**	In patients with severe headache and papilledema, intracranial hypertension can be reduced and symptoms relieved through a therapeutic lumbar puncture [Class III] Despite a lack of randomized trials, acetazolamide is used to relieve symptoms (headache, vision loss) of increased intracranial pressure [Class III].

iv) Vision Issues

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Liu et al. 2020 **USA** **Retrospective study**	NA	65 patients with CVT identified from 7 tertiary care neuro-ophthalmology clinics, seen between 2008 and 2016 with documented papilledema who received serial eye examinations. Mean age was 33.8 years, 69.2% were women.	Description of the presentation, progression and outcomes of patients are presented. The papilledema was graded according to the Frisén scale (0 to 5) at the time of patient presentation in 54 patients. In 11 cases papilledema reported as present or absent. Papilledema with progression was defined as worsening by ≥ 1 grade on the Frisén scale in one or both eyes. Resolution of papilledema was defined as Frisén grade 0 on follow-up examination with or without optic atrophy.	**Primary outcomes:** Time from diagnosis to papilledema documentation, papilledema progression, time to papilledema resolution, and final visual outcomes	Papilledema was documented in 31 cases prior to, or at the time of CVT diagnosis, while in 30 cases, it was diagnosed after CVT onset. The average time from CVT diagnosis to papilledema documentation was 29 days. The average Frisén grade was 2.7. In 33 patients the Frisén grade was ≥3. In 14 cases, there was progression of papilledema over an average of 55 days from initial eye exam. In 48 cases there was no progression. In all cases, there was resolution of papilledema in an average of 184 days. In persons with progression, the average time to resolution was 240 days. Following resolution, the average final visual acuity was 20/25. 26 patients had visual field defects at final assessment. 6 patients had neurologic sequelae (headache was most common). Risk factors for visual field loss at the final assessment were Frisén grade ≥3 (OR=10.21; 95% CI 2.00- 52.3) and papilledema progression (OR=3.5, 95% CI 1.01-12.8).
Koban et al. 2019 **Turkey** **Case control study**	NA	28 patients recovering from CVT with no vision complaints and 30 healthy volunteers with normal optic nerve appearance. Mean ages of cases and controls were 27.7 and 29.8 years, respectively. Among the cases and controls, there were 3 and 5 men, respectively.	Ophthalmologic examinations were completed at 9 to 12 months in CVT patients including macular and optic retinal nerve fiber layer thickness (RNFL) measured with spectral domain-optical coherence tomography (SD-OCT). Results were	**Primary outcomes:** Macular thickness, SD-OCT RNFL thickness	Four mean macular thickness parameters (mm) were significantly lower in cases compared with controls (Inferior inner macula: 300.9 vs. 328.7, p=0.009, Temporal inner macula: 296.3 vs. 309.2, p=0.001, Superior inner macula: 312 vs. 333.3, p=0.026 and Temporal outer macula: 256.1 vs. 272.5, p=0.014). There were no significant differences between the groups in fovea thickness, nasal inner macula, inferior outer macula, superior outer macula or nasal outer macula.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			compared between cases and controls.		There was a single difference between groups in mean RNFL parameters. Inferior temporal was significantly lower in the cases compared with the controls (146.1 vs. 156.6, p=0.02). There were no significant differences between groups in any other RNFL parameters including superior temporal, superior nasal, temporal upper, nasal upper, temporal lateral, nasal lateral and Inferior nasal.
Ding et al. 2019 **China** **Prospective study**	NA	94 patients with CVT who underwent a lumbar puncture at admission with cerebrospinal fluid pressure (CSFp) > 180 mm. Mean age was 34.5 years, 72% were women.	Patients were classified with intracranial hypertension according to CSFp at admission: mild IH (≥180 and <250 mmH_2O, n=35), moderate IH (250–330 mmH_2O, n=27), and severe IH (≥330 mmH_2O, n=32).	**Primary outcome:** Visual deterioration (severe papilledema, visual field defect or fading eyesight)	11/ 94 patients with normal vision at admission, displayed severe visual deterioration during hospitalization. (6 in the moderate group and 5 in the severe group) Visual deterioration occurred more frequently in the high vs. moderate vs. low CSFp groups (75% vs. 44%. vs. 14.3%). Among patients without visual symptoms at admission, visual deterioration occurred within 9.4 days after admission in the severe group vs. 30.5 days in the moderate group (p = 0.024). The odds of visual deterioration were significantly higher in the severe IH group compared with the other 2 groups (adj OR for severe vs. moderate IH: 3.8, 95% CI 1.3–11.8, p = 0.019; severe vs. mild IH: 4.6, 95% CI 2.3–9.1, p < 0.001; and moderate vs. mild IH: 4.0, 95% CI 1.1–14.1, p = 0.030).
Wall et al. 2014, Kupersmith et al. 2015, Wall et al. 2016, ten Hove et al. 2016 **USA** **RCT** ***The Idiopathic Intracranial***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	165 participants, enrolled from 38 sites with Idiopathic Intracranial Hypertension (IIH) and mild visual loss, with a perimetric mean deviation (PMD) between −2 dB and −7 dB. Mean age was 27 years. 161 patients were women.	Participants were randomized to receive a low-sodium weight-reduction diet plus the maximally tolerated dosage or acetazolamide (up to 4 g/d, n=86) or matching placebo (n=79) + diet for 6 months.	**Primary outcome:** Change in PMD from baseline to end of treatment **Secondary outcomes:** Changes in papilledema grade, quality of life (Visual Function Questionnaire	The mean improvement in PMD was greater with acetazolamide (1.43 dB, from −3.53 dB at baseline to −2.10 dB at month 6; n = 86) than with placebo (0.71 dB, from −3.53 dB to −2.82 dB;n = 79). The mean difference was 0.71 dB (95% CI, 0 to 1.43 dB; P= .050). There were significant improvements in all of the secondary outcomes favouring the acetazolamide group.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hypertension Treatment Trial				25 [VFQ-25] and 36-Item Short Form Health Survey), headache disability, and weight	**Wall et al. 2016** 125 patients had perimetry at baseline and 6 months. The average study eye had 36 of 52 test locations with improving sensitivity over 6 months, with no significant difference between treatment groups. When including subjects who met criteria for treatment failure, the percentages (acetazolamide and placebo) were 7.2% and 17.5% worse, 35.1% and 31.7% with no change, and 56.1% and 50.8% improved. **ten Hove et al. 2016 (safety and tolerability)** Among participants randomized to the acetazolamide group, 44.1% tolerated the maximum allowed dosage. 10 participants permanently discontinued the study drug: 9 in the acetazolamide group and 1 in the placebo group. There were 676 adverse events (AE) (acetazolamide, n = 480, placebo, n = 196) and 9 serious AEs (acetazolamide, n = 6, placebo, n = 3). **Kupersmith et al. 2015 Spectral domain optical coherence tomography (SD-OCT) results** At 6 months, patients in the acetazolamide group had greater reduction than the placebo group for retinal nerve fiber layer (175 µm vs 89 µm, p=0.001), total retinal thickness (220 µm vs 113 µm, p=0.001), and optic nerve volume (4.9 mm^3 vs 2.1 mm^3, p=0.001).

v) Endovascular therapy +/- Intravenous thrombolysis

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Coutinho et al. 2020 **The Netherlands** **RCT** ***Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO ACT)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	67 patients, recruited from 8 hospitals, with CVT that occurred within the previous 10 days, who had at least 1 risk factor for a poor outcome (mental status disorder, coma state, ICH, or thrombosis of the deep venous system). Median age was 40 years, 75% were women. Median baseline NIHSS score was 12.	Patients were randomized to receive standard medical care (SMC) + EVT within 24 hours of randomization (intervention group) or guideline-based standard medical care only (control group). The EVT consisted of mechanical thrombectomy, local intrasinus application of alteplase or urokinase, or a combination of both strategies	**Primary outcome:** Good outcome (mRS 0-1) at 12 months **Secondary outcomes:** Good outcome at 6 months, mRS score of 0-2 at 6 and 12 months, complete recanalization, surgical intervention related to CVT **Safety outcome:** Major hemorrhagic complications and symptomatic ICH within 1 week of randomization, all-cause mortality at 6 and 12 months, and all serious adverse events during the follow-up period.	The trial was halted after the first interim analysis for reasons of futility. There was no significant difference between groups in the percentage of patients who had a good outcome at 12 months (67% intervention vs. 68% control; RR=0.99, 95% CI 0.71-1.38) or at 6 months (55% intervention vs. 41% control; RR=1.32, 95% CI 0.80-2.20). There was no significant difference between groups in the percentage of patients who had a mRS score of 0-2 at 6 months (82% intervention vs. 85% control; RR=0.96, 95% CI 0.79-1.19) or at 12 months (85% intervention vs. 82% control; RR=1.03, 95% CI 0.83-1.27). There were 4 surgical interventions related to CVT in each group. There was complete recanalization of the superior sagittal sinus at 6-12 months in a significantly higher percentage of patients in the intervention group (79% vs. 52%; RR=1.52, 95% CI 1.02-2.27), but not for the straight sinus at 6 months (96% intervention vs. 86% control). Mortality at 6 and 12 months was 4 in the intervention group and 1 in the control group (p=0.20). There was one case of symptomatic ICH in the intervention group and 3 in the control group (p=0.61). There were 6 major hemorrhagic complications in the intervention group and 8 in the control group (p=0.59).
Ilyas et al. 2017 **USA**	NA	17 retrospective studies including 235 patients treated with endovascular mechanical	Pooled analysis of outcomes of interest.	**Primary outcomes:** Post procedure radiological outcome,	87.6% of patients received endovascular thrombolysis concurrently.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review & meta-analysis		thrombectomy following acute CVT. Median ages ranged from 5-58 years, 42%-100% were women. Symptom duration was <21 days. 40.2% of patients presented with encephalopathy or coma.		complications, recurrence, good neurological outcome (mRS 0-2), poor outcome (mRS 3-5) and death	Mean/median duration of follow-up was 5-42.3 months. Complete and partial radiographic resolution of thrombus was achieved in 69.0% and 26.3% of patients, respectively. Catheter-related complications occurred in 6.3% of patients, 8.7% experienced new or worse ICH. Recurrence was 1.2%. 76% of patients had a good neurological outcome, 10.8% had a poor outcome and 14.3% of patients died.
Siddiqui et al. 2015 **USA** **Systematic review & meta-analysis**	NA	42 studies including 185 patients with CVT who were treated with mechanical thrombectomy. Median age was 35 years, 64% were women. 60% of patients had a pretreatment intracerebral hemorrhage and 47% were stuporous or comatose at baseline.	The outcomes of patients who received mechanical thrombectomy +/- thrombolysis were examined.	**Primary outcome:** Good outcome (mRS 0-2) at the end of follow-up, death, recanalization, periprocedural complications	Intrasinus thrombolysis was used in 131 patients. Overall, 156 patients had a good outcome, 7 had a poor outcome, and 22 died. Post procedure recanalization data were available for 184 patients. Out of these, 5% patients had no recanalization, 21% had partial, and 74% had near to complete recanalization. A periprocedural complication was reported in 48 of 185 (26%) patients. The major periprocedural complication besides death was new or increased ICH, which occurred in 18 patients (10%). Patients with pretreatment stupor/coma had poorer outcomes.
Viegas et al. 2014 **Germany** **Systematic review & meta-analysis**	NA	16 studies including 26 patients with CVT. Symptom onset was acute in 5 patients, subacute in 12, chronic in one and no information was provided about 8 patients. Mean age was 31 years, 65.4% were women. The superior sagittal sinus was involved in 21 patients.	Studies examined the outcomes of patients who received systemic thrombolytic therapy, with or without additional treatments, except for local chemical and/or mechanical thrombolysis.	**Primary outcome:** Partial or complete recanalization, independence (assessed using mRS) intracranial and extracranial hemorrhagic complications	The median delay from symptom onset to admission was 3 days, and 4 days from symptom onset to diagnosis. The median delay from symptom onset to thrombolytic treatment was 3.5 days. Urokinase (n=18 patients), streptokinase (n=3 patient) and t-PA (n=2 patients) were used. Duration of

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					treatment was 1 to 9 days. 24 patients also received anticoagulation therapy. Partial and complete recanalization was achieved in 6 and 10 patients, respectively. Outcome data were missing for 10 patients. At the end of follow-up, 2 patients had died, 22 regained independence, 1 remained dependent and one patient was discharged alive but was lost to follow-up. Following thrombolysis, there were 3 cases of intracranial hemorrhages, 2 of which resulted in death. Extracranial hemorrhages were reported in 5 cases. In total, there were 8 hemorrhagic complications in 7 patients.
Dentali et al. 2010 **Italy** **Systematic review & meta-analysis**	NA	15 studies including a total of 156 patients with CVT.	The outcomes of patients treated with systemic (n=5) and local thrombolysis (n=151), were examined.	**Primary outcomes:** Mortality, major bleeding complications	Urokinase was used in 110 patients, alteplase in 45 patients and both urokinase and alteplase in one case. Additional mechanical thrombolysis was used in 60 patients. 12 patients died (7 with intracranial hemorrhage) and 15 patients had a major bleeding complication (12 intracranial) after thrombolysis

vi) Surgical Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Salottolo et al. 2020 **USA** **Systematic review**	NA	243 patients included in 15 studies who had undergone decompressive surgery following CVT. The outcomes of 4 patients treated at the author's centre are also included.	The timing of resumption of oral anticoagulation therapy following surgery from each study is presented.	**Primary outcome:** Timing of resumption of anticoagulation therapy	Anticoagulation therapy was started or resumed 12-48 hours after surgery in most cases. In the case series, timing of anticoagulation was started or resumed within 38 to 44 hours postoperatively in 3 patients and was started at the time of decompressive surgery without interruption in 1 patient.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Raza et al. 2014 **Pakistan** **Retrospective study**	NA	7 patients from a single centre treated with decompressive hemicraniectomy for malignant CVT during a 12-year period. Mean age was 40 years, 4 were men. 6 patients presented with ICH and 6 patients had a GCS score of 9-15.	A description of cases is presented.	**Primary outcome:** Short and long-term outcomes	The median time to surgery from initial presentation was 5 days. 2 patients died, 1 was discharged in a comatose state against medical advice, and 4 had a favourable outcome (mRS 0-2). The 4 survivors were discharged on oral anticoagulation with warfarin and followed up for a median duration of 18 months. On day 1 post-op, 4 patients had a GCS score of 9-15, 6 patients had urinary and/or respiratory tract infections, 3 had seizures and 1 had cardiac failure. Mean length of hospital stay was 21 days.
Ferro et al. 2011 **Portugal** **Retrospective study**	NA	69 cases of malignant CVT (38 from the International Study on Cerebral Vein and Dural Sinus Thrombosis registry and 31 provided from the literature) treated with decompressive surgery or hematoma evacuation. Median age was 42 years, 52 were women. 49 patients had a GCS score <9 at admission.	The outcomes of patients treated with decompressive craniectomy (n=45) or hematoma evacuation (n=7) or both interventions (n=17), were examined.	**Primary outcome:** Favorable outcome (mRS score 0 – 4) **Secondary outcomes:** Complete recovery (mRS score 0 –1), independence (mRS score, 0 –2), severe dependence (mRS score, 4 –5), and death at last available follow-up.	7 patients who underwent the operation died. At last follow-up (median, 12 months) 26 patients had recovered completely, 39 patients were independent, 4 patients were severely dependent, and 11 patients had died.
Theaudin et al. 2010 **France** **Retrospective study**	NA	12 patients with malignant CVT from 3 stroke units. Mean age was 45 years, 9 were women. Median GCS score was 14.	The outcomes of patients who underwent surgical decompression (n=8 including external decompression [n=4] both external and internal decompression [n=3], and internal decompression in 1 case) and those who did not undergo surgery (n=4), are described.	**Primary outcome:** Mortality, complete recovery (mRS 0 –1), independence (mRS, 2), or dependency (mRS, 3–5)	Median time to surgery was 36 hours. The 4 patients who did not undergo surgery (because their situation was deemed too severe), died within 5 days of diagnosis. In the other group, 1 patient who was neurologically improving died at day 9 of a PE. The other 7 survived, with a median ICU stay of 9.5 days (range 4 to 52 days). Total hospital stay ranged from 27 days to 10 months. 5 patients

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					were discharged to a rehabilitation service and 2 were discharged home. At 6 months, 2 patients had a complete recovery, 1 patient was independent and 4 patients were dependent. At the end of long-term follow-up (median 23.1 months), 6 patients had a complete recovery and one remained dependent.

Post-Acute Management

i) *Anticoagulation*

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Anticoagulation					
NCT04660747 **Sweden** ***Direct Oral Anticoagulants for the Treatment of Cerebral Venous Thrombosis (DOAC-CVT)***	NA	200 patients (planned) with CVT, with oral anticoagulant treatment (DOAC or VKA) started within 30 days	The outcomes of patients who received either DOACs or VKAs will be compared.	**Primary outcome:** Major bleeding and recurrent VTE within 6 months **Secondary outcomes:** Mortality, symptomatic VTE, major bleeding, recurrent CVT	TBA Estimated study completion is July 2024.
Field et al. 2023 **Canada** **RCT** ***Study of Rivaroxaban for CeREbral Venous Thrombosis (SECRET)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	55 patients recruited from 12 centres aged ≥18 years with acute CVT who could be randomized within 14 days of ictus. Median age was 48.0 years, 66% were women.	Patients were randomized to receive 20 mg rivaroxaban daily (15 mg daily in persons with renal insufficiency) or standard care (unfractionated heparin or LMWH with transition to an oral vitamin K antagonist or continuation with LMWH)	**Primary safety outcome:** Composite of all-cause mortality, symptomatic intracranial bleeding, or major extracranial bleeding at 180 days **Secondary outcomes:** Individual components of the primary outcome,	The recruitment rate was 21.3 participants/year, with 57% of eligible candidates consenting. 180-day data were available for 25/27 patients in the rivaroxaban group and for 26/28 patients in the standard care group. There were no deaths in either group, one symptomatic intracranial hemorrhage, 2 clinically relevant nonmajor bleeding events, and one

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			for 180 days, with optional extension up to 365 days.	partial or complete recanalization at 6 months and one year, mRS 0-1 at one year and patient reported outcomes.	recurrent CVT by day 180, all in the rivaroxaban group. At 1 year, there was complete recanalization in 9 (36%) patients in the rivaroxaban group vs. 13 (52%) in the standard care group (difference in proportions −16.0, 95% CI −43.25 to 11.2). The distribution of mRS scores at 180 and 365 days was similar between groups. There were no significant differences between groups in mean change scores from baseline on patient reported outcomes at 180 or 365 days (EQ-5D, Population Health Questionnaire-9 Headache Impact Test-6, Fatigue Assessment Scale, or MoCA).
Yaghi et al. 2022 **USA** **Systematic review & meta-analysis**	All 16 observational studies had at least moderate risk bias, while the risk of bias in 2 RCTs was judged as high.	19 studies, including 16 observational studies (n=1,735) and 3 RCTs (n=215) of adult persons with CVT. Where reported, the mean/median age ranged from 25 to 48 years. Where reported, the percentage of men ranged from 18% to 56%.	Trials compared treatment with DOACs vs. VKAs	**Primary outcome:** Recurrent venous thromboembolism **Secondary outcomes:** Complete recanalization, major hemorrhage and death	Compared with VKAs, the risk of the primary outcome was not significantly lower in persons who received DOACs (RR=0.85, 95% CI, 0.52–1.37). Compared with VKAs, the risks of the major hemorrhage and intracranial hemorrhage were not significantly lower in persons who received DOACs (RR=0.70, 95% CI, 0.40–1.21 and RR=0.58, 95% CI, 0.30–1.12, respectively). Compared with VKAs, the risks of the complete recanalization and death were not significantly higher in persons who received DOACs (RR=0.98, 95% CI, 0.87–1.11 and RR=1.14, 95% CI, 0.54–2.43, respectively).
Yaghi et al. 2022 **USA** **Retrospective study**	NA	845 patients consecutively admitted to 27 centres over 6 years (2015-2020) with CVT. Mean age was 44.8 years, 64.7% were women.	Models were developed to examine the association between oral anticoagulation (OAC) type (warfarin vs. DOAC) and recurrent CVT, death, and venous recanalization, using	**Primary outcome:** Recurrent venous thromboembolism (VTE) or CVT during follow-up **Imaging outcomes:**	33.0% of patients received DOAC only, 51.8% received warfarin only, and 15.1% received both treatments at different times. Median duration of follow-up was 345 (IQR 140–720) days.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Anticoagulation in the Treatment of Cerebral Venous Thrombosis study (ACTION-CVT)			propensity matched analysis.	Recanalization status on last venous imaging study abstracted from radiology reports (no recanalization, partial recanalization, or complete recanalization) **Safety outcomes:** Major hemorrhage, or major extracranial hemorrhage	During follow-up, there were 5.68 recurrent venous thromboses (17 VTE, 27 recurrent CVT, 2 had both VTE, and recurrent CVT), 3.77 major hemorrhages (23 intracranial hemorrhage [19 symptomatic and 4 asymptomatic] and 9 extracranial hemorrhages), and 1.84 deaths per 100 patient-years. Among 525 patients who met inclusion criteria for the recanalization outcome analysis, 36.6% had complete, 48.2% had partial, and 15.2% had no recanalization. The risk of recurrent CVT was similar between OAC groups (5.26 [DOAC] vs. 5.87 per 100 patient years [warfarin], HR=0.86, 95% CI 0.47–1.56). The risk of death was similar between OAC groups (1.81 [DOAC] vs. 1.90 per 100 patient years [warfarin], HR=1.02, 95% CI 0.36–2.84). The odds of partial/complete recanalization were not significantly higher with DOAC use (OR=1.16, 95% CI 0.70–1.94). In adjusted analysis, DOAC use was associated with a lower risk of major hemorrhage (aHR=0.35 95% CI, 0.15–0.82).
Bose et al. 2021 **Canada** **Systematic review & meta-analysis**	Using GRADE, certainty is low for the absolute treatment effect.	33 studies (1 RCT, 5 observational cohorts and 27 case series) including 279 patients with CVT.	The outcomes of 279 patients treated with DOAC for CVT: 41% dabigatran, 47% rivaroxaban, 10% apixaban and 2% edoxaban were compared with 315 patients treated with standard therapy.	**Primary outcome:** Recurrent CVT, recanalization, favourable outcome (mRS score 0-2) **Secondary outcomes:** All-cause mortality, intracranial haemorrhage (ICH) or other adverse events	Recurrent CVT: There were 2 cases treated with apixaban, 3 cases treated with dabigatran and 13 cases treated with warfarin. DOAC RR=0.45, 95% CI 0.05 to 4.4. There was so significant difference between groups in recanalization (RR=0.96, 95% CI 0.71 to 1.29) or favourable outcome (RR=1.11, 95% CI 0.96 to 1.25).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			The time to initiation of anticoagulation ranged from 1 to 7 days. Duration of treatment ranged from 4 to 13.5 months.		There was no significant difference between groups in all-cause mortality (RR=2.12, 95% CI 0.29 to 15.59. There were 2 cases of new ICH in the DOAC groups and 10 in the warfarin treated groups.
Ferro et al. 2019, 2020, 2022 **Portugal** **RCT** ***RE-SPECT CVT***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	150 patients recruited from 51 tertiary sites in 9 countries, with CVT, including those with intracranial hemorrhage, who were stable after 5 to 15 days of acute treatment with parenteral heparin. Mean age was 45.2 years, 55.0% were women. Most patients had baseline NIHSS scores of 0-4.	Patients were randomized (1:1) to receive 150 mg dabigatran, twice daily, or dose-adjusted warfarin (INR 2.0-3.0) for 24 weeks.	**Primary outcome:** Recurrent venous thrombotic events (VTEs) or major bleeding at the end of follow up (7 days after end of treatment) **Secondary outcomes:** Cerebral venous recanalization and clinically relevant non–major bleeding events Recanalization was also assessed in 2021 publication by change score from baseline to end of treatment using the cerebral venous occlusion score (CVOS), scored as improved or no change and modified Qureshi scale, scored as full, partial or no recanalization	Eleven patients in total (7 in the dabigatran group and 4 in the warfarin group) discontinued medication before 24 weeks. There were no recurrent VTEs in either group. There was one case of a major bleeding event (intestinal) in the dabigatran group, and 2 cases (intracranial) in the warfarin group. One additional patient in the warfarin group experienced a clinically relevant non–major bleeding event. Recanalization occurred in 33 patients in the dabigatran group and in 35 patients in the warfarin group. 8 patients in the dabigatran group and 6 patients in the warfarin group had a serious adverse event. *Intracranial dural arteriovenous fistulae (dAVF) (Ferro et al. 2020)* 112 patients were included in the analysis of dAVF. At 6 months follow-up, dAVF was found in one patient allocated to the warfarin group; however, this dAVF was already present at baseline. *Recanalization (2022)* 60% of patients in the dabigatran group had improved recanalization using CVOS criteria compared with 67.3% in the warfarin group (p=ns).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The mean CVOS change from baseline was similar in the two treatment groups (dabigatran -0.8; warfarin -1.0). Using the Modified Qureshi score criteria, 43.6% of patients in the dabigatran group had full recanalization compared with 35.8% in the warfarin group. Comparable percentages for partial recanalization were 41.8% and 49.1% and 14.5% and 15.1% for no recanalization
Wasay et al. 2019 **Pakistan** **Prospective study**	NA	11 patients with CVT recruited from 9 centres in 4 countries. Mean age was 39.3 years, 57% were women.	The outcomes of 45 patients who were treated within 7 days of diagnosis with NOACs (rivaroxaban 15 to 20 mg or dabigatran 75 to 150 mg twice a day) were compared with 66 patients treated with warfarin (INR target 2.0-3.0).	**Primary outcomes:** Hospital mortality, mRS score at hospital discharge and 6 months.	4 patients died during hospital stay (one in the NOAC arm and three in the warfarin arm). Two patients in the warfarin groups had an extracranial hemorrhage during hospitalization. At hospital discharge, 75% of patients in the NOAC group had an mRS of 0-2 compared with 69% of patients in the warfarin group. At 6 months, 2 additional patients were dead (one in each group). 91% of patients in the NOAC group had an mRS of 0-2 compared with 80% of patients in the warfarin group. Six patients reported systemic bleeding at follow-up, (2 in the NOAC arm and 4 in the warfarin arm).
Mendonca et al. 2015 **Portugal** **Retrospective study**	NA	15 patients with CVT who chose to start treatment with dabigatran following initial treatment with UFH, LMWH, or both. Mean age was 41.2 years, 80% were women. Median NIHSS score was 1 (range 0-13). Presentation was acute in 7 cases and subacute in 7 cases. Dabigatran was started in 11 patients, and warfarin was started in 7. Four patients on warfarin were switched to	The outcomes of patients treated with dabigatran are described. Median treatment time was 6 months (range: 2–32).	**Primary outcomes:** Excellent outcome at 6 months (mRS 0-1), recanalization, mortality at 6 months, recurrent CVT	Median duration of follow-up was 19 months. 13 patients had an excellent outcome. There were no fatalities or CVT recurrence at follow-up. Four adverse effects were noted in 3 patients. There were 2 reports of gastrointestinal complaints and 2 reports of alopecia. Full or partial recanalization was observed in 12 patients.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		dabigatran because of adverse effects.			
Geisbüsch et al. 2014 **Germany** **Retrospective study**	NA	17 patients with CVT admitted to a single institution. Median age was 36 years, 13 patients (81%) were women.	The outcomes of 7 patients treated with rivaroxaban were compared with those who were treated with a VKA (phenprocoumon, target INR 2.0-3.0). Oral anticoagulation was started on day 5 (median).	**Primary outcomes:** Excellent outcome (mRS 0-1), recanalization, bleeding complications	Median duration of follow-up was 8 months. 15/16 patients had an excellent outcome at the end of follow-up. The remaining patient had an mRS score of 2. There was no significant difference between groups in the number of patients who had complete (4 vs. 4) or partial recanalization (5 vs. 3). There were 2 minor bleeding complications in patients who received rivaroxaban and one in a patient who received a VKA.
Duration of anticoagulation					
Miranda et al. 2018 **Portugal** **EXCOA-CVT study (ISRCTN25644448)**	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,428 patients (749 per arm) planned, with CVT sustained within the previous 30 days.	Institutions were randomized to provide patients with short-term (3–6 months) vs. long-term (12 months) anticoagulation as soon as their clinical situation was stable. Any type of anticoagulation could be used.	**Primary efficacy outcome:** Symptomatic and confirmed fatal/nonfatal venous thromboembolic events at 24 months. **Secondary outcomes:** Recurrent CVT, DVT, PE, arterial thrombosis, any arterial and venous thrombotic events, and death **Primary safety outcomes:** Major and non-major bleeding events	Results not yet available.
Anticoagulation in patients with antiphospholipid syndrome					

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Woller et al. 2022 **USA** **RCT** ***Apixaban for Secondary Prevention of Thromboembolism Among Patients with AntiphosPholipid Syndrome (ASTRO-APS)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	48 patients (200 planned) with antiphospholipid syndrome (APS) and a history of venous thrombosis for which they were receiving anticoagulation therapy for the prevention of recurrent thrombosis. Patients were recruited between February 2015 and March 2019. Mean age was 47.3 years, 83.3% were women. APS status was definite in 41.7%, likely in 25% and 33.3% historical.	Patients were randomized to received warfarin with target INR of 2-4 or 5 mg apixaban for 12 months. The first 25 patients received an apixaban dose of 2.5 mg, 2x/day. The dose was increased based on an interim analysis showing excess strokes in the apixaban group.	**Primary outcomes:** Clinically overt thrombosis events (arterial and venous), and vascular death, **Secondary outcome:** Net clinical benefit **Safety outcomes:** Major and clinically relevant non-major bleeding (CRNMB)	The trial was halted early. There were 6 thrombotic events among patients randomized to apixaban, all of which were strokes (318 events per 1000 person-years). There were no thrombotic events among patients in the warfarin group. There was 1 major bleeding event in the warfarin group and no CRNMB events (40 per 1000 person-years). No patient randomized to apixaban experienced a major bleed or CRNMB. When combining the primary efficacy and safety (major bleeding and CRNMB) outcomes, the rate of adverse outcomes per 1000 person-years was 318 for apixaban and 40 for warfarin.
Ordi-Ros et al. 2019 **Spain** **RCT (non-inferiority)**	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	190 adults (aged 18 to 75 years) with thrombotic antiphospholipid syndrome. Median age was 48 years, 64% were women.	Participants were randomized (1:1) to receive 20 mg/day rivaroxaban (or 15 mg/d, according to renal function) or dose adjusted VKAs (target INR 2.0 to 3.0 (or 3.1 to 4.0 in patients with a history of recurrent thrombosis) for the duration of the trial. The threshold for the upper limit of the 95% CI non-inferiority was set at 1.40 for rivaroxaban	**Primary outcomes:** New thrombotic events, major bleeding	Duration of follow-up was 3.0 years. In the per-protocol analysis, recurrent thrombosis occurred in 11.6% of patients in the rivaroxaban group vs. 6.3% in the VKA group (RR=1.83, 95% CI, 0.71 to 4.76). Stroke occurred significantly more frequently in the rivaroxaban group (9 vs. 0 events, RR=19.00, 95% CI 1.12 to 321.9). Major bleeding occurred in 6.3% of patients in the rivaroxaban group compared with 7.4% in the VKA group (RR= 0.86, 95% CI 0.30 to 2.46).
Pengo et al. 2018 **Italy** **RCT (non-inferiority)** ***Trial on Rivaroxaban in***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑	120 patients with thrombotic antiphospholipid syndrome, who tested triple positive for lupus anticoagulant, anticardiolipin, and anti–b2-glycoprotein I antibodies (triple positivity) and had previous thromboembolic events. Mean	Patients were randomized 1:1 to receive 20 mg rivaroxaban, once daily (15 mg once daily based on kidney function) or warfarin (target INR of 2.5).	**Primary outcomes:** Thromboembolic events, major bleeding, and vascular death	The trial was terminated early due to excessive bleeding events in the rivaroxaban group. Mean duration of follow-up was 569 days. The risk of the primary outcome was significantly higher in the rivaroxaban group (22% vs. 3%, HR=7.4, 95% CI 1.7-32.9).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
AntiPhospholipid Syndrome (TRAPS)	ITT: ☑	age was 46.4 years, 64% were women.			There were 4 cases of ischemic stroke and 3 cases of MI in the rivaroxaban group, but none in the warfarin group. There was one case of venous thromboembolism in the rivaroxaban group and none in the warfarin group. There were 4 cases of major bleeding in the rivaroxaban group and 2 in the warfarin group P=0.30). There were 9 patients in the rivaroxaban group and 3 in the warfarin group who permanently stopped their assigned therapy before the end of the study.
Pediatric anticoagulation					
Connor et al. 2020 **EU** **RCT** ***EINSTEIN-Jr CVT***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	114 children, recruited from 51 sites in 20 countries, aged 0-17 years, with CVT. 70% of children were aged 2-11 years, 61% were girls.	After initial heparinization for 5-9 days, patients were randomized (2:1), to treatment with rivaroxaban, with dosing based on body weight or standard anticoagulants (continued on heparin or switched to vitamin K antagonist), for 3 months.	**Primary outcome:** Symptomatic recurrent VTE, composite of overt major and clinically relevant nonmajor bleeding	There were no recurrent VTEs in the rivaroxaban group compared with one in the standard therapy group (absolute difference= 2.4%, 95% CI 2.6% to 13.5%). There were no recurrent VTEs or major bleeding in the rivaroxaban group compared with 2 in the standard therapy group (absolute difference= 4.9%, 95% CI -0.4% to 17.1%). Clinically relevant bleeding occurred in 5 patients in the rivaroxaban group and in one patient in the standard anticoagulant group (absolute difference=4.4%, 95% CI 26.7% to 13.4%). Partial or complete recanalization occurred in 78% of patients in the rivaroxaban group and in 73% of patients in the standard anticoagulant group.

ii) Follow-up Vascular Neuroimaging

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Aguiar de Sousa et al. 2020 **Portugal** **Prospective study**	NA	68 patients with CVT. Mean age was 40 years, 82% were women. Mean time from symptom onset to diagnosis was 10 days. 30 patients had parenchymal lesions.	Standardized magnetic resonance imaging was performed at inclusion (≤24 hours of therapeutic anticoagulation), days 8 and 90.	**Primary outcome:** Early recanalization using a modified version of the Qureshi classification and brain lesion progression at day 8. **Secondary outcomes:** Headache at days 8 and 90) and favourable outcome (mRS score 0-1) at days 8 and 90	At day 8, 43 patients (68%) had partial recanalization and 4 (6%) had full recanalization. The only independent baseline predictor of early recanalization was younger age (OR= 0.62 per 10-year increase, 95% CI, 0.40–0.97). Early recanalization was associated with early improvement of nonhemorrhagic lesions and a lower risk of worsening of nonhemorrhagic lesions. Early favorable functional outcome was achieved in 68% of patients with early recanalization and in 50% of patients with persistent venous occlusion (p=0.19). Mental status disorder was an independent predictor of poor outcome at both days 8 and 90. 71% of patients reported headache between day 2 and 8 after starting anticoagulation treatment. In this group, early recanalization did not reduce the frequency of headache at day 8. By day 90, 41% of patients had partial recanalization and 54% had full recanalization. Favorable functional outcome was achieved in 85% of patients with early recanalization and in 74% of patients with worse recanalization. There was so significant difference between groups in the frequency of persons reporting headache symptoms.
Arauz et al. 2016 **Mexico** **Prospective study**	NA	102 patients with confirmed first-ever, non-septic CVT admitted to a single institution from 2000-2013. Mean age was 33 years, 78.4% were women. The median period from symptom onset to diagnosis was 8 days.	All patients received anticoagulation for 12 months or until complete recanalization, assessed using MR venography (MRV) every 3 months until partial or complete recanalization or for 12	**Primary outcome:** Any of complete recanalization, good functional outcome (mRS 0-1) at the end of follow-up	The median time to last MRV was 224 days and was significantly longer in patients with partial or no recanalization than in patients with complete recanalization. At the last MRV follow-up, recanalization was complete (grade III) in 67 patients (65.8%) and

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			months after diagnosis. The association between recanalization status and outcome was assessed. Recanalization status was determined based on MRV, using the Qureshi criteria (grade I [partial recanalization], grade II [complete recanalization of one sinus], grade III [complete recanalization]) and no recanalization.		partial (grade I and II) in 28 (27.5%). In seven patients (6.7%) there was no recanalization. 50% of patients had any recanalization by 64 days and complete recanalization by 169 days. Age <50 years was a predictor of any and complete recanalization (adjusted HR=11.56; 95% CI 1.58 to 84.46 and adj HR=4.79; 95% CI 1.69 to 13.51, respectively). Patients with complete recanalization had a greater chance of good functional outcome (HR=5.17; 95% CI 2.8 to 9.53).

iii) Residual Headaches

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ji et al. 2021 **China** **Prospective study**	NA	325 patients aged ≥14 years, admitted to a comprehensive stroke centre between January 2012 and December 2018 with a confirmed CVT, who received initial anticoagulation with heparin and for whom 6-month outcome data were available. Median age was 37 years, 58.8% were women. 17.5% had a history of chronic headache before CVT.	Independent predictors of severe residual headache (defined as headache related to CVT or a history of chronic headache before CVT, requiring bedrest or hospital admission) within 1 month before the last follow-up visit were identified among all survivors an in those with a favorable functional outcome (mRS score, 0–2).	**Primary outcome:** Independent predictors of severe headache	Median duration of follow-up was 13 months. At the end of follow-up, 43 patients (13.2%) reported severe headache, and 71 (21.8%) patients had a mild or moderate headache. 211 (64.9%) patients had no residual headache. Independent predictors of severe headache were isolated intracranial hypertension (OR= 3.31, 95% CI, 1.43–7.63), CVT recurrence (OR= 4.72 95% CI, 1.64–13.60), and no recanalization (OR=10.16 [95% CI, 4.19–24.60). Among the 300 patients who had a favourable outcome at last follow-up, 32 (10.7%) had a severe headache. In this group, isolated intracranial hypertension (OR=3.24, 95% CI,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					1.27–8.26) and no recanalization (OR=7.86, 95% CI, 3.12–19.81) were independent predictors.
Wasay et al. 2010 **Pakistan** **Retrospective study**	NA	200 patients aged ≥8 years with confirmed CVT admitted to 10 hospitals in the US between 1991 and 2001. Mean age was 37 years, 60% were women.	The frequency, pattern and location of headache was described and its relationship to site of sinus involvement or presence of hemorrhage was examined.	**Primary outcomes:** Frequency and duration of headache	136 patients reported having a headache, the duration of which was 1-3 days in 60% of patients, 4-14 days in 24% of patients and was chronic (>10 days) in 10% of patients. The location of headache was reported in 101 patients. It was unilateral in 48 persons, localized (frontal, temporal, occipital, and neck) in 25 patients, and diffuse in 28 patients. The most common location of the thrombus was the superior sagittal sinus alone 59 (29%) and the transverse sinus (TS) alone 44 (22%). There was no association between headache and presence of hemorrhage on CT and MRI (P = 0.1) or hydrocephalus (P = 0.09). There was no association between localization of headache and site of sinus thrombosis except sigmoid sinus thrombosis, where 17 out of 28 patients with involvement of sigmoid sinus alone or in combination with transverse sinus had pain in the occipital and neck region (P<0.05). There was no association between lateralization of pain and site of thrombosis (P = 0.66).
Koopman et al. 2009 **The Netherlands** **Case-control study**	NA	44 patients ≥15 years with CVT diagnosed between January 1997 and July 2006 who were functionally independent (mRS score ≤ 2) at least 12 months after CVT. Median age was 31 years, 82% were women. 44 healthy age and sex-matched controls.	A mail in questionnaire was administered a median of 63 weeks after CVT to determine frequency of headache, fatigue, depression, and concentration impairment; and to determine the impact of these sequelae on daily life and employment. The primary and secondary outcome scores were compared	**Primary outcomes:** Headache, measures using the 6-item Headache Impact Test (HIT), Fatigue, measured using the Fatigue Severity Scale (FSS). A score of ≥5 indicated fatigue, depression assessed using the Center for Epidemiological Studies Depression	Significantly more persons with CVT reported headaches, fatigue, depression and concentration problems compared with controls (43% vs. 9%, 30% vs. 7%, 30% vs. 7% and 75% vs. 23%, respectively). Mean HIT, FSS, CES-D and the EQ-6D (cognition domain) were all significantly higher (worse) in persons with CVT. Mean SIP scores were significantly higher (worse) for persons with CVT.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			between CVT and control groups.	Scale (CES-D), whereby a score of ≥16 was positive for depression and the ‘‘cognition’’ dimension of the 6-dimensional EuroQol (EQ-6D) **Secondary outcomes:** Total scores on the psychological dimension (17 items) and social dimension (21 items) of the Severity Impact Profile (SIP) 68	

Special Considerations in the Longer-term Management of CVT Patients

i) Pregnancy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Bistervels et al. 2022 **The Netherlands** **RCT** ***Comparison of Low and***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑	1,100 pregnant women, recruited from 70 hospitals in 9 countries with a history of previous venous thromboembolism (VTE) prior to 14 weeks of gestation. The mean age was 32·0 years. 81% had a history of VTE related to	Participants were randomized 1:1 to receive a regimen of weight-adjusted fixed low dose of LMWH (nadroparin, enoxaparin, dalteparin or tinzaparin) or an intermediate dose of LMWH, daily for the	**Primary outcome:** Symptomatic VTE during pregnancy and 6 weeks postpartum **Safety outcomes:** Major bleeding (primary), major or clinically relevant non-	Median duration of follow-up was 247 days. VTEs occurred in 11 (2%) women in intermediate-dose group and in 16 (3%) women in the fixed low-dose group (RR= 0·69, 95% CI 0·32–1·47). VTEs occurred antepartum in 5 (1%) women in the intermediate dose group and in 5 (1%) women in the fixed low-dose group. VTEs

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Intermediate Dose Low-molecular-weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy (Highlow)	ITT: ☑	hormone use, pregnancy, or the postpartum period.	duration of the trial (duration of pregnancy + 6 weeks postpartum), with interruption during the delivery period (24-48 hours).	major bleeding (secondary)	occurred in the postpartum, in 6 (1%) women in the intermediate dose group and in 11 (2%) women in the fixed low-dose group. In the on-treatment safety analysis, the primary safety outcome occurred in 23 (4%) of 520 women receiving intermediate-dose low LMWH and in 20 (4%) of 525 receiving low-dose LMWH (RR=1·16, 95% CI 0·65–2·09). The secondary safety outcome occurred in 10% of women receiving intermediate-dose LMWH and 9% of women receiving low-dose LMWH heparin (RR=1·16, 95% CI 0·65–2·09).
Aguiar de Sousa et al. 2017 **UK** ***ISCVT-2 PREGNANCY Study***	NA	119 women of child-bearing age from 32 centres with a history of CVT, included in the ISCVT cohort.	Patients were interviewed by local neurologists to assess VTE events, pregnancy outcomes, and antithrombotic prophylaxis during subsequent pregnancies.	**Primary outcome:** CVT and noncerebral VTEs	During a median of 14 years of follow-up, there were 82 new pregnancies in 47 women. 8 pregnancies occurred in women whose index CVT occurred during pregnancy/puerperium. In 68 cases, some form of antithrombotic prophylaxis was given during at least 1 trimester of pregnancy or puerperium. There was 1 recurrent CVT and 2 noncerebral VTE during pregnancy. Two of the 3 women were on prophylactic low-molecular-weight heparin at the time of the event.
Aguiar de Sousa et al. 2016 **UK** **Systematic review**	12 studies were of moderate methodological quality	13 studies including pregnant women with previous CVT. 8 studies reported long-term follow-up of patients with CVT, and 5 studies evaluated complications during subsequent pregnancies in women with previous cerebrovascular disease.	The pooled frequencies of CVT and noncerebral VTEs were estimated.	**Primary outcome:** CVT and noncerebral VTEs	There were 2 CVT recurrences reported in 217 pregnancies (9/1,000; 95% CI 3–33) and 5 noncerebral VTE in 186 pregnancies (27/1,000 95% CI 12–61). One recurrent CVT occurred in a woman who was not receiving prophylaxis. 77 pregnancies and 89 puerperal periods were completed without CVT recurrence in women receiving low molecular-weight heparin.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					10 pregnancies and 2 puerperal periods were completed without CVT recurrence in women receiving antiplatelets.

Considerations Related to CVT in Special Circumstances: Trauma

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Alghamdi et al. 2022 **Saudi Arabia** **Systematic review & meta-analysis***	NA	25 studies including 34 individual case reports of adults diagnosed with cerebral venous sinus thrombosis after closed head injuries. Mean age was 38.2 years, 74% were men. Closed head injuries were caused by motor vehicle accidents, falls, strikes to the head and from polytrauma/blast injuries.	Narrative review of patient characteristics, signs and symptoms, radiological findings and outcomes. *No pooled analyses were actually conducted.	**Primary outcome:** Non stated a priori	At initial presentation, the most common presenting symptoms were loss of consciousness or decreased GCS (41%), headache (26%), scalp abrasions/lacerations (21%), paralysis (21%), visual disturbance (21%), and nystagmus (15%). Five cases (15%) reported no focal neurological findings. Thrombosis was the most frequently reported radiological finding among all the cases (76%), followed by skull fracture (47%), contusion (32%) intraparenchymal hemorrhage (18%) and subdural hematoma (15%). 50% of cases involved a single sinus, 50% multiple sinuses. 14 patients required surgical intervention (4 for elevation of bony fragments, 4 for placement of an external ventricular drain, 3 for decompressive craniectomy, 3 for evacuation of hemorrhage, and 2 for burr hole). Most cases were managed with anti-coagulation (56%), using heparin (26%), and low molecular weight heparin (18%). The percentage of patients with total resolution of symptoms or with minor sequelae was significantly higher among those who did not receive surgery (21% vs. 89%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Symptoms resolved in 34% of cases with treatment. In 25% of cases, there were minor persistent neurological deficits, without requiring further rehabilitation, 22% of cases required rehabilitation and 19% of patients died.
Bokhari et al 2020 **Saudi Arabia** **Systematic review & meta-analysis**	In 10 studies, NOS scores was 8/9. The scores for the remaining studies were 6 (n=1) and 7 (n=2).	13 studies that reported the prevalence of dural venous sinus thrombosis (DVST) among pediatric (n=4) and adult (n=8) and both pediatric and adult (n=1) patients with TBI who underwent a vascular imaging study (n=1,422).	The pooled prevalence of DVST was estimated.	**Primary outcome:** Pooled point prevalence	The overall prevalence of DVST in all patients with TBIs was 4% (95% CI 1.6%-9.8%, n=8 studies). In patients with skull fractures adjacent to a venous sinus, the prevalence was 26.2% (95% CI 19.4%-34.4%, n=13 studies). Percentages were similar in adult and pediatric groups.
Qureshi et al. 2020 **USA** **Retrospective study**	NA	453,775 patients included in the National Trauma Data Bank, representing data from 900 trauma centres from 2009 to 2010, who had been admitted with head and neck trauma. Of this group, 76 patients had been admitted with CVT. 66% were men.	Demographic and clinical characteristics, in-hospital complications, ICU days, hospital length of stay, ventilator days, in-hospital mortality, and discharge destination were compared between patients with and without traumatic injury of major cerebral venous sinuses.	**Primary outcomes:** Non stated a priori	Patients with CVT were significantly younger compared to those without CVT (mean 27.6 vs. 37.6 years) and their baseline GCS score was significantly lower (9.2 vs. 12.9). Patients with traumatic injury of major cerebral venous sinuses had significantly more cases of intracranial hemorrhages (subdural, subarachnoid, epidural and intracerebral). The odds of in-hospital mortality were significantly higher for patients with traumatic injury of major cerebral venous sinuses after adjusting for age, gender, admission, GCS score, injury severity and the presence of intracranial hemorrhage (OR=6.93, 95% CI 1.34–36.0). The odds of discharge to a nursing home were also significantly higher for patients with traumatic injury of major cerebral venous sinuses after adjustment for baseline factors (OR=1.84, 95% CI 1.18–2.85).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Grangeon et al. 2017 **France** **Retrospective study**	NA	A case series of 5 patients (all men, 4 adults, 1 pediatric) admitted to a neurosurgery department of tertiary care hospital between October 2014 and June 2016 for head injury complicated by CVT. Mean age was 38.4 years. Initial GCS scores were 3 (n=2), 10, 14 and 15. Trauma was caused by falls, motor vehicle accidents and blunt trauma.	Summary of care and outcomes with 3 month follow up.	**Primary outcome:** Non stated a priori	During the study period, 168 patients were admitted to the neurosurgical unit for head trauma, of whom 5 (2.9%) were diagnosed with CVT. Three patients presented with disturbances of consciousness, 2 needed intubation due to their neurological state at admission., both of whom underwent emergency surgery for associated cerebral edema and acute subdural hematoma, respectively. The pediatric patient had no altered consciousness. Initial CT without contrast showed indirect signs of thrombosis, with a hyperdense sinus in4 cases, all of which presented with occipital or temporal bone fractures crossing the thrombosed sinus. All patients, except one received anticoagulation therapy with UFH, followed by treatment with LMWH for 3 weeks (n=1) and 3 months (n=3), with no hemorrhagic complications. The patient who did not receive anticoagulation, worsened and died on day 14. In the other patients, follow-up imaging performed 15 days after the introduction of heparin treatment showed no extension of thrombosis or venous infarcts. The pediatric patients had complete resolution of the thrombus, and antithrombotic therapy was stopped immediately. In two patients, follow-up MRI at 3 months revealed complete sinus recanalization. At 3 months, 3 patients returned home while one remained in a rehabilitation facility with an mRS score of 3.

Abbreviations

AED: antiepileptic drug	CA: concealed allocation	CI: confidence interval

DOAC: direct oral anticoagulants	DVT: deep vein thrombosis	GCS: Glasgow Coma Scale
HR: hazard ratio	ICU: intensive care unit	INR: International normalized ratio
IQR: interquartile range	ITT: intention-to-treat	LMWH: low molecular weight heparin
mRS: modified Rankin Scale	NA: not assessed	NIHSS: National Institutes of Health Stroke Scale
NOS: Newcastle Ottawa Scale Score	OR: odds ratio	PE: pulmonary embolism
ROC: receiver operating characteristic	RR: relative risk	VKA: vitamin K antagonist
VTE: venous thromboembolism		

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