Guideline

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European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis – Endorsed by the European Academy of Neurology

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Abstract

The current proposal for cerebral venous thrombosis guideline followed the Grading of Recommendations, Assessment, Development, and Evaluation system, formulating relevant diagnostic and treatment questions, performing systematic reviews of all available evidence and writing recommendations and deciding on their strength on an explicit and transparent manner, based on the quality of available scientific evidence. The guideline addresses both diagnostic and therapeutic topics. We suggest using magnetic resonance or computed tomography angiography for confirming the diagnosis of cerebral venous thrombosis and not screening patients with cerebral venous thrombosis routinely for thrombophilia or cancer. We recommend parenteral anticoagulation in acute cerebral venous thrombosis and decompressive surgery to prevent death due to brain herniation. We suggest to use preferentially low-molecular weight heparin in the acute phase and not using direct oral anticoagulants. We suggest not using steroids and acetazolamide to reduce death or dependency. We suggest using antiepileptics in patients with an early seizure and supratentorial lesions to prevent further early seizures. We could not make recommendations due to very poor quality of evidence concerning duration of anticoagulation after the acute phase, thrombolysis and/or thrombectomy, therapeutic lumbar puncture, and prevention of remote seizures with antiepileptic drugs. We suggest that in women who suffered a previous cerebral venous thrombosis, contraceptives containing oestrogens should be avoided. We suggest that subsequent pregnancies are safe, but use of prophylactic low-molecular weight heparin should be considered throughout pregnancy and puerperium. Multicentre observational and experimental studies are needed to increase the level of evidence supporting recommendations on the diagnosis and management of cerebral venous thrombosis.

Keywords

Cerebral venous thrombosis, dural sinus thrombosis, Grading of Recommendations, Assessment, Development, and Evaluation, angiography, venography, D dimers, prothrombotic screening, cancer screening, anticoagulation, heparin, thrombolysis, thrombectomy, acetazolamide, steroids, decompressive surgery, hemicraniectomy, lumbar puncture, shunt, pregnancy, puerperium, contraception, antiepileptic drugs

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Objectives

Current guidelines on cerebral venous thrombosis (CVT) diagnosis and management were issued by the European Federation of Neurological Societies (EFNS) in 2010[1] and by the American Heart Association (AHA) and American Stroke Society (ASA) in 2011.[2] These guidelines followed the traditional methodology of combining review of scientific evidence with expert opinion and classifying evidence and recommendations in complex grading systems, using a matrix combining classes of recommendations with levels of evidence.

Since 2010–2011 new information has accumulated on multiple aspects of the diagnosis and management of CVT. We aim to update previous EFNS guidelines using a clearer and evidence base methodology. To achieve that aim, the current proposal for CVT guidelines followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system,[3] formulating relevant diagnostic and treatment questions, performing systematic reviews of all available evidence, writing recommendations and deciding on their strength on an explicit and transparent manner.

Background

CVT is a type of stroke where the thrombosis occurs in the venous side of the brain circulation, leading to occlusion of one or more cerebral veins and dural venous sinus. The incidence of CVT is estimated nowadays to be 1.32/100,000/year in Western Europe.[4] The incidence is higher in developing countries. CVT is more frequent in women. The age distribution of CVT is different from that of ischemic stroke, CVT being more frequent in children and young adults.

CVT has a variable clinical presentation ranging from mild cases presenting only headache, headache plus papilledema or other signs of intracranial hypertension, focal deficits such as aphasia or paresis often combined with seizures, to severe cases featuring encephalopathy, coma or status epilepticus. The confirmation of the diagnosis of CVT by imaging requires the demonstration of thrombi in a dural sinus or cerebral vein. Currently, CVT is diagnosed with increased frequency due to higher awareness and easier access to magnetic resonance (MR) imaging.

CVT is not associated with classic arterial vascular risk factors. CVT has multiple risk factors, which can be grouped into: (1) transient risk factors, such as oral contraceptives and other medications with prothrombotic effects, pregnancy and puerperium, infections, especially those involving the central nervous system or the paranasal sinus, the ear and the mastoid and (2) permanent risk factors, which are in general prothrombotic medical conditions, including genetic thrombophilic diseases, antiphospholipid syndrome, myeloproliferative disorders and malignancies. In around 13% of adult CVT no risk factors are identified.[5]

The outcome of CVT patients has been improving over the last decades, not only due to the increase in diagnosis of milder forms of CVT and to improved care, but also due to the substantial decrease of septic CVT.[6] Mortality in the Western world is now below 5% and about 80% of the patients make a complete recovery.[5] Death is mainly caused by fatal brain herniation, secondary to large hemispheric haemorrhagic infarcts.[7] Other deaths are related to the underlying condition, status epilepticus, infection and very rarely to pulmonary embolism. Validated risk scores can be used to help identifying CVT patients with a higher risk of unfavourable outcome.[8]

Treatment of CVT includes: (1) aetiological treatment or removal of the identified risk factors, (2) antithrombotic treatment and (3) symptomatic treatment of intracranial hypertension, seizures and other complications. Evidence to support diagnostic and treatment decisions is accumulating but is still scarce. For recent comprehensive reviews on CVT see Martinelli,[9] Ferro and Canhão,[10] Coutinho[11] and Ferro et al.[12]

Method

These guidelines were prepared following the GRADE methodology[3,13–15] and the European Stroke Organization (ESO) standard operating procedures[16] (Table 1).

Some members of the panel attended GRADE workshops. The publications on the GRADE methodology were distributed between the panel members, who become familiarised with the method.

The first step in the production of the guidelines was the selection of the relevant topics, both diagnostic and therapeutic, to be evaluated for recommendations. A list of the topics which were considered to be more relevant clinically and where it was plausible to find some scientific information was produced and agreed by all the panel members. A list of outcomes, mostly patient centred, was produced and agreed by all panel members. The importance of these outcomes was rated from 1 to 9 by all panel members. Accordingly to that vote outcomes were classified as critical, important and less important (Table 2).

For each of the topics, one or more patient, intervention, comparator, outcome (PICO) questions were phrased, circulated and agreed by the panel chair and the members of the panel who had been assigned that topic. For each PICO question a systematic review of the literature using a predefined search strategy was performed. Pertinent studies were identified, their eligibility assessed and data relevant to the PICO question

Table 1. Steps followed in the production of cerebral venous thrombosis (CVT) guidelines.

1. The chair of CVT guidelines (JMF) was appointed by the ESO guidelines committee.
2. The chair invited the other members of the guideline panel, using the following criteria:
   a. Senior members with previous scientific and clinical expertise with CVT and peer recognition as CVT experts;
   b. Balanced geographical distribution;
   c. Including specialities other than neurology;
3. Senior members were encouraged to invite and involve a junior colleague.
4. All panel members filed a declaration of conflicts of interest form.
5. Relevant topics, both from a patient and a health care professional perspective, where scientific evidence could be available, were selected.
6. Topics were grouped in diagnostic and therapeutic.
7. Members of the panel were appointed specific topics.
8. A list of outcomes was produced and approved.
9. The importance of the different outcomes was rated by each member of the panel.
10. A final grading of the outcomes was calculated from individual votes and approved.
11. Patients, intervention, comparator, outcome (PICO) questions for each topic were formulated, discussed and approved.
12. Search terms and strategies were designed for the different PICO questions.
13. Searching, selection and extraction of information was performed by at least two members of the panel, disagreements being solved by consensus.
14. Evaluation of the quality of scientific evidence followed the GRADE method.
15. For each PICO question, quality of evidence was classified as very low, low, moderate or high.
16. Based on the quality of evidence, recommendations for each PICO question were written.
17. The strength of the recommendations was rated, based on the quality of evidence, as uncertain, weak or strong.
18. Following the GRADE methodology, strength of recommendations for a few PICO questions could be upgraded or downgraded.
19. The grading of evidence, strength of recommendation and statement of the recommendations were discussed among panel members by e-mail, telephone and occasional informal face-to-face meetings.
20. The final text of the guidelines was discussed in a teleconference.
21. Each PICO question was voted for approval.
22. Members with intellectual conflicts of interest, such as being author/principal investigator of a randomised controlled trial, did not participate in the vote of the corresponding recommendation.
23. The draft of the guidelines text was circulated for final editing.
24. The final text of the guidelines was approved by all panel members.

ESO: European Stroke Organization; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation.

extracted. Quality of the body of evidence available for each outcome selected to answer each PICO question was assessed and graded as high, moderate, low or very low. The overall rating of quality across all outcomes selected for each PICO was based on those outcomes panellists considered critical to their recommendation. Members of the panel responsible for each topic wrote a draft of the respective section, of the responses to the PICO questions and of the recommendations. The direction of the recommendations was defined as for or against the intervention and the strength of the recommendations was graded as strong or weak. In case of uncertainty about a recommendation due to the very poor evidence the panel decided a priori to try to avoid not formulating a recommendation. The panel considered that it is in the interest of all stakeholders, patients, health care professionals, third-party payers and policy-makers, to have recommendations to consolidate practice for a time period, to minimise practice variation and allow access of the patients to a particular procedure or treatment. Exceptions to this option were a few PICO questions where ongoing research can provide substantial new evidence in a short forthcoming period. For a few other PICO questions where it was impossible to formulate a recommendation, a consensual remark with additional information expressing a diagnostic or therapeutic option was written, without grading it. Consensus was obtained by discussion and nominal vote.

Extensive discussion between the members of the panel took place during the preparation of the guidelines. A consensus meeting via teleconference was organised for discussing and voting the strength and final approval of the recommendations. Members of the panel having intellectual conflicts of interest in a particular recommendation could participate in the discussion but not vote the recommendation.

Description of the analytic process

Study identification

We systematically searched MEDLINE (accessed via Pubmed) and The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library).

Table 2. Relevant outcomes – panel votes.

Outcome	Score
Critical outcomes	
Death	9
Death dependency	9
Complete recovery	9
Fatal bleeding	9
Severe dependence	9
Intracranial bleeding	9
Dependency	7
Any serious bleeding	7
Quality of life	7
Vision	7
Important outcomes	
Recurrence of CVT/VTE	6
Pregnancy outcomes	6
Seizure/epilepsy	6
Return to paid work	6
Depression/anxiety	6
Caregiver burden	4
Headache	4

CVT: cerebral venous thrombosis; VTE: venous thromboembolism.

An additional strategy to identify studies involved searching the reference lists of review articles and included studies. The full text of potentially relevant articles was retrieved. Publications written in the following languages were eligible: English, French, German, Spanish, Portuguese, Italian and Dutch. The search strategy was developed in accordance with the clinical question. The search terms for CVT were uniform for all PICO questions: (((sinus*[TI] AND thrombosis[TI]) OR (thrombosis[TI] AND cerebral [TI] AND (venous[TI] OR vein*[TI] OR sinus*[TI])) OR (''Sinus Thrombosis, Intracranial''[MESH]) OR (intracranial[TI] AND thrombosis[TI]))) AND specific diagnostic test or intervention (s) relevant for the PICO question.

Study eligibility

The titles and abstracts of the identified citations were reviewed for relevance to the clinical questions and the following inclusion criteria:

(1) Diagnosis of CVT objectively confirmed by accepted imaging methods (MR imaging with MR venography (MRV) or CT venography or conventional angiography), surgery or autopsy;
(2) To evaluate the diagnostic accuracy of the specific tests, we included systematic reviews, cohort studies, case–control studies and case series;
(3) To evaluate the outcomes, we included systematic reviews, controlled randomised or quasi-randomised trials, cohort and case–control studies and case series with follow-up at least at hospital discharge;
(4) To evaluate treatments or interventions, we included systematic reviews, controlled randomised or quasi-randomised trials, cohort and case–control studies and case series.

Data extraction and quality assessment

Two authors independently reviewed articles and completed data abstraction. Discrepancies were resolved through discussion and, if necessary, by involving a third reviewer. Using the GRADE system method for each PICO question, we analysed the body of evidence available for each outcome assessing all factors that might decrease or increase quality of evidence. Factors that may decrease quality of evidence include study limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias. Factors that might increase quality of evidence were large magnitude of effect, plausible confounding, which would reduce a demonstrated effect and dose–response gradient.

Quality of evidence was graded as follows

- High: if we were very confident that the true effect lies close to that of the estimate of the effect.[17,18]
- Moderate: if we were moderately confident in the effect estimate. The true effect was likely to be close to the estimate of the effect, but there was a possibility that it was substantially different.
- Low: if our confidence in the effect estimate was limited. The true effect might be substantially different from the estimate of the effect.
- Very low: if we had very little confidence in the effect estimate. The true effect was likely to be substantially different from the estimate of effect.

Part I: Diagnostic recommendations

A summary of recommendations is available as supplemental content (Supplemental Table 1, which is available online with this article, http://journals.sagepub.com/doi/full/10.1177/2396987317719364).

Section A: Confirmation of the clinical diagnosis of CVT

Topic: Neuroimaging

Question 1: In patients suspected of CVT should MRV versus digital subtraction angiography (DSA) be used to diagnose CVT?

After the PubMed search, six articles were selected. MRV 2D time of flight (TOF) was performed in 39 patients, of whom 10 had also DSA.[19] Only two patients had superior sagittal sinus thrombosis, objectified on MRV. In patients in whom DSA was performed a good concordance was seen between the two techniques, but none of the patients had CVT. MRV reliably demonstrated large cerebral veins and sinuses visualised with DSA. In a study of 42 patients with clinical findings suggestive of CVT, CVT was diagnosed on MRV in 17.[20] In nine patients, DSA was available and confirmed the diagnosis of thrombosis. The authors reported that in two patients, DSA was more sensitive than MR angiography in evaluating the smaller, ascending cortical veins. In five patients, it revealed more clearly the status of the deep subcortical veins. In a study including 20 patients with CVT, all documented by DSA, MRI and MRV together provided the diagnosis of CVT in all cases.[21] The sensitivity of MRI alone was 90%. MRV was performed in 15 patients and showed abnormalities in all cases, but not of the entire thrombosed sinus in each individual patient (18 thrombosed sinuses of the 15 patients). In another study including 24 patients with CVT diagnosed by MRI and MRV,[22] DSA was carried out additionally in 12 cases and essentially confirmed the MR-imaging data. In a study comparing 3D contrast-enhanced magnetisation-prepared rapid gradient-echo (MP RAGE) sequence with 2D-TOF MRV and digital subtraction angiography, 35 patients were evaluated, including 18 with suspected dural sinus thrombosis.[23] Dural sinus thrombosis was diagnosed at 26 sites in 12 patients by DSA. Thrombosis of the dural sinus was better seen with 3D contrast-enhanced MP RAGE than with 2D-TOF MRV. Three-dimensional contrast-enhanced MP RAGE showed the highest diagnostic accuracy on receiving operating characteristic (ROC) curves in the diagnosis of CVT. Sensitivity, specificity, positive and negative predictive values for 3D contrast-enhanced MP RAGE and for 2D-TOF MRV were 83.3, 99.6, 97.5, 96.8 and 51.0, 92.5, 56.8 and 91.0, respectively.

More recently, in a study of 62 cases of CVT, MRI, MRV and DSA examinations were performed in 21 patients. Among the 20 patients whose MRI and MRV were positive, 19 cases were positive for DSA and the K agreement rate between the two techniques was 0.95.[24]

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

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

Question 2: In patient with suspected CVT should CT venography versus digital subtraction angiography be used to diagnose CVT?

Our search found only two studies with data pertinent for this question. In a study including 25 patients, CT venography had a high sensitivity for depicting the intracerebral venous circulation compared with DSA. All large sinuses were depicted on multi-planer reformatted (MPR) images as compared with DSA images. Using DSA as the standard of reference, MPR images had an overall sensitivity of 95% (specificity 19%) and maximum intensity projection (MIP) images a sensitivity of 80% (specificity 44%) in depicting the cerebral venous anatomy. This study included only three patients with CVT, but they were all correctly recognised.[25] In a sample of young or non-hypertensive patients with acute spontaneous intracerebral haemorrhages (ICHs) (109 patients), DSA-positive pathologies causing haemorrhage were identified in 37 (33%) patients, which included CVT in seven patients (6%). All patients had CT angiography and venography (multidetector CT). DSA was performed the next day. CT angiography and venography were able to detect all CVT. No details on thrombosis location and extension were reported.[26]

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

Recommendation: we suggest that CT venography 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

Question 3: In patients suspected of CVT, should CT venography versus MRI and MRV be used to diagnose CVT?

The search listed 585 titles, from which we selected 24 devoted to CVT imaging and finally included three studies directly comparing CT venography to MRV[27–29] and two additional studies concerning multidetector-row CT angiography (MDCTA) in CVT diagnosis.[30,31]

These three studies included 85 patients with suspicion of CVT. The diagnosis was confirmed in 45 patients with CT venography and 43 patients with MRV (Table 3). CT venography more easily and more frequently showed sinuses or small cerebral

Table 3. Studies comparing CT venography versus MRI and MR venography for the diagnosis of CVT.

References	Total number of patients	Number of patients with suspected CVT	CVT confirmed by CT venography	CVT confirmed by MR venography	Comment
Casey et al.[27]	33	18	7	5	CT venograms easier to interpret, fewer artifacts
Ozsvath et al.[28]	24	17	8	8 (but TS thrombosis not seen in one patient)	CT venography more frequently visualises sinuses or smaller cerebral veins with low flow as compared with MR venography
Khandelwal et al.[29]	50	50	30	30	Total number of sinuses involved were 81 (CT venography) and 77 (MR venography) When using MR venography as the gold standard, CT venography had both a sensitivity and a specificity of 75–100%, depending on the sinus and vein involved.

CT: computed tomography; CVT: cerebral venous thrombosis; MRI: magnetic resonance imaging; TS: transverse sinus.

veins with low flow than MRV.[28] When MRV was used as the gold standard, CT venography was found to have both a sensitivity and a specificity of 75–100% depending on the sinus or veins involved.[29]

Of the two additional studies concerning MDCTA in CVT diagnosis,[30,31] one compared MDTCA to MRV and MRI in 19 patients suspected of CVT, diagnosis was confirmed in 10. In the second study, MDCTA, MRV and MRI were performed in 33 patients. Diagnosis of CVT was made in 20 patients, the consensus reading being considered as the gold standard.

Reported advantages of CT venography compared with MR imaging techniques are rapid image acquisition, no contraindication to pacemaker and ferromagnetic devices. Disadvantages of CT venography are significant exposure to ionising radiation and the need for IV contrast material. CT venography is as accurate as MRV in diagnosing CVT. Literature data are lacking about the comparison of CT venography with MRI + MRV. MRI has the advantage to show the thrombus itself and to be more sensitive to detect parenchymal lesions.

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

Recommendation: we suggest that CT venography 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

Question: In patients suspected of acute cerebral venous thrombosis, should D-dimer be measured before neuroimaging to diagnose CVT?

Whether D-dimer can play a similar role in the diagnostic approach in patients with suspected CVT remains controversial. Studies evaluating the diagnostic accuracy of the D-dimer test in the diagnosis of CVT were systematically searched for by two reviewers and 16 studies were finally selected: one systematic review and meta-analysis of the literature and 14 original studies.

Most of available literature data about sensitivity and/or specificity of D-dimer in the diagnosis of CVT are summarised in a recent meta-analysis.[32] A total of 14 studies were analysed to obtain data on 363 patients with a confirmed diagnosis of CVT. D-dimer was elevated in 325 patients for a weighted mean sensitivity (WMS) of 89.1% (95% confidence interval (CI) 84.8–92.8; $I^2 = 30\%$, range: 60–100%). In addition, when some specific clinical sub-settings have been evaluated, D-dimer elevated in 80 of 92 patients with a longer duration of symptoms (WMS: 83.1%, 95% CI 70.4–92.8), in 50 out of 62 patients with isolated headache (WMS: 81.6%, 95% CI 65.7–93.3) and in 64 of 74 patients with a single sinus involvement (WMS: 84.1%, 95% CI 75.3–91.3).

Seven out of the 14 studies[33–46] included in the meta-analysis provided data on 155 patients in whom CVT was objectively confirmed and on 771 patients in whom CVT was objectively ruled out. D-dimer was elevated in

145 of 155 patients with CVT with a WMS of 93.9% (95% CI 87.5–97.1; range 83.3–100%), whereas D-dimer resulted normal in 692 of 771 patients in whom CVT was objectively ruled out (bivariate weighted mean specificity 89.7%; 95% CI 86.5–92.2; range 83.1–100%).

Some interesting data on potential predictors of false-negative D-dimer results in patients with CVT have been derived by the analysis of four studies. A prolonged duration of symptoms was significantly associated with false-negative D-dimer levels in two of the four studies. However, in the two studies that did not find a difference in D-dimer levels according to the duration of symptoms, patients with duration of symptoms of more than one month were excluded. In three studies, the risk of false-negative D-dimer results appeared to be doubled in patients with involvement of a single sinus as compared with patients with CVT located in multiple sinuses. Further confirming this finding, a significant correlation between the extension of CVT and D-dimer levels was reported by Kosinski et al.[33] Clinical presentation with isolated headache was significantly associated with false negative D-dimer results in two of the three studies that evaluated the clinical presentation as a potential predictor. On the other hand, D-dimer levels were not significantly different in patients with and without focal neurologic signs in the study performed by Kosinski et al.[33] Age was not associated with false-negative D-dimer results in two studies, whereas in one study younger patients had a marginally higher risk of false-negative D-dimer results than older patients.

Overall, the accuracy of D-dimer in patients with suspected CVT was evaluated by use of the ROC curve, showing a pooled positive likelihood ratio of 9.1 (95% CI 6.8–12.2) and a pooled negative likelihood ratio of 0.07 (95% CI 0–0.14).

After the publication of the meta-analysis, a further study has been published about this topic.[47] A total of 233 patients with a suspected CVT were evaluated. In 34 cases the CVT was confirmed by imaging examinations, whereas the other 199 cases served as controls with symptoms mimicking CVT. In addition, 34 age- and gender-matched healthy controls were included in the study. The average plasma D-dimer level in the CVT group ($987.7 \pm 324\,\mu g/l$) was significantly higher than either the mimic ($343.23 \pm 102\,\mu g/l$) or healthy control ($320.22 \pm 98\,\mu g/l$) groups. Overall, the sensitivity and specificity of D-dimer in predicting CVT were 94.1% and 97.5%, with a corresponding positive predicting value of 86.5% and a negative predicting value of 98.9%.

Thus, results of this study are in line with data reported in the above-mentioned meta-analysis, consistently suggesting that D-dimer is a potentially useful tool with which to improve the diagnostic approach to patients with suspected CVT and to predict probable CVT before imaging examination, with a high sensitivity and specificity.

The quality of the evidence was judged as low because all studies were observational with some risk of bias.

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. more than 1 week) before the test.

Quality of evidence: low

Strength of recommendation: weak

Section B: Identification of associated conditions

Topic: Screening for thrombophilia

PICO question: In patients with CVT, does a policy of screening for thrombophilia prevents recurrent venous thrombosis, reduces death and improves functional outcome?

We searched for articles reporting the association between thrombophilia and recurrent venous thrombosis, death or functional outcome in patients with CVT. The search yielded 521 titles, from which nine full text articles were selected independently by the two authors. None of the studies compared a policy of screening for thrombophilia with a policy of non-screening. All the selected studies were cohort studies and thrombophilia screening was performed in all patients after the event. Generally, but with broad differences among the studies, thrombophilia screening included the search of (1) antithrombin deficiency; (2) protein C deficiency; (3) protein S deficiency; (4) factor V Leiden mutation; (5) prothrombin (factor II) G20210A mutation; (6) hyperhomocysteinaemia; (7) high levels of clotting factor VIII; (8) presence of antiphospholipid antibodies including anticardiolipin and/or anti-beta 2 glycoprotein 1 antibodies and/or lupus anticoagulant. Four studies investigated the risk of recurrent venous thrombosis in patients with thrombophilia, all with a considerable sample size varying from 145 to 706 patients, but with contrasting results. The association between thrombophilia and recurrent venous thrombosis encompasses no effect (hazard ratio (HR) 1.4, 95% CI 0.7–2.9 in Miranda et al.[48]; HR 1.1, 95% CI 0.7–1.8 in Dentali et al.[49]), and an increased risk effect.[50,51] Narayan et al.'s study[51] only reported hyperhomocysteinaemia as a risk factor for recurrence (odds ratio (OR): 3.7, 95% CI: 1.5–9.0). Apart from the study by Martinelli et al.[50] that reported a hazard ratio for recurrent venous thrombosis of 4.0 (95% CI 1.2–135) for severe thrombophilia defined as the presence of antiphospholipid antibodies, antithrombin, protein C or protein S-deficiency, homozygous factor V Leiden or prothrombin mutation and combined abnormalities, the remaining studies did not

systematically searched for thrombophilia, and therefore their results might be biased. No study was found on the association between thrombophilia testing and the outcome 'death'. Three studies reported that patients with thrombophilia had a worse functional outcome compared to patients without thrombophilia. Worse functional outcome was defined as follows: persistence of remote seizures (OR 5.9, 95% CI 1.2–28.4[52]); persistence of remote seizures combined with a bad functional performance (risk ratio (RR) 2.9, 95% CI 1.5–5.7[53] and RR 2.7, 95% CI 1.2–6.0[54]). At variance, two studies found no association between thrombophilia and worse functional outcome defined as modified Rankin Score >2.[55,56] These studies were performed in small cohorts of patients (except for the one by Girot et al.[56]), had a short follow-up (the longest was 44 months), and thrombophilia was not systematically tested.

For patients with the more common deep vein thrombosis and pulmonary embolism[57] it is recommended to perform thrombophilia screening in those with high pre-test probability to carry severe thrombophilia (i.e. a personal and/or family history of venous thrombosis, young age at venous thrombosis, idiopathic venous thrombosis).

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

Recommendation: we do not suggest thrombophilia screening to reduce death or improve functional outcome or prevent recurrent venous thrombosis in patients with CVT.

Quality of evidence: very low.

Strength of the recommendation: weak.

Additional information: Thrombophilia screening may be performed in patients with high pre-test probability to carry severe thrombophilia (i.e. a personal and/or family history of venous thrombosis, young age at CVT, CVT without a transient or a permanent risk factor) to prevent recurrent venous thrombotic events.

Topic: Malignancy screening

PICO question: In patients with CVT, does screening for an occult malignancy (including haematological malignancies) improves outcome?

We performed a systematic review of the frequency of malignancy in CVT patients in prospective studies or case series which were derived from prospective registries. If studies reported results from retrospective and prospective patient data, they were only eligible for analysis if the prospective data were presented separately.

We identified 11 studies,[5,51,58,59,61–66] which fulfilled these criteria and reported on the frequency of solid or haematological malignancies. They included a total of 1780 patients and any malignancy as predisposing risk factors were reported in 99 patients (5.6%). None of these studies reported a systematic screening for occult malignancy.

We identified 13 prospective studies[5,50,51,59–66] in which data on idiopathic CVT cases were reported. They included 1984 patients and in 294 cases (14.8%) no predisposing factors could be identified. There were also no data on a systematic screening for occult malignancies in these patients and its possible effect on outcome.

A recent randomly assigned study comparing limited occult-cancer screening (basic blood testing, chest radiography and screening for breast, cervical and prostate cancer) and limited screening plus abdomen and pelvis CT in patients with unprovoked venous thromboembolism (VTE) found a low (3.9%) prevalence of occult cancer and no differences between the two screening strategies.[67]

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

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

Part II: Therapeutic recommendations

A summary of recommendations is available as supplemental content (Supplemental Table I).

Section 1: Antithrombotic treatment

Topic: Acute anticoagulant treatment

PICO question: In patients with acute cerebral venous thrombosis, does anticoagulation improve clinical outcome compared to no anticoagulation?

The search listed 99 titles, from which we selected 16 full text articles. We included two randomised trials, which were also analysed in a recently updated Cochrane review.[68] Meta-analysis of these two randomised trials[60,69] with a total of 79 adult patients showed that anticoagulation with heparin (unfractionated (UFH) or low-molecular weight heparin (LMWH)) was associated with a reduction in poor outcome which did not reach statistical significance (RR for death or dependency 0.46, 95% CI 0.16–1.31; RR for death 0.33, 95% CI 0.08–1.21). Thirty-four of 79 patients (43%) had an ICH at baseline (prior to randomisation). After randomisation, three patients developed a new ICH and all were allocated to placebo. No information was available on whether these haemorrhages were symptomatic, but at least one of these patients later died and two of the ICHs occurred in patients who did not have a haemorrhage at baseline. Major extracranial

bleeding occurred in one patient randomised to heparin (RR for major haemorrhagic complications (heparin vs. placebo) 2.90, 95% CI 0.12–68.50). If the ICHs were to be considered symptomatic, the RR for major haemorrhagic complications for heparin vs. placebo would be 0.33 (95% CI 0.035–2.99). Two randomised trials were excluded from the Cochrane review because patients were diagnosed using unenhanced CT-scan only, or because the results have been published only as an abstract.[68] No new trials have been performed since the publication of the Cochrane review. There are no data from randomised trials in children with CVT.

The quality of the evidence was judged as moderate because the randomised controlled trials had a moderate risk of bias.

Recommendation: we recommend treating adult patients with acute cerebral venous thrombosis with heparin in therapeutic dosage. This recommendation also applies to patients with an intracerebral haemorrhage at baseline.

Quality of evidence: moderate.

Strength of recommendation: strong

Additional information: no recommendation can be given for children.

Topic: Type of heparin in acute CVT

PICO question: In patients with acute cerebral venous thrombosis does LMWH improve clinical outcome compared to UFH?

Both LMWHs and UFH are used for the treatment of CVT.[70] UFH is usually generally given intravenously and requires dose adjustments based on APTT values. It has a short half-life and its anticoagulant effect can be reversed with protamine sulphate. The anticoagulant effect of UFH, however, is unpredictable, and patients are often over- or underdosed.[71,72] LMWH is given as subcutaneous injections based on body weight. It has more predictable pharmacokinetics, but its effect can only partially be reversed with protamine sulphate. In certain patient groups, such as those with severe renal insufficiency, LMWH is contraindicated.

Our PubMed search returned 99 articles, of which two were relevant for this PICO question. One randomised trial directly compared LMWH to UFH in adult patients with CVT.[73] In total, 66 patients were included. Six of 32 patients (19%) allocated to UFH died during hospital admission, compared to 0 of 34 (0%) allocated to LMWH (RR LMWH vs. UFH 0.073, 95% CI 0.0043–1.24). Patients treated with LMWH had more often recovered completely after three months (RR 1.37, 95% CI 1.02–1.83). A major haemorrhagic complication occurred in three patients treated with UFH (all extracranial), compared to 0 patients in the LMWH arm (RR 0.13, 95% CI 0.0072–2.51). This trial did have a number of methodological limitations. For instance, no information on pre-planned interim analyses was provided, even though the trial was terminated prematurely because of superiority of LMWH. Furthermore, there was no allocation concealment or blinded endpoint measurement, and the trial protocol was not published in a trial registry. Patients allocated to UFH also were in a more severe baseline condition.

Results from a non-randomised study also suggest that LMWH is associated with better outcomes than UFH (adjusted OR for death or dependency 0.42, 95% CI 0.18–1.0) and less new ICHs (adjusted OR 0.29, 95% CI 0.07–1.3).[74] A Cochrane meta-analysis of randomised studies in patients with leg-vein thrombosis and pulmonary embolism shows that LMWH has a significantly lower risk of mortality (OR 0.62, 95% CI 0.46–0.84) and severe haemorrhagic complications (OR 0.50, 95% CI 0.29–0.85) compared to UFH in these conditions.[75]

The quality of the evidence was judged as low because the included randomised controlled trial and the observational studies had a high risk of bias.

Recommendation: we suggest treating patients with acute cerebral venous thrombosis with LMWH instead of UFH.

Quality of evidence: low

Strength of recommendation: weak

Additional information: 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).

Topic: Thrombolysis and thrombectomy in acute CVT

PICO 3: Does thrombolysis improve clinical outcome compared to anticoagulation in patients with acute cerebral venous thrombosis?

The search listed 148 titles, from which we selected 14 full text articles. We found no published randomised trials on thrombolysis for CVT. There is one ongoing trial, in which adult patients with CVT and a high risk of poor outcome are randomised to endovascular thrombolysis or control treatment.[76] Results of this trial are expected in 2018. Many case reports and cases series on thrombolysis for CVT have been published. A recent systematic review[77] calculated a mean rate for major haemorrhagic complications of 9.8% (95% CI 5.3–15.6%). A symptomatic intracranial haemorrhage occurred in 7.6% and mortality was 9.2%. A different systematic review that included 185 patients who underwent mechanical thrombectomy found a mean recanalisation rate (partial or complete) of 95%.[78] All these data, however, are based almost

exclusively on small retrospective studies without a control group and are subject to a high risk of publication bias. There are no data from randomised trials or large non-randomised studies with a control group and proper adjustment for confounding variables.

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

Acute CVT patients presenting a CVT risk score <3[8] or none of the following – coma, mental status disturbance, thrombosis of the deep venous system or ICH – have a very low risk of poor outcome. Therefore it is unwise to expose them to aggressive and potentially harmful treatments such as thrombolysis. Also, the ongoing Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) randomised trial[76] is excluding such low-risk patients.

Recommendation: we cannot provide a recommendation on thrombolysis for cerebral venous thrombosis.

Quality of evidence: very low

Strength of recommendation: uncertain

Additional information: we suggest not using thrombolysis in acute CVT patients with a pre-treatment 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 (<6 months)?

PICO question 2: For patients with previous CVT, does treatment with long-term anticoagulation reduce recurrence of venous thrombotic events, compared with treatment with short-term anticoagulation?

We identified 965 studies using our search strategy. We excluded 849 after screening for duplicated and evaluation of titles and abstracts using the predefined inclusion and exclusion criteria. We retrieved 117 studies in full text for detailed evaluation and verification of overlaps in study populations. Additional studies were obtained from manually reviewing references of retrieved articles for full-text evaluation. We found 33 studies[38,48,50,53,54,60,69,73,79–103] that described long-term outcome in patients with CVT treated with anticoagulation and/or after anticoagulation discontinuation. Two studies were subsequently excluded because they presented an overlapping population with another study.[102,103] Although several of these cohorts evaluated the recurrence rates of CVT and other thrombotic venous events, all have important limitations. Also, there have been no randomised controlled trials, prospective controlled studies or cases control studies assessing optimal duration of oral anticoagulation for the prevention of recurrent CVT and other VTE.

A retrospective study of 706 patients with a median follow-up of 40 months reported CVT recurrence in 4.4% and non-cerebral VTE in 6.5% of the patients, for an overall incidence of recurrence of 23.6 events per 1000 patient-years (95% CI 17.8–28.7) and of 35.1 events/1000 patient years (95% CI 27.7–44.4) after anticoagulant therapy withdrawal. History of VTE was the only significant predictor of recurrence in the multivariate analysis. However, in a prospective cohort study including 624 CVT patients and in which 2.2% of the patients had a recurrent CVT and 4.3% a VTE in other sites, a significant proportion of patients were on anticoagulation at the time of recurrence (58.3% with VTE and 64.3% with CVT recurrence).[48] Of all VTE, 63% occurred within the first year. Besides, a steady increase in the cumulative risk of thrombotic recurrences was observed, regardless of the duration of anticoagulation (cumulative incidence of a recurrent CVT event after 3, 6, and 12 months, 2 years and 3 years was 0.2%, 0.9%, and 1.7%, 2.3% and 5.7%, respectively). In this cohort only male gender and polycythaemia/thrombocythaemia were significant independent risk factors associated with a higher risk of recurrence. In another cohort of 145 patients followed after discontinuation of anticoagulation (median duration of therapy: 12 months) the recurrence rates were 2.03 per 100 person-years for all VTE and 0.53 per 100 person-years for recurrent CVT.[50]

Despite the similarities in risk factors and outcomes, the choice of using the indirect evidence about the relative effects of thromboprophylaxis in patients with deep vein thrombosis or pulmonary embolism to estimate the optimal duration of anticoagulation in patients with CVT is hindered by the knowledge that CVT has a particular pathophysiology and course. Although its clinical impact is not clear, it has been shown that recanalisation can occur up to 11 months.[104] Therefore, for patients in whom medical conditions associated with high recurrence risk are not identified and before data from trials are available (EXCOA-CVT[105]), we suggest a particular a time-limited course of therapy (between 3 and 12 months).

As a remark, we mention that in patients in whom a particular prothrombotic condition is identified, specific recommendations for antithrombotic treatment in this condition should be followed. It is beyond the scope of the current guidelines for CVT to review or update guidelines for each prothrombotic condition.

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

Recommendation: we suggest using oral anticoagulants (vitamin K antagonists) for 3 to 12 months after

CVT to prevent recurrent CVT and other venous thromboembolic events (VTEs).

Quality of evidence: very low

Strength of recommendation: weak

Additional information: 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 VTEs in those conditions.

Topic: New oral anticoagulants

PICO question: In patients with cerebral venous thrombosis, does treatment with new oral anticoagulants (NOACs) improve clinical outcome, reduce major haemorrhagic complications and reduce thrombotic recurrences, compared to conventional anticoagulation (heparin and vitamin K antagonists).

NOACs, also termed direct oral anticoagulants, are a relatively novel group of drugs that differ from conventional anticoagulants by the fact that they directly inhibit factor Xa or thrombin. Randomised trials in patients with atrial fibrillation, deep vein thrombosis of the leg and pulmonary embolism have shown that, compared to conventional anticoagulation, NOACs have similar anti-thrombotic efficacy but with a 50% relative risk reduction for ICHs.[106–109] The pathophysiological mechanism is not fully understood, but lower affinity for tissue factor and lower permeability of the blood–brain barrier for NOACs are believed to play a role.[108,110]

We systematically searched for studies that reported on the use of NOACs in patients with CVT. Because we expected a low yield, all study designs except case reports were eligible. The search returned four hits, of which two case reports were excluded. Geisbusch et al.[111] reported a retrospective observational study of 16 patients of whom seven were treated with rivaroxaban and nine with phenprocoumon. All patients received heparin treatment in the acute phase and rivaroxaban was started after a median of six days. Only two of seven patients in the rivaroxaban group had an ICH at baseline. There were no major haemorrhagic complications or thrombotic recurrences in any patient from either group. Mendonça et al.[112] reported on 15 patients with CVT treated with dabigatran (4 switched from warfarin due to adverse events). Excellent outcome was observed in 87% of patients and recanalisation in 80%. No major haemorrhagic complications were reported. All patients first received heparin and dabigatran was started a median of 12 days after initiation of heparin treatment.

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias.

Recommendation: we do not recommend using NOACs (factor Xa or thrombin inhibitors) for the treatment of CVT, especially during the acute phase.

Quality of evidence: very low

Strength of recommendation: weak

Section 2: Treatment of intracranial hypertension

Topic: Therapeutic lumbar puncture

PICO question 1: For patients with acute CVT and symptoms or signs of increased intracranial pressure, does therapeutic lumbar puncture (LP) improve outcome, compared with standard treatment?

PICO question 2: For patients with previous CVT and symptoms or signs of increased intracranial pressure, does therapeutic LP improve headache or visual disturbances?

We identified 55 studies using our search strategy. All the retrieved articles were case reports or case series dealing with LP in CVT. Additional studies were obtained from manually reviewing references of retrieved articles for full-text evaluation. We have found no studies assessing the effect of therapeutic LP on the prognosis, headache or visual disturbances of patients with CVT.

In a prospective study, therapeutic LP was performed in 44 (75%) out of 59 patients with CVT presenting with isolated ICH. Overall outcome was favourable but there are insufficient data to allow an evaluation of the effect of this intervention.[113] In the prospective International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) study,[5] with 624 patients, LP was performed in 224 patients (35.9%). There was no difference in the frequency of 'death or dependency at 6 months' between patients with or without LP (13.4% vs. 14.4%; OR = 0.9, 95% CI 0.6–1.5; $p = 0.739$). LP was not associated with 'worsening after hospitalisation' (21.5% vs. 23.5%; OR = 0.9, 95% CI 0.6–1.3; $p = 0.577$), 'acute death' (3.6% vs. 3.3%; OR = 1.1, 95% CI 0.5–2.7; $p = 0.844$) or 'complete recovery' (79.9% vs. 76.6%; OR = 1.2, 95% CI 0.8–1.7; $p = 0.484$).[114] However, these data regard LP performance during CVT assessment, without specified therapeutic purpose.

We performed an analysis of ISCVT data[5] to compare death or dependence at last follow-up between patients submitted to specified therapeutic LP and the remaining patients (no published data): 23 among 624 CVT patients (3.7%) undergone therapeutic LP, eight with the isolated intracranial hypertension syndrome clinical presentation. Patients treated with therapeutic LP had a similar outcomes as the remaining (1/23 dead or dependent versus 84/600, OR = 0.28; 95% CI 0.0–2.1). Analysis of the same cohort[5] was performed to compare visual loss during follow-up between patients treated with

therapeutic LP and the remaining patients (non-published data). We observed that most patients who developed visual loss during follow-up (42 patients) did not receive therapeutic LP (38 vs. 4 patients). The proportion of patients who developed visual loss was non-significantly higher in the group of patients who undergone therapeutic LP (4/23 (17.4%) vs. 38/563 (6.7%), OR = 2.9; 95% CI 0.9–8.9; $p = 0.127$). However, of the patients with visual loss at follow-up, half of those who were treated with therapeutic LP already had visual loss at presentation (2/4). We also conducted an analysis in order to compare severe headache during follow-up in patients treated with therapeutic LP and in the remaining patients. We observed that most patients who developed severe headaches during follow-up (88 patients) did not receive therapy with therapeutic LP during the hospital admission (82 vs. 6 patients). The proportion of patients who developed severe headache was non-significantly higher in the group of patients who undergone therapeutic LP (6/23 (26.1%) vs. 82/562 (14.6%), OR = 2.1; 95% CI 0.8–5.4; $p = 0.131$).

Overall quality of evidence across all critical outcomes for both questions 1 and 2 was very low. In conclusion, observational studies indicate that LP is safe in patients with CVT, but there are no randomised controlled trials on the effect of therapeutic LP in the outcome of patients with CVT. There is no adequate information on the effect of therapeutic LP on visual loss and occurrence of severe headache at long-term in patients with CVT. On the basis of the available evidence, no conclusions can be drawn regarding the efficacy of treatment with therapeutic LP in patients with CVT.

Recommendation: No specific recommendation can be made regarding therapy with therapeutic LP to improve outcome in patients with cerebral venous thrombosis and signs of intracranial hypertension.

Quality of evidence: very low

Strength of recommendation: uncertain

Additional information: therapeutic LP may be considered in patients with CVT and signs of intracranial hypertension, because of a potential beneficial effect on visual loss and/or headache, whenever its safety profile is acceptable.

Topic: Acetazolamide and diuretics

PICO questions:

1. For patients with acute CVT and symptoms or signs of increased intracranial pressure, does treatment with carbonic anhydrase inhibitors improve outcome, compared with standard treatment?

2. For patients with previous CVT and symptoms or signs of increased intracranial pressure, does treatment with carbonic anhydrase inhibitors improve headache or visual disturbances?

We identified 17 studies using our search strategy. All the retrieved articles were case reports or reviews/recommendations. Additional studies were obtained from manually reviewing references of retrieved articles for full-text evaluation. We found no studies that assessed the effect of acetazolamide (ACZ) or diuretics on the prognosis, headache or visual disturbances of patients with CVT.

Biousse et al.[113] reported a good prognosis regarding visual loss (56/59) in the group of CVT patients with isolated raised intracranial pressure but visual field testing was not systematically performed and therapy with ACZ or steroids was done only in 44% of these patients.

We performed an analysis of ISCVT data[5] to compare death or dependence at last follow-up between patients treated with ACZ and the remaining patients.[115] Sixty-one patients were treated with ACZ among 624 CVT patients (9.8%). Patients treated with ACZ had a similar outcome as the remaining (9/61 dead or dependent versus 76/486, OR = 0.93; 95% CI 0.4–2.0). Treatment with ACZ was not associated with outcome in two strata of the CVT risk score (dichotomised in ≥ 3 or <3 points). Treatment with ACZ was not a predictor of outcome in a multivariate logistic regression model ($p = 0.574$). ACZ was not associated with improved outcome in 26 patients who presented with isolated intracranial hypertension syndrome and were treated with ACZ.

We also performed an analysis of ISCVT data[5] to compare visual loss during follow-up between patients treated with ACZ and the remaining patients (no published data). We observed that most patients who developed visual loss during follow-up did not receive therapy with ACZ (33/42; 79%). Of the patients with visual loss at follow-up, two-thirds of those who were treated with ACZ already had visual loss at presentation (6/9, 67%). Considering patients who had no visual loss at baseline ($n = 538$), 90% of those which developed visual loss during follow-up were not treated with ACZ. However, the proportion of patients who developed de novo visual loss during follow-up in the group treated with ACZ (3/41; 7.3%) was not significantly different from the proportion of patients who developed visual loss in the non-treated group (5.4%).

A recent trial showed that, in patients with idiopathic intracranial hypertension and mild visual loss, the use of ACZ with a low-sodium weight-reduction diet compared with diet alone resulted in modest improvement in visual field function.[116] However, since idiopathic intracranial hypertension is a different condition from CVT, these results cannot be directly

extrapolated to patients with intracranial hypertension related with CVT.

The overall quality of evidence across all critical outcomes for PICO questions 1 was low and for PICO 2 very low. In conclusion, there are no randomised controlled trials on the effect of carbonic anhydrase inhibitors or diuretics in the outcome of patients with CVT. Information is limited to one case series and one non-randomised study. There is no reliable or unbiased information on the effect of carbonic anhydrase inhibitors or diuretics in headache and visual loss in patients with CVT.

Recommendation: we suggest not using acetazolamide for patients with acute CVT, to prevent death or to improve functional outcome.

Quality of information: low

Strength of recommendation: weak

Additional information: in isolated intracranial hypertension secondary to CVT, causing severe headaches or threatening vision, ACZ may be considered if its safety profile is acceptable.

Topic: Steroids

PICO question 1: For patients with acute CVT and symptoms or signs of increased intracranial pressure, does treatment with steroids improve outcome, compared with standard treatment?

PICO question 2: For patients with acute CVT and associated inflammatory diseases (e.g. Behçet's, lupus) does treatment with steroids improve outcome, compared with standard treatment?

We identified 78 studies using our search strategy. We excluded 73 after evaluation of titles and abstracts using the predefined inclusion and exclusion criteria. We retrieved five studies in full text for detailed evaluation and verification of overlaps in study populations. Additional studies were obtained from manually reviewing references of retrieved articles for full-text evaluation. Finally we included four publications: Canhão et al.[117] (prospective); Aguiar de Sousa et al.,[118] (systematic review); Vidailhet et al.,[119] (retrospective); Hatemi et al.[120] (recommendations).

Only one prospective non-randomised study aimed to assess the efficacy of steroids in CVT.[117] In this study no significant difference in poor outcomes was found whether patients were treated with steroids or not. Patients without parenchymal lesion treated with steroids had worse outcome. When patients were stratified according to the number of prognostic factors, treatment with steroids was still not associated with better outcome.

Concerning the role of steroids in inflammatory diseases associated with CVT, we found studies in Behçet's disease (BD) and systemic lupus erythematous (SLE). In a systematic review that evaluated patients with CVT associated with BD, including available data on therapeutic interventions, more than 90% of the patients with CVT associated with BD received corticosteroids.[118] There are several case reports and a series of five cases of CVT associated with SLE, which also include a review of another five published cases[119] treated with steroids, with improvement in all cases. The EULAR recommendations for the management of BD recommend treatment with corticosteroid for dural sinus thrombosis.[120]

We found some reports and expert reviews suggesting the use of steroids to prevent permanent visual loss in patients with intracranial hypertension but no studies to assess its efficacy. Biousse et al.[113] reported a good outcome regarding visual loss (56/59) in the group of CVT patients with isolated raised intracranial pressure but visual field testing was not systematically performed and therapy with ACZ or steroids was done only in 44% of these patients.

Recommendation: we suggest not using steroids in patients with acute CVT to prevent death or to improve functional outcome.

Quality of information: low

Strength of recommendation: weak

Recommendation: we suggest to use steroids in patients with acute CVT and BD and other inflammatory diseases (e.g. SLE) to improve outcome.

Quality of information: very low

Strength of recommendation: weak

Topic: Shunt (external ventricular drain, ventriculoperitoneal, ventriculoatrial or ventriculojugular shunt)

PICO question 1: For patients with acute or recent CVT and parenchymal lesion(s) with impending herniation does shunting (without other surgical treatment) improve outcome, compared with standard treatment?

PICO question 2: For patients with acute or recent CVT and hydrocephalus does shunting (without other surgical treatment) improve outcome, compared with standard treatment?

CVT rarely causes severe hydrocephalus. Exceptions are some cases with space-occupying posterior fossa lesions or intraventricular bleeding. Mild ventricular enlargement can be found in thrombosis of the deep venous system due to thalamic oedema and in the contralesional side in CVT complicated by large hemispherical lesions.[121]

In the literature review we found 736 titles, from which we selected 30 full text articles and included 10 studies. Studies were case reports, case series and a systematic review of cases.[122] The systematic review found only 15 CVT patients treated with shunting. These patients had a death rate of 22.2%, a death

or dependency rate of 55.6% and a severe dependency rate 16.7%. Three patients with intracranial hypertension and no parenchymal lesions were treated with ventriculo-peritoneal shunt and regained independence.[122]

In a recent case series of 14 CVT patients with acute hydrocephalus only one patient had a shunt.[121] Despite shunting the patient died.

The quality of the evidence was judged as very low because all studies were observational with a high risk of bias. Considering the lack of evidence on the efficacy of shunting for acute hydrocephalus, safety concerns, and the potential life-saving effect of shunting, we decided not to formulate a recommendation regarding shunting for acute hydrocephalus.

Recommendation: we suggest not to use routine shunting (without other surgical treatment) in patients with acute CVT and impending brain herniation due to parenchymal lesions to prevent death.

Quality of evidence: very low

Strength of recommendation: weak

Recommendation: no recommendation can be made for the use of shunting to prevent death or improve outcome for patients with acute or recent CVT and hydrocephalus.

Quality of evidence: very low

Strength of recommendation: uncertain

Topic: Decompressive surgery

PICO question: For patients with acute CVT and parenchymal lesion(s) with impending herniation, does decompressive surgery (hemicraniectomy or haematoma evacuation) improve outcome, compared with conservative treatment?

The search listed 582 tittles, from which we read 58 full text articles to include 30 studies.

The studies[123–131] included case reports (39 patients), case series (166 patients), two systematic reviews[125,131] and two non-randomised controlled studies.[123,124] The average death rate among patients treated with decompressive surgery (hemicraniectomy or haematoma evacuation) was 18.5%, the death or disability rate was 32.2%, the severe dependency rate only 3.4% and the complete recovery rate 30.7%.

No randomised controlled trials were found. There were two non-randomised studies comparing decompressive surgery with no surgery in (a) 12 patients with malignant CVT,[123] of whom eight were operated, (b) the patients included in ISCVT who were operated (8 patients) with three control groups of patients with lesions >5 cm and either CGS <14 (36 patients), GCS <9 (9 patients) or clinical worsening attributable to mass effect and herniation (22 patients).[124] In the French study[123] all non-operated patients died, in contrast with only one the operated group ($p = 0.02$). One operated patient was alive with a modified Rankin Scale (mRS) score of 3, while four recovered completely. Also in ISCVT none of the operated patients died, while in the three control groups mortality rates were 19%, 22% and 41%, respectively. Three operated patients had a mRS of 3, only one had a mRS of 4 and four did a complete recovery. Despite the low numbers, these figures point that decompressive surgery prevents death and does not result in an excess of severe disability.

Despite the low quality of evidence regarding decompressive surgery in CVT, the panel decided to come out with a strong recommendation based on the following reasoning:

(1) Quality of evidence: quality of evidence is currently low, but a randomised controlled trial is unlikely for ethical and feasibility reasons. There is an ongoing prospective multicentre registry.
(2) Balance of benefits and harms: surgery saves lives and produces acceptable sequels, as very few patients are left with severe dependency.
(3) Values and preferences: CVT patients are young. Few operated patients are left with severe dependency.

This upgrade judgment was based on the best available evidence (systematic review) and transparent, as it was voted favourably by all the members of the panel.

Recommendation: we recommend using decompressive surgery for patients with acute CVT and parenchymal lesion(s) with impending herniation to prevent death.

Quality of evidence: low

Strength of recommendation: strong

Section 3: Symptomatic treatments

Topic: Prevention of seizures and antiepileptic drugs (AEDs)

PICO question 1: In patients with acute or recent CVT do AEDs improve outcome, compared with no antiepileptic treatment?

PICO question 2: In patients with acute or recent CVT do AEDs prevent seizures, compared with no antiepileptic treatment?

We identified 159 studies using our search strategy. We excluded 140 after screening for duplicated and evaluation of titles and abstracts using the predefined inclusion and exclusion criteria. We retrieved 19 studies in full text for detailed evaluation and verification of overlaps in study populations. Additional studies were obtained from manually reviewing references of retrieved articles for full-text evaluation. In total, 18 studies were subsequently excluded because they did not report outcome data stratified according with the

prescription of AEDs. We found no randomised controlled clinical trials. A Cochrane systematic review of the effects of AEDs for the primary and secondary prevention of seizures after intracranial venous thrombosis also identified a lack of evidence concerning this indication.[132]

Seizures were associated with acute death in some series[64,93,133,134] but this finding was not consistently reported.[135] However, none of these studies reported association between antiepileptic treatment and functional outcome.

Regarding seizure prevention, one study reported a risk reduction of early seizures associated with use of AED, in patients with supratentorial lesions and presenting seizures (OR = 0.006, 95% CI = 0.001–0.05).[135] Supratentorial lesion was a predictor of seizures in several studies.[52,135,136]

Seizures are common in CVT and may be a cause of early death. This was the reason to upgrade the strength of the recommendation from uncertain to weak, which was formally achieved by a unanimous consensus through a nominal group technique. Safety concerns regarding the prolonged use of AEDs were the main reason not to make a recommendation for the prevention of remote post-CVT seizures.

Recommendation: we suggest using AEDs in patients with acute CVT with supratentorial lesions and seizures to prevent early recurrent seizures.

Quality of evidence: low

Strength of recommendation: weak

No recommendations can be made for the prevention of remote seizures.

Quality of evidence: very low

Strength of recommendation: uncertain

Section 4: Pregnancy and contraception after CVT

A particular feature of CVT epidemiology is the marked female preponderance (3:1) in the young adult age.[5] This pattern of gender disparity is associated with female gender specific risk factors such as pregnancy, puerperium, contraception and hormonal replacement therapy.[137]

Topic: Cerebral venous thrombosis during pregnancy

Pregnancy and postpartum are associated with an increased risk of thromboembolic diseases and cerebrovascular complications.[138–142]

We performed a systematic review selecting original case series or studies reporting at least 10 cases of CVT associated with pregnancy. To limit the possible bias towards diagnosis of CVT in young pregnant patients with neurological symptoms before neuroimaging methods were readily available, we decided to restrict the search strategy to works published during or after 1980.

We identified 426 studies using our search strategy. We excluded 378 after screening for duplication and evaluation of titles and abstracts using predefined inclusion and exclusion criteria. We retrieved 48 studies in full text for detailed evaluation and verification of overlaps in study populations. Additional studies were obtained from manually reviewing references of retrieved articles for full-text evaluation. In total, 11 studies were subsequently excluded because they did not report at least 10 cases of pregnancy related CVT. After analysis of references, seven studies case series/cohort studies were added. Finally, 42 studies were included. We found 21 original case series reporting at least 10 cases of CVT associated with pregnancy and 21 publications focused only in the description of patients with pregnancy related CVT.

The 21 included cohorts reported 460 cases of pregnancy related CVT amongst 2457 women.[5,50,65,73,81,93,143–156] Considering studies distinguishing CVT occurrence pre or postpartum, we found reports of 65 cases during pregnancy and 199 cases associated with puerperium (ratio 1:3). A summary of the number of CVT cases associated with pregnancy/puerperium, the male:female ratio and the proportion of women with CVT associated with pregnancy in each cohort is described in Table 4. Considering all the included studies, the overall proportion of pregnancy related CVT amongst women was 25% (95% CI 20–30; $I^2 = 89\%$) (Figure 1). However, these results also point out the geographical variation in the incidence of pregnancy related CVT. Possible explanations for this differences include home deliveries in unhygienic environments, certain traditions, such as water deprivation during immediate postpartum period, diverse birth rates and different habits regarding contraceptive use.[153]

PICO question 1: In pregnant and puerperal women with CVT, does the use of anticoagulant therapy improve the outcome without causing major risks to mother and foetus?

One study conducted in India described the outcomes of 73 puerperal women with CVT treated with low dose of heparin and 77 patients who did not receive heparin, admitted during the same period.[157] Puerperal CVT was defined as CVT occurring within one month of delivery or abortion, confirmed with imaging (CT or conventional angiography). Twenty-seven of the women in each therapeutic arm had a haemorrhagic brain lesion. The heparin regimen in the treated puerperal women was 2500 units of subcutaneous heparin, three times a day. The mean duration of treatment is not specified but the authors state this was started within 24 h of hospitalisation at was continued at least

Table 4. Proportion of female patients affected by pregnancy-related CVT in described cohorts (with at least 10 cases of pregnancy-related CVT).

	Country	Male: Female ratio	Total of female patients/ total cohort[a]	Pregnancy	Puerperium	Proportion (%)[b]
Karadas et al.[143]	Turkey	2:11	43/51	8	17	58
Sidhom et al.[65]	Tunisia	6:13	28/41	2	7	32
Souirti et al.[145]	Morocco	4:9	18/26	0	10	56
Pai et al.[144]	India	5:3	219/573[c]	15		8
Uzar et al.[146]	Turkey	1:2	31/47[c]	6	8	45
Dentali et al.[49]	Italy/ Czech Republic/ USA	5:14	520/706	55		11
Kumral et al.[147]	Turkey	4:9	152/220	34		22
Misra et al.[39,d]	India	3:5	41/66	12		29
Algahtani et al.[148]	Saudi Arabia	6:23	73/92	17		23
Wasay et al.[149]	Asia[e]	-	204[f]	9	40	24
Ruiz-Sandoval et al.[150]	Mexico	2:11	50/59	6	21	54
Ben Salem-Berrabah et al.[151]	Tunisia	5:21	21/26	2	8	48
Martinelli et al.[187]	Italy	7:19	106/145	14		13
Koopman et al.[152]	Netherlands	3:14	65/79	12		18
Ferro et al.[5]	Multinational	1:3	465/624	24	53	17
Khealani et al.[153]	Pakistan/ United Arab Emirates	7:8	58/109[c]	–	18	31
Wasay et al.[154]	USA	2:3	109/182[c]	13		12
Sagduyu et al.[155d,g]	Turkey	2:5	33/46	7	7	42
Stolz et al.[93]	Germany	5:17	61/79	13		21
Ferro et al.[156]	Portugal	2:5	101/142	1	10	11
Preter et al.[81]	France	8:11	59/102	11		19
Studies distinguishing CVT in pregnancy or puerperium				65	199	
Total		1:2[h]	2253/3415[h]	460		25

CVT: cerebral venous thrombosis.
[a]Whenever possible only adult patients were considered.
[b]Proportion of pregnancy-related CVT amongst all females included in each cohort. Total is the pooled estimated calculated using a random model of meta-analysis.
[c]Children included (Pai et al.[144]: minimum age 3 y; Uzar et al.[146]: minimum age 5 y; Khealani et al.[153]: minimum age 10 y; Wasay et al.[154]: minimum age 13 y).
[d]Non-consecutive patient inclusion.
[e]Pakistan, Iran, Singapore, India and Sri Lanka.
[f]Only women at fertile age included.
[g]Only patients with vein thrombosis (cortical or deep system) without sinus thrombosis.
[h]Wasay et al.[149] was excluded from the ratio calculation because the study only described women.

until the 30th day after partum, with tapering over one week. The criteria for patient selection are not described and the therapeutic and control groups are not well balanced. There were eight deaths in the heparin group (all in patients with haemorrhagic brain lesions) and 19 deaths in the control group (8 in patients without haemorrhagic lesions and 11 in patients with ICH). Thus, although the authors report a more favourable outcome and no new haemorrhages (intracranial or systemic) in the puerperal patients treated with heparin, these findings cannot be generalised confidently, as a result of the small number of patients and the general low quality of the evidence.

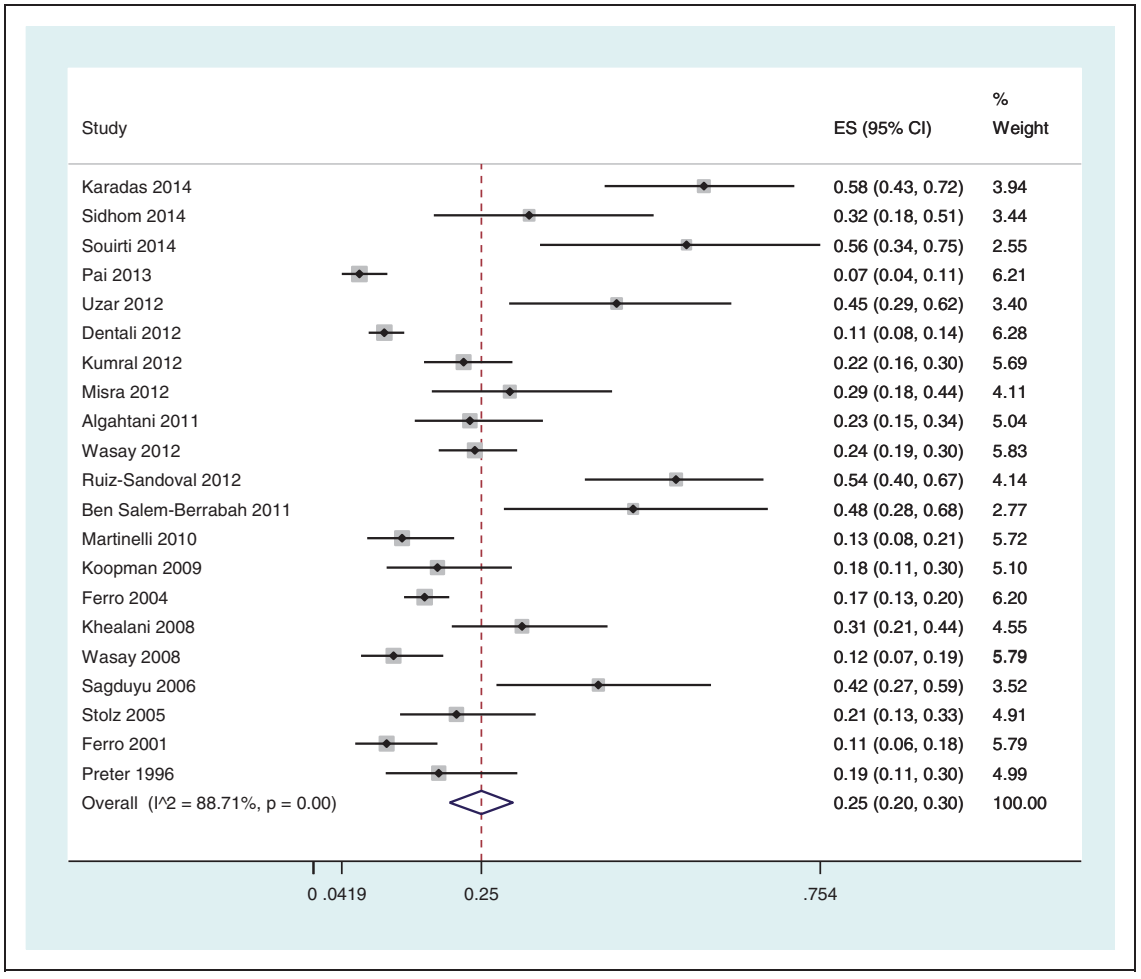

Figure 1. Proportion estimates of pregnancy-related CVT in women with CVT (only cohorts including least 10 cases of pregnancy related CVT were considered).
CVT: cerebral venous thrombosis.

In a series of 19 patients with CVT during pregnancy treated with full dose LMWH[158] there were no haemorrhagic complications. In two women enoxaparin was replaced by tinzaparin because of cutaneous reactions related with therapy and complete resolution of symptoms was achieved. In this series, caesarean section was the preferred route of delivery. In five patients with consciousness disturbances spinal anaesthesia was avoided. There were no infant deaths (nor during pregnancy neither up to 3 months after delivery), neonatal haemorrhages or congenital abnormalities. In another retrospective series with 15 Asian patients with CVT associated with puerperium there were also no cases of obstetric haemorrhage.[99]

We also did not found any report of obstetric (maternal or foetal) haemorrhagic complications related to anticoagulation in the CVT cohorts included in the review. However, only a few studies clearly stated that women with pregnancy-related CVT received anticoagulation[73,100] and obstetric complications were not a pre-specified outcome in most studies.[81,93,137,144,145,148–150,153,154,156] The anticoagulation trial by Misra et al.[73] also included 12 patients with CVT related to pregnancy and, although two patients receiving UFH had vaginal bleeding, there was no reference to specific obstetric complications in pregnant or puerperal women.

Vitamin K antagonists cross the placenta and have the potential to cause teratogenicity as well as pregnancy loss, foetal bleeding and neurodevelopmental deficits, with a risk of congenital anomalies estimated as 4–6%[159,160] (Table 5). Pregnant women were excluded from participating in clinical trials evaluating the oral direct thrombin and factor Xa inhibitors. These agents are likely to cross the placenta and their human reproductive risks are unknown.[161,162]

Although there are no studies comparing different anticoagulation regimens in pregnant patients with

Table 5. Antithrombotic use during pregnancy.

Drug	FDA category[a]	Placenta permeable	Transfer to breast milk	Adverse effects
Acenocoumarol, warfarin	X[b]	yes	Yes (no adverse effects reported)	Embriopathy (mainly in the first trimester), bleeding
Low-molecular weight heparin	B[c]	No	No	Long-term application: seldom osteoporosis and markedly less thrombocytopenia than UF heparin
Unfractionated heparin	B[c]	No	No	Long-term use: osteoporosis and thrombocytopenia
Danaparinoid	B[c]	No	No	No side effects but limited human data
Fondaparinux	B[c]	Yes	No	Limited experience
Acetylsalicylic acid (low dose)[d]	B[c]	Yes	Well tolerated	No teratogenic effects known (large datasets)

[a]US Department of Health and Human Services classifications for the use of drugs during pregnancy and breastfeeding range from category A (safest) to category X (known danger – do not use).
[b]Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
[c]Unclear risk. Either animal studies have not demonstrated any foetal risk, but no controlled studies have been done in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in pregnant women.
[d]According to the 'ESC Guidelines on the management of cardiovascular diseases during pregnancy', Regitz-Zagrosek et al.[169]

CVT, prior systematic reviews suggest that the incidence of bleeding in pregnant women receiving LMWH is low for antepartum haemorrhage (0.43%, 95% CI 0.22–0.75%), postpartum haemorrhage (0.94%, 95%CI 0.36–0.98%) and wound haematoma (0.61%, 95% CI 0.36–0.98%).[163] With respect to foetal safety (teratogenicity, congenital malformations, foetal bleeding) there is ample experience with UFH and LMWH in pregnant women. These agents do not cross the placenta and are considered safe to use in pregnancy.[163] It was also shown that LMWH carry a lower risk of osteoporosis than UFH.[164] Thus, mostly considering indirect evidence from other conditions occurring in pregnancy,[165] LMWH is commonly preferred for treatment of pregnant women with established CVT due to its favourable safety and efficacy profile.

Management of delivery options and possible discontinuation of anticoagulants prior to induction of labour or caesarean section (or expected time of neuraxial anaesthesia) should be considered by a multidisciplinary team and follow the available obstetric guidelines.[165–170] LMWH is usually suspended 12–24 h before delivery.[170,171]

We found two series[172,173] describing 23 cases of severe puerperal CVT submitted to endovascular thrombolytic therapy with urokinase, 14 in comatose patients. In 18 patients complete recanalisation was achieved. The remaining had partial recanalisation. Full recovery was reported in 20 of the 23 cases. No mention of haemorrhagic complications associated with the procedure is found in these reports.

There are no studies assessing optimal duration of anticoagulant therapy for treatment of pregnancy-related CVT. However, given the increased risk of CVT following delivery, it often suggested that anticoagulants be continued throughout postpartum period, usually at least for six weeks.[158] This is also recommended for other venous thromboembolic conditions associated with pregnancy.[137,174] The information regarding CVT associated with assisted reproductive technology is limited to case reports.[175–179]

During the postpartum period and for breast-feeding women LMWH, UFH and warfarin are all acceptable.[180–183] Since there are no clinical data on the effect of non-vitamin K oral anticoagulants on breast-fed infants and there is some evidence that these agents might be secreted into breast milk, use of new oral direct thrombin and factor Xa inhibitors should be avoided in breast-feeding women until further studies are available.[184]

Recommendation: we suggest therapy with subcutaneous LMWH in pregnant and puerperal patients with acute CVT.

Quality of evidence: low

Strength of recommendation: weak

Topic: Contraceptive use after cerebral venous thrombosis

PICO question 1: In women with prior CVT does use of combined oral hormonal contraception increase the risk of recurrent CVT or other VTE?

Several studies and a recent systematic review showed that oral contraceptives carry an increased risk of CVT with an overall relative RR of 7.6.[185] This risk may be even higher in carriers of prothrombotic conditions.[186,187] Oral contraceptives are the most frequent gender specific risk factor for CVT in women.[5,137] The association between hormonal factors (oral contraceptive use or pregnancy) is stronger for CVT than for lower-limb deep vein thrombosis.[50] The increased risk associated with oral contraception remains in newer generation products.[188,189] However, data regarding the effect of duration of use or of the use of progestogen-only contraception is lacking. Also, we found no studies on the risk of recurrent venous thrombotic events in women with prior CVT using oral contraceptives.

Considering the available data, it is likely that after a first episode of CVT, the avoidance of oral contraceptives may reduce the probability of venous thrombosis recurrence.

Recommendation: women in fertile age and prior CVT should be informed about the risks of combined hormonal contraception and advised against its use.

Quality of evidence: very low

Strength of recommendation: weak

Topic: Safety of pregnancy following CVT

PICO question: In females with previous history of CVT is a policy of not contraindicating future pregnancies associated with recurrence of CVT or other VTEs (lower or upper limb deep vein thrombosis, pulmonary embolism, abdominal or pelvic venous thrombosis) and unfavourable pregnancy outcome?

For obvious ethical reasons no randomised studies can address this question. Also pregnancy outcomes can only be evaluated in pregnant women. Therefore, to try to formulate recommendations regarding future pregnancies we reviewed the evidence concerning the following clinical questions:

(1) In females with previous history of CVT does the risk of pregnancy-related CVT recurrence or other VTEs (lower or upper limb deep vein thrombosis, pulmonary embolism, abdominal or pelvic venous thrombosis) is increased?

Compared with individuals without a history of CVT, women with prior CVT are at increased risk of future episodes of CVT and also non-cerebral VTEs. A systematic review of published observational studies which together reported 217 pregnancies[5,50,53,81,86,90,93,190–195] found a low absolute risk of pregnancy related venous thrombosis (9 CVT and 27 non-cerebral VTE per 1000 pregnancies) but a significantly higher rate of both recurrent CVT and other VTEs, comparing with the baseline risk described in the general population for pregnant women.[196] These results probably underestimate the true incidence because a large proportion of women included in these cohorts were receiving antithrombotic prophylaxis during pregnancy and/or puerperium. However, we must also take in consideration that it was not possible to account for the risk factors for the index CVT and that the use of a population based rate of CVT as an historical control has several limitations, as it is estimated from hospital discharge data associated with delivery, collected in a single developed country.

In women with a prior history of CVT is the risk of unfavourable pregnancy outcome increased?

Despite being highly variable across studies, the rate of spontaneous abortion is usually estimated to occur in 10–15% of clinically recognised pregnancies and previous studies based on self-reported data reported a rate of about 20%.[197]

Despite the fact that history of prior extracerebral venous thrombotic event is associated with adverse pregnancy outcome,[198] current data from a systematic review of observational studies do not show a significant increase in the rate of spontaneous abortion in women with prior CVT (33/186; 18%; 95% CI 13–24).[196]

Recommendation: for all women with prior history of CVT, we suggest to inform on the absolute and relative risks of venous thrombotic events and abortion during subsequent pregnancies and to not contraindicate future pregnancies based only in the past history of CVT.

Quality of evidence: low

Strength of recommendation: weak

PICO question: For pregnant women with previous history of CVT, does prophylaxis with antithrombotic drugs reduce the risk of thromboembolic events or affect pregnancy outcome?

The data addressing the use of antithrombotic prophylaxis in pregnant women with prior CVT consists of predominantly small observational studies with important methodological limitations. Table 6 summarises the findings of a systematic review of 13 observational studies describing the use of antithrombotic prophylaxis during pregnancy and VTE (both CVT recurrence and non-cerebral VTEs) in women with previous history of CVT.[196] The wide CIs around the point estimates illustrate the uncertainty of the findings. Besides, it was not possible to account for the risk factors for the index CVT. However, one recurrent CVT and two out of the three reported non-cerebral VTEs occurred in women not receiving any antithrombotic prophylaxis.

Table 6. Crude risk of CVT and other VTE related to pregnancy according antithrombotic prophylaxis.

Antithrombotic prophylaxis in women with prior CVT	VTEs (non-cerebral)		Recurrent CVT	
	Pregnancy	Puerperium	Pregnancy	Puerperium
No antithrombotic prophylaxis	2/43 47 per 1000 95% CI 13–155		1/57 18 per 1000 95% CI 3–93	
Heparin	0/73 0 per 1000 95% CI 0–50	1/76 13 per 1000 95% CI 2–71	0/77 0 per 1000 95% CI 0–48	0/89 0 per 1000 95% CI 0–41
Antiplatelet	0/5 0 per 1000 95% CI 0–435	0/2 0 per 1000 95% CI 0–658	0/10 0 per 1000 95% CI 0–278	0/2 0 per 1000 95% CI 0–658

CVT: cerebral venous thrombosis; VTE: venous thromboembolism.

Given the low quality of the direct evidence, we decided to use also indirect evidence about the relative effects of thromboprophylaxis from other patient populations to inform our recommendations for prevention of VTE in women with prior CVT. Our choice of indirect evidence is based assuming similarities in risk of VTE, the type and duration of intervention (prophylactic dose LMWH), and outcomes (symptomatic VTE and major bleeding events). A prior Cochrane systematic review[199] identified two small randomised controlled trials that evaluated the safety and efficacy of prophylaxis in pregnant women with prior non-cerebral VTE[200,201] and that, despite the small sample size and major methodological weaknesses, also showed a trend in favour of antithrombotic prophylaxis without increase in haemorrhagic complications.

Regarding the effect of thromboprophylaxis on pregnancy outcome, a systematic review showed a trend towards lower abortion rate in patients receiving antithrombotics (19% vs. 11%). However, these estimates do not have statistical power to detect differences between groups and, therefore, it is not possible to establish or refute an association between antithrombotic prophylaxis and pregnancy outcome.[196]

Considering the available evidence of increased risk of VTEs in this population, particularly CVT recurrence, the trend towards lower rate of spontaneous abortion in women receiving antithrombotics, the indirect evidence regarding the effects of thromboprophylaxis from other patient populations and the unlikely implementation of large-scale randomised trials to test this indication in pregnant women with prior CVT, a decision to upgrade the strength of the recommendation from uncertain to weak was formally achieved by a unanimous consensus through a nominal group technique.

Recommendation: we suggest prophylaxis with sc LMWH during pregnancy/puerperium, for pregnant women with previous history of CVT and without contraindication for prophylaxis or indication for anticoagulation in therapeutic dosage.

Quality of evidence: very low

Strength of recommendation: weak

Limitations of the guidelines

As for other relatively rare diseases, evidence to support diagnostic and therapeutic decisions in CVT is slowly accumulating but is still rather scarce. Concerning diagnostic procedures, studies have looked mostly at accuracy and predictive values. Neuroimaging studies mostly compared individual imaging modalities. There is very few information on the influence of performing a diagnostic test and of its results on patient outcome. Regarding treatments, few randomised controlled trials have been performed in this disease and most of the available RCTs had small sample size and other methodological problems. Most of the evidence had to be derived from observational studies, whose bias to evaluate the efficacy of interventions are well known. Recent efforts have led to important multicentre registries and trials.

Future directions

Multicentre academic collaboration is a key element to improve our knowledge on CVT. Indeed single centres studies are always underpowered and biased, while the industry is unlikely to support experimental studies in CVT, due to the relatively low prevalence of CVT. In the next few years numerous observational studies and treatment trials on several uncertain issues (e.g. thrombectomy, NOACs, decompressive surgery,

pregnancy after CVT, duration of oral anticoagulation) will increase the level of evidence that currently supports the management of CVT.

Declaration of Conflicting Interests

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JMF.

Contributorship

José M Ferro coordinated the work of the group. All authors prepared specific PICO questions, reviewed the literature and wrote the first draft of that section. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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