

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

J. M. Ferro^{a,b}, M.-G. Bousser^c, P. Canhão^{a,b}, J. M. Coutinho^d, I. Crassard^c, F. Dentali^e, M. di Minno^{f,g}, A. Maino^h, I. Martinelli^h, F. Masuhrⁱ, D. Aguiar de Sousa^a  and J. Stam^d, for the European Stroke Organization

^aDepartment of Neurosciences, Servico de Neurologia, Hospital de Santa Maria, Lisboa; ^bUniversidade de Lisboa, Lisboa, Portugal; ^cService de Neurologie, Hôpital Lariboisière, Paris, France; ^dDepartment of Neurology, Academic Medical Center, Amsterdam, The Netherlands; ^eDepartment of Clinical Medicine, Insubria University, Varese; ^fDepartment of Clinical Medicine and Surgery, Regional Reference Centre for Coagulation Disorders, 'Federico II' University, Naples; ^gUnit of Cell and Molecular Biology in Cardiovascular Diseases, Centro Cardiologico Monzino, IRCCS, Milan; ^hA. Bianchi Bonomi Hemophilia and Thrombosis Centre, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan, Italy; and ⁱDepartment of Neurology, Bundeswehrkrankenhaus, Berlin, Germany

Keywords:

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

Received 2 June 2017
Accepted 27 June 2017

European Journal of Neurology 2017, **24**: 1203–1213

doi:10.1111/ene.13381

Background and purpose: Current guidelines on cerebral venous thrombosis (CVT) diagnosis and management were issued by the European Federation of Neurological Societies in 2010. We aimed to update the previous European Federation of Neurological Societies guidelines using a clearer and evidence-based methodology.

Method: We followed the Grading of Recommendations, Assessment, Development and Evaluation system, formulating relevant diagnostic and treatment questions, performing systematic reviews and writing recommendations based on the quality of available scientific evidence.

Results: We suggest using magnetic resonance or computed tomographic angiography for confirming the diagnosis of CVT and not routinely screening patients with CVT for thrombophilia or cancer. We recommend parenteral anticoagulation in acute CVT and decompressive surgery to prevent death due to brain herniation. We suggest preferentially using low-molecular-weight heparin in the acute phase and not 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 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 have suffered a previous CVT, 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.

Conclusions: Multicentre observational and experimental studies are needed to increase the level of evidence supporting recommendations on the diagnosis and management of CVT.

Correspondence: J. M. Ferro, Department of Neurosciences, Servico de Neurologia, Hospital de Santa Maria, Lisboa, Portugal (tel/fax: + 351217957474; e-mail: jmferro@medicina.ulisboa.pt).

This is a Continuing Medical Education article, and can be found with corresponding questions on the EAN website, LEARN section <https://www.ean.org/CME.2714.0.html>. Certificates for correctly answered questions will be issued by EAN directly, you simply have to be logged-in. With positive results, EAN recommends accreditation of 1 hour of CME, which may be claimed with the national body in charge of CME accreditation.

Introduction

The current guidelines on cerebral venous thrombosis (CVT) diagnosis and management were issued by the European Federation of Neurological Societies in 2010 [1] and by the American Heart Association and American Stroke Society 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 aimed to update previous European Federation of Neurological Societies guidelines using a clearer and evidence-based methodology. To achieve that aim, the current proposal for CVT guidelines followed the Grading of Recommendations, Assessment, Development and Evaluation system [3].

Methods

These guidelines were prepared following the Grading of Recommendations, Assessment, Development and Evaluation methodology [3], and the European Stroke Organization standard operating procedures [4].

The panel selected relevant topics, both diagnostic and therapeutic, to be evaluated for recommendations. 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. According to that vote, outcomes were classified as critical, important and of limited importance. For each of the topics, one or more PICO (patient, intervention, comparator, outcome) questions were phrased. For each PICO question, a systematic review of the literature using a pre-defined search strategy was performed. Pertinent studies were identified, their eligibility assessed and data relevant to the PICO question extracted. The 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 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, healthcare professionals, third-party payers and policy-makers to have recommendations

to consolidate practice for a time period to minimize practice variation and allow access of 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 period of time. For a few PICO questions where it was impossible to formulate a recommendation, a good practice point expressing a diagnostic or therapeutic option was written, without grading it.

For a complete description of the method and results, and complete list of references see the extended version of this guideline [5].

Results for diagnostic recommendations (Part 1)

A summary of the recommendations is available in Table S1.

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?

Six studies compared MR venography (MRV) with DSA [6–11]. A good concordance was seen between the two techniques. MRV reliably demonstrated large cerebral veins and sinuses visualized with DSA. In one study and in a few patients, DSA was more sensitive than MR angiography in evaluating the smaller, ascending cortical veins and the status of the deep subcortical veins. In a study including 20 patients with CVT, all documented by DSA, magnetic resonance imaging (MRI) and MRV together provided the diagnosis of CVT in all cases [8]. The K agreement index between the two techniques was 0.95 [11].

The quality of 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.

PICO question 2: in patients with suspected CVT, should computed tomographic (CT) venography versus DSA be used to diagnose CVT?

There were only two studies with data pertinent for this question. In a study including 25 patients, CT venography (CTV) had a high sensitivity for depicting the intracerebral venous circulation compared with DSA [12]. In a sample of young or non-hypertensive patients with acute spontaneous intracerebral haemorrhages that included CVT in seven patients (6%), all patients had

CT angiography and venography, and DSA was performed the next day. CT angiography and venography were able to detect all CVTs [13].

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

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.

PICO question 3: in patients suspected of CVT, should CTV versus MRI and MRV be used to diagnose CVT?

Three studies directly compared CTV with MRV [14–16] in 85 patients with suspicion of CVT. The diagnosis was confirmed in 45 patients with CTV and 43 patients with MRV. CTV showed sinuses or small cerebral veins with low flow more easily and more frequently than MRV. Two additional studies compared multidetector-row CT angiography with MRV and MRI in CVT diagnosis [17,18]. The advantages of CTV are rapid image acquisition and no contraindication to pacemaker and ferromagnetic devices. The disadvantages of CTV are significant exposure to ionizing radiation and the need for intravenous contrast material. CTV is as accurate as MRV in diagnosing CVT. MRI has the advantage of showing the thrombus itself and being more sensitive in detecting parenchymal lesions.

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

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?

In a recent meta-analysis [19] including a total of 14 studies and 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% CI, 84.8–92.8; $I^2 = 30\%$; range, 60–100%). In addition, D-dimer was elevated in 80 of 92 patients with a longer duration of symptoms (WMS, 83.1%; 95% CI, 70.4–92.8), in 50 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 studies 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 was normal in 692 of 771 patients in whom CVT was objectively ruled out (bivariate WMS, 89.7%; 95% CI, 86.5–92.2; range, 83.1–100%).

A prolonged duration of symptoms was significantly associated with false-negative D-dimer levels in two of the four studies. Clinical presentation with isolated headache was significantly associated with false-negative D-dimer results in two studies. Overall, the accuracy of D-dimer in patients with suspected CVT was evaluated by use of the receiving operating characteristic 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).

The quality of evidence was judged as low because all studies were observational with low 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. >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?

There are no studies comparing a policy of screening for thrombophilia with a policy of non-screening. 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. In two studies the association between thrombophilia and recurrent venous thrombosis encompassed no effect [20,21], while an increased risk effect was described in another two studies [22,23]. 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 and higher risk of remote seizures [24–26].

The quality of 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, 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?

Eleven studies including a total of 1780 patients described malignancy as a predisposing risk factor. Malignancy was reported in 99 patients (5.6%). None of these studies reported a systematic screening for occult malignancy. Thirteen studies reporting on idiopathic CVT cases 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.

The quality of 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.

Results for therapeutic recommendations (Part 2)

A summary of the recommendations is available in Table S1.

Section 1: antithrombotic treatment

Topic: acute anticoagulant treatment

PICO question: in patients with acute CVT, does anticoagulation improve clinical outcome compared with no anticoagulation?

Two randomized trials [27,28], which were also analysed in a recently updated Cochrane review [29], with a total of 79 adult patients showed that anticoagulation with heparin [unfractionated (UFH) or low-molecular-weight (LMWH) heparin] was associated with a reduction in poor outcome that did not reach statistical significance [relative risk (RR) for death or dependency, 0.46; 95% CI, 0.16–1.31; RR for death, 0.33; 95% CI, 0.08–1.21]. After randomization, three patients developed a new intracerebral haemorrhage and all were allocated to placebo. One of these patients later died. Two of the intracerebral haemorrhages occurred in patients who did not have a

haemorrhage at baseline. Major extracranial bleeding occurred in one patient randomized to heparin [RR for major haemorrhagic complications (heparin vs. placebo), 2.90; 95% CI, 0.12–68.50].

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

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?

One randomized trial including 66 patients directly compared LMWH with UFH in adult patients with CVT [30]. Six of 32 patients (19%) allocated to UFH died during hospital admission compared with 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 3 months (RR, 1.37; 95% CI, 1.02–1.83). A major haemorrhagic complication occurred in three patients treated with UFH (all extracranial) compared with 0 patients in the LMWH arm (RR, 0.13; 95% CI, 0.0072–2.51). This trial did have a number of methodological limitations. Results from a non-randomized study also suggest that LMWH is associated with better outcomes than UFH [adjusted odds ratio (OR) for death or dependency, 0.42; 95% CI, 0.18–1.0] and fewer new intracerebral haemorrhages (adjusted OR, 0.29; 95% CI; 0.07–1.3) [31].

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

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.

Topic: thrombolysis and thrombectomy in acute CVT

PICO question: does thrombolysis improve clinical outcome compared with anticoagulation in patients with acute CVT?

There are no published randomized trials on thrombolysis for CVT. There is one ongoing trial in which

adult patients with CVT and a high risk of poor outcome are randomized to endovascular thrombolysis or control treatment [32]. Many case reports and cases series on thrombolysis for CVT have been published. A recent systematic review [33] 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 recanalization rate (partial or complete) of 95% [34].

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

Patients with acute CVT presenting a CVT risk score <3 [35] or none of the following – coma, mental status disturbance, thrombosis of the deep venous system or intracerebral haemorrhage – 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 randomized trial [32] is excluding such low-risk patients.

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 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 VTEs compared with treatment with short-term anticoagulation?

There are no randomized controlled trials, prospective controlled studies or case-control studies assessing optimal duration of oral anticoagulation for the prevention of recurrent CVT and other VTEs. A retrospective study of 706 patients with a median follow-up of 40 months [21] reported CVT recurrence in 4.4% and non-cerebral VTEs in 6.5% of the patients for an overall incidence of recurrence of 23.6 events/1000 patient-years (95% CI, 17.8–28.7) and 35.1 events/1000 patient-years (95% CI, 27.7–44.4) after anticoagulant therapy withdrawal. In a prospective cohort study including 624 patients with CVT and in which 2.2% of the patients had a recurrent CVT and 4.3% had 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) [20,36]. Of all VTEs, 63% occurred within the first year. In another cohort of 145 patients followed after discontinuation of anticoagulation (median duration of therapy, 12 months), the recurrence rates were 2.03/100 person-years for all VTEs and 0.53/100 person-years for recurrent CVT [22]. Therefore, for patients in whom medical conditions associated with high recurrence risk are not identified and before results from ongoing trials are available (EXTending oral antiCOAgulation treatment after acute Cerebral Vein Thrombosis [37]), we suggest a time-limited course of oral anticoagulant therapy (between 3 and 12 months).

The quality of 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 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)

Two case series reported on the use of direct oral anticoagulants (rivaroxaban [38] and dabigatran [39]) in patients with CVT. All patients received heparin treatment in the acute phase. There were no major haemorrhagic complications or thrombotic recurrences in any patient.

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

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.

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 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%) of 59 patients with CVT presenting with isolated intracranial hypertension. Overall outcome was favourable but there are insufficient data to allow an evaluation of the effect of this intervention [40]. In the prospective International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) study [36], diagnostic LP was performed in 224 patients (35.9%). There was no difference in the frequency of 'acute death', 'worsening after hospitalization', 'death or dependency at 6 months' or 'complete recovery' between patients with or without LP. Also, patients treated with therapeutic LP had outcomes that were similar to those of the remaining patients.

The overall quality of evidence across all critical outcomes for both questions 1 and 2 was very low.

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

Quality of evidence Very low.

Strength of recommendation Inconclusive.

Good clinical practice point 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 question 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?

PICO question 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?

There are no randomized controlled trials on the effect of carbonic anhydrase inhibitors or diuretics on the outcome of patients with CVT. Information is limited to one case series [40] and one non-randomized study [41]. 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.

The overall quality of evidence across all critical outcomes for PICO question 1 was low and for PICO question 2 very low.

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.

Good clinical practice point In isolated intracranial hypertension secondary to CVT, causing severe headaches or threatening vision, acetazolamide may be considered if its safety profile is acceptable.

Topic: steroids

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

Only one prospective non-randomized study aimed to assess the efficacy of steroids in CVT [42]. In this study, no significant difference in poor outcomes was found whether or not patients were treated with steroids. Patients without parenchymal lesions treated with steroids had worse outcomes. When patients were stratified according to the number of prognostic factors, treatment with steroids was still not associated with better outcome. In a systematic review that evaluated patients with CVT associated with Behcet's disease, including available data on therapeutic interventions, >90% of the patients with CVT associated with Behcet's disease received corticosteroids [43]. There are several case reports and a series of five cases of CVT associated with Systemic Lupus Erythematosus (SLE), which also include a review of another five published cases [44] treated with steroids, with improvement in all cases. The European League Against Rheumatism (EULAR) recommendations for the management of Behcet's disease recommend treatment with corticosteroid for dural sinus thrombosis [45].

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

Quality of information Low.

Strength of recommendation Weak.

Recommendation We suggest using steroids in patients with acute CVT and Behcet's disease or 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?

Cerebral venous thrombosis 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 [46]. A systematic review found only 15 patients with CVT [47] 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 of 16.7%. Three patients with intracranial hypertension and no parenchymal lesions were treated with ventriculo-peritoneal shunt and regained independence [47]. In a recent case series of 14 CVT patients with acute hydrocephalus, only one patient had a shunt [46]. The patient died despite shunting.

The quality of 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 using 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 Inconclusive.

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?

No randomized controlled trials were found, but there are several case series, two systematic reviews [48,49] and two non-randomized controlled studies [50,51] comparing decompressive surgery with no surgery. 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 was

only 3.4% and the complete recovery rate was 30.7%. Despite the low numbers, the results of the two non-randomized controlled studies demonstrate 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 formulate a strong recommendation based on the following judgement. (i) Quality of evidence is currently low, but a randomized controlled trial is unlikely for ethical and feasibility reasons; there is an ongoing prospective multicentre registry. (ii) Balance of benefits and harms: Surgery saves lives and produces acceptable results, as very few patients are left with severe dependency. (iii) Values and preferences: Patients with CVT are young; few operated patients are left with severe dependency.

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

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

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

A Cochrane systematic review of the effects of antiepileptic drugs for the primary and secondary prevention of seizures after intracranial venous thrombosis identified a lack of evidence concerning this indication [52]. Seizures were associated with acute death in some series but this finding was not consistently reported [53]. None of these studies reported an association between antiepileptic treatment and functional outcome. Regarding seizure prevention, one study reported a risk reduction of early seizures associated with use of antiepileptic drugs in patients with supratentorial lesions and presenting seizures (OR, 0.006; 95% CI, 0.001–0.05) [53]. Supratentorial lesion was a predictor of seizures in several studies [24,53,54].

Seizures are common in CVT and may be a cause of early death. This was the reasoning behind upgrading the strength of the recommendation from uncertain to weak.

Due to safety concerns regarding the prolonged use of antiepileptic drugs, we did not make a recommendation for the prevention of remote post-CVT seizures.

Recommendation We suggest using antiepileptic drugs 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 Inconclusive.

Section 4: pregnancy and contraception after CVT

Topic: CVT during pregnancy

PICO question: 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 a low dose of subcutaneous heparin and 77 patients who did not receive heparin, admitted during the same period [55]. The authors report a more favourable outcome (8 vs. 19 deaths) and no new haemorrhages (intracranial or systemic) in the puerperal patients treated with heparin, but these findings cannot be generalized confidently, as a result of the small number of patients and the general low quality of evidence. In a series of 19 patients with CVT during pregnancy treated with full-dose LMWH [56], there were no haemorrhagic complications. There were also no infant deaths (during pregnancy and 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 [57]. We also found no report of obstetric (maternal or foetal) haemorrhagic complications related to anticoagulation in the CVT cohorts included in our systematic review. The anticoagulation trial of Misra *et al.* [30] 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.

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 CVT

PICO question: 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 RR ratio of 7.6 [58]. This risk may be even higher in carriers of pro-thrombotic conditions [59,60]. The association between hormonal factors (oral contraceptive use or pregnancy) is stronger for CVT than for lower limb deep vein thrombosis [22]. The increased risk associated with oral contraception remains in newer generation products [61,62]. However, data regarding the effect of duration of use or use of progestogen-only contraception is lacking. Also, we found no studies on the risk of recurrent VTEs 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 of fertile age and with 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 1: 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 randomized 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, is the risk of pregnancy-related CVT recurrence or other VTEs (lower or upper limb deep vein thrombosis, pulmonary embolism, abdominal or pelvic venous thrombosis) 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 that together reported 217 pregnancies found a low absolute risk of pregnancy-related venous thrombosis (9 CVT and 27 non-cerebral VTEs/1000 pregnancies) but a significantly higher relative rate of both recurrent CVT and other VTEs, compared with the baseline risk described in the general population for pregnant women [63].

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

Despite being highly variable across studies, spontaneous abortion is usually estimated to occur in 10–15% of clinically recognized pregnancies and previous studies based on self-reported data reported a rate of about 20% [64]. Results 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] [63].

Recommendation For all women with prior history of CVT, we suggest informing as to the absolute and RRs of VTEs and abortion during subsequent pregnancies and not contraindicating future pregnancies based only on the past history of CVT.

Quality of evidence Low.

Strength of recommendation Weak.

PICO question 2: 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. 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 [63] found one recurrent CVT and three VTEs. The recurrent CVT and two of the three reported non-cerebral VTEs occurred in women not receiving any antithrombotic prophylaxis. Given the low quality of the direct evidence, indirect evidence about the relative effects of thromboprophylaxis in other patient populations was also reviewed. A prior Cochrane systematic review [65] identified two small randomized controlled trials that evaluated the safety and efficacy of prophylaxis in pregnant women with prior non-cerebral VTE [66,67] and 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%) [63].

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, indirect evidence regarding the effects of thromboprophylaxis from other patient populations and unlikely implementation of large-scale randomized 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.

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.

Discussion

Limitations of the guideline

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. There is very little information on the influence of performing a diagnostic test and of its results on patient outcome. Regarding treatments, few randomized controlled trials have been performed in CVT and most of the available randomized controlled trials had small sample sizes and other methodological problems. Most of the evidence had to be derived from observational studies, whose bias to evaluate the efficacy of interventions is well known (Table S1). Recent efforts have led to important multicentre registries and trials.

Future directions

Multicentre academic collaboration is a key element to improve our knowledge of CVT. Single-centre studies are always underpowered and biased, and the industry is unlikely to support experimental studies in CVT, due to its relatively low prevalence. In the next few years numerous observational studies and treatment trials on several uncertain issues (e.g. thrombectomy, direct oral anticoagulants, decompressive surgery, pregnancy after CVT, duration of oral anticoagulation) will increase the level of evidence that currently supports the management of CVT.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of all clinical questions and related recommendations.

References

1. Einhäupl K, Stam J, Boussier MG, *et al.* EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. *Eur J Neurol* 2010; **17**: 1229–1235.
2. Saposnik G, Barinagarrementeria F, Brown RD Jr, *et al.* 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.
3. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. <http://www.guideline-development.org/handbook/> (accessed 18/04/2017)
4. Ntaios G, Bornstein NM, Caso V, *et al.* The European Stroke Organisation Guidelines: a standard operating procedure. *Int J Stroke* 2015; **10**: 128–135.
5. Ferro JM, Boussier 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. *European Stroke Journal* 2017; DOI: 10.1177/2396987317719364. [Epub ahead of print].
6. Mattle HP, Wentz KU, Edelman RR, *et al.* Cerebral venography with MR. *Radiology* 1991; **178**: 453–458.
7. Vogl TJ, Bergman C, Villringer A, Einhäupl K, Lissner J, Felix R. Dural sinus thrombosis: value of MR angiography for diagnosis and follow-up. *AJR Am J Roentgenol* 1994; **162**: 1191–1198.
8. Lafitte F, Boukobza M, Guichard JP, *et al.* MRI and MRA for diagnosis and follow-up of cerebral venous thrombosis (CVT). *Clin Radiol* 1997; **52**: 672–679.
9. Flotho E, Druschky KF, Niederstadt T. Diagnostic value of combined conventional magnetic resonance imaging and magnetic resonance angiography in sinus venous thrombosis (article in German). *Fortschr Neurol Psychiatr* 1999; **67**: 95–103.
10. Liang L, Korogi Y, Sugahara T, *et al.* Evaluation of the intracranial dural sinuses with a 3D contrast-enhanced MP-RAGE sequence: prospective comparison with 2D-TOF MR venography and digital subtraction angiography. *AJNR Am J Neuroradiol* 2001; **22**: 481–492.
11. Qu H, Yang M. Early imaging characteristics of 62 cases of cerebral venous thrombosis. *Exp Ther Med* 2013; **5**: 233–236.
12. Wetzel SG, Kirsch E, Stock KW, Kolbe M, Kaim A, Radue EW. Cerebral veins: comparative study of CT venography with intraarterial digital subtraction angiography. *AJNR Am J Neuroradiol* 1999; **20**: 249–255.
13. Wong GK, Siu DY, Abrigo JM, *et al.* Computed tomographic angiography and venography for young or non-hypertensive patients with acute spontaneous intracerebral hemorrhage. *Stroke* 2011; **42**: 211–213.
14. Casey SO, Alberico RA, Patel M, *et al.* Cerebral CT venography. *Radiology* 1996; **198**: 163–170.
15. Ozsvath RR, Casey SO, Lustrin ES, Alberico RA, Hasankhani A, Patel M. Cerebral venography: comparison of CT and MR projection venography. *AJR Am J Roentgenol* 1997; **169**: 1699–1707.
16. Khandelwal N, Agarwal A, Kochhar R, *et al.* Comparison of CT venography with MR venography in cerebral sinovenous thrombosis. *AJR Am J Roentgenol* 2006; **187**: 1637–1643.
17. Linn J, Ertl-Wagner B, Seelos KC, *et al.* Diagnostic value of multidetector-row CT angiography in the evaluation of thrombosis of the cerebral venous sinuses. *AJNR Am J Neuroradiol* 2007; **28**: 946–952.
18. Gaikwad AB, Mudalgi BA, Patankar KB, Patil JK, Ghondade DV. Diagnostic role of 64-slice multidetector row CT scan and CT venogram in cases of cerebral venous thrombosis. *Emerg Radiol* 2008; **15**: 325–333.
19. Dentali F, Squizzato A, Marchesi C, Bonzini M, Ferro JM, Ageno W. D-dimer testing in the diagnosis of cerebral vein thrombosis: a systematic review and a meta-analysis of the literature. *J Thromb Haemost* 2012; **10**: 582–589.
20. Miranda B, Ferro JM, Canhão P, *et al.* Venous thromboembolic events after cerebral vein thrombosis. *Stroke* 2010; **41**: 1901–1906.
21. Dentali F, Poli D, Scoditti U, *et al.* Long-term outcomes of patients with cerebral vein thrombosis: A multicenter study. *J Thromb Haemost* 2012; **10**: 1297–1302.
22. Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannucci PM. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. *Circulation* 2010; **121**: 2740–2746.
23. Narayan D, Kaul S, Ravishankar K, *et al.* Risk factors, clinical profile, and long-term outcome of 428 patients of cerebral sinus venous thrombosis: Insights from Nizam's Institute Venous Stroke Registry, Hyderabad (India). *Neurol India* 2012; **60**: 154–159.
24. Davoudi V, Keyhanian K, Saadatnia M. Risk factors for remote seizure development in patients with cerebral vein and dural sinus thrombosis. *Seizure* 2014; **23**: 135–139.
25. Appenzeller S, Zeller CB, Annichino-Bizzachi JM, *et al.* Cerebral venous thrombosis: influence of risk factors and imaging findings on prognosis. *Clin Neurol Neurosurg* 2005; **107**: 371–378.
26. Stolz E, Kemkes-Matthes B, Potzsch B, *et al.* Screening for thrombophilic risk factors among 25 German patients with cerebral venous thrombosis. *Acta Neurol Scand* 2000; **102**: 31–36.
27. de Bruijn SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. *Stroke* 1999; **30**: 484–488.
28. Einhäupl KM, Villringer A, Meister W, *et al.* Heparin treatment in sinus venous thrombosis. *Lancet* 1991; **338**: 597–600.
29. Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. *Cochrane Database Syst Rev* 2011; Aug 10 (8): CD002005.
30. Misra UK, Kalita J, Chandra S, Kumar B, Bansal V. Low molecular weight heparin versus unfractionated heparin in cerebral venous sinus thrombosis: a randomized controlled trial. *Eur J Neurol* 2012; **19**: 1030–1036.
31. Coutinho JM, Ferro JM, Canhão P, *et al.* Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. *Stroke* 2010; **41**: 2575–2580.
32. Coutinho JM, Ferro JM, Zuurbier SM, *et al.* Thrombolysis or anticoagulation for cerebral venous thrombosis: rationale and design of the TO-ACT trial. *Int J Stroke* 2013; **8**: 135–140.
33. Dentali F, Squizzato A, Gianni M, *et al.* Safety of thrombolysis in cerebral venous thrombosis. A systematic review of the literature. *Thromb Haemost* 2010; **104**: 1055–1062.
34. Siddiqui FM, Dandapat S, Banerjee C, *et al.* Mechanical thrombectomy in cerebral venous thrombosis: systematic review of 185 cases. *Stroke* 2015; **46**: 1263–1268.

35. Ferro JM, Bacelar-Nicolau H, Rodrigues T, *et al.* Risk score to predict the outcome of patients with cerebral vein and dural sinus thrombosis. *Cerebrovasc Dis* 2009; **28**: 39–44.
36. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004; **35**: 664–670.
37. Ferro JM. EXCOA-CVT study: the benefit of EXtending oral antiCOAgulation treatment after acute Cerebral Vein Thrombosis. ISRCTN, 2014. Available at: <https://doi.org/10.1186/isrctn25644448> (accessed 04/02/2017).
38. Geisbusch C, Richter D, Herweh C, Ringleb PA, Nagel S. Novel factor xa inhibitor for the treatment of cerebral venous and sinus thrombosis: first experience in 7 patients. *Stroke* 2014; **45**: 2469–2471.
39. Mendonca MD, Barbosa R, Cruz-E-Silva V, Calado S, Viana-Baptista M. Oral direct thrombin inhibitor as an alternative in the management of cerebral venous thrombosis: a series of 15 patients. *Int J Stroke* 2015; **10**: 1115–1118.
40. Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. *Neurology* 1999; **53**: 1537–1542.
41. Aguiar de Sousa D, Ferro JM, Canhão P, *et al.* Acetazolamide in acute cerebral venous thrombosis: a case-control study (abstract). *Cerebrovasc Dis* 2014; **37**(suppl. 1): 541.
42. Canhão P, Cortesão A, Cabral M, *et al.* Are steroids useful to treat cerebral venous thrombosis? *Stroke* 2008; **39**: 105–110.
43. Aguiar de Sousa D, Mestre T, Ferro JM. Cerebral venous thrombosis in Behcet's disease: a systematic review. *J Neurol* 2011; **258**: 719–727.
44. Vidailhet M, Piette JC, Wechsler B, Bousser MG, Brunet P. Cerebral venous thrombosis in systemic lupus erythematosus. *Stroke* 1990; **21**: 1226–1231.
45. Hatemi G, Silman A, Bang D, *et al.* Management of Behcet disease: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for the management of Behcet disease. *Ann Rheum Dis* 2009; **68**: 1528–1534.
46. Zuurbier SM, van den Beg R, Troost D, Majoie CB, Stam J, Coutinho J. Hydrocephalus in cerebral venous thrombosis. *J Neurol* 2015; **262**: 931–937.
47. Lobo S, Ferro JM, Barinagarrementeria F, *et al.* Shunting in acute cerebral venous thrombosis: a systematic review. *Cerebrovasc Dis* 2014; **37**: 38–42.
48. Ferro JM, Crassard I, Coutinho JM, *et al.* Decompressive surgery in cerebrovenous thrombosis: a multicenter registry and a systematic review of individual patient data. *Stroke* 2011; **42**: 2825–2831.
49. Raza E, Shamim MS, Wadiwala MF, Ahmed B, Kamal AK. Decompressive surgery for malignant cerebral venous sinus thrombosis: a retrospective case series from Pakistan and comparative literature review. *J Stroke Cerebrovasc Dis* 2014; **23**: e13–e22.
50. Théaudin M, Crassard I, Bresson D, *et al.* Should decompressive surgery be performed in malignant cerebral venous thrombosis? *Stroke* 2010; **41**: 727–731.
51. Ferro JM, Bousser MG, Canhão P, *et al.* A case control study of decompressive surgery in cerebrovenous thrombosis. Presented at the 19th World Congress of Neurology, Bangkok, Thailand, 2010.
52. Price M, Günther A, Kwan JS. Antiepileptic drugs for the primary and secondary prevention of seizures after intracranial venous thrombosis. *Cochrane Database Syst Rev* 2014; Aug 2 (8): CD005501.
53. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F, ISCVT Investigators. Early seizures in cerebral vein and dural sinus thrombosis: risk factors and role of antiepileptics. *Stroke* 2008; **39**: 1152–1158.
54. Kalita J, Chandra S, Misra UK. Significance of seizure in cerebral venous sinus thrombosis. *Seizure* 2012; **21**: 639–642.
55. Nagaraja D, Haridas T, Taly AB, Veerendrakumar M, SubbuKrishna DK. Puerperal cerebral venous thrombosis: therapeutic benefit of low dose heparin. *Neurol India* 1999; **47**: 43–46.
56. Demir CF, Inci MF, Özkan F, Yıldız M, Özdemir H. Clinical and radiological management and outcome of pregnancies complicated by cerebral venous thrombosis: a review of 19 cases. *J Stroke Cerebrovasc Dis* 2013; **22**: 1252–1257.
57. Gao H, Yang BJ, Jin LP, Jia XF. Predisposing factors, diagnosis, treatment and prognosis of cerebral venous thrombosis during pregnancy and postpartum: a case-control study. *Chin Med J (Engl)* 2011; **124**: 4198–4204.
58. Amoozegar F, Ronksley PE, Sauve R, Menon BK. Hormonal contraceptives and cerebral venous thrombosis risk: a systematic review and meta-analysis. *Front Neurol* 2015; **6**: 7.
59. de Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in [correction of who are] carriers of hereditary prothrombotic conditions. The Cerebral Venous Sinus Thrombosis Study Group. *BMJ* 1998; **316**: 589–592.
60. Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. *Blood* 2003; **102**: 1363–1366.
61. de Bruijn SF, Stam J, Vandenbroucke JP. Increased risk of cerebral venous sinus thrombosis with third-generation oral contraceptives. *Lancet* 1998; **351**: 1404.
62. Scoditti U, Buccino GP, Pini M, Pattacini C, Mancina D. Risk of acute cerebrovascular events related to low oestrogen oral contraceptive treatment. *Ital J Neurol Sci* 1998; **19**: 15–19.
63. Aguiar de Sousa D, Canhão P, Ferro JM. Safety of pregnancy following cerebral venous thrombosis – a systematic review. *Stroke* 2016; **47**: 713–718.
64. Buss L, Tolstrup J, Munk C, *et al.* Spontaneous abortion: a prospective cohort study of younger women from the general population in Denmark. Validation, occurrence and risk determinants. *Acta Obstet Gynecol Scand* 2006; **85**: 467–475.
65. Bain E, Wilson A, Tooher R, Gates S, Davis LJ, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane Database Syst Rev* 2014; Feb 11 (2): CD001689.
66. Gates S, Brocklehurst P, Ayers S, Bowler U, Thromboprophylaxis in Pregnancy Advisory Group. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low-molecular-weight heparin. *Am J Obstet Gynecol* 2004; **191**: 1296–1303.
67. Howell R, Fidler J, Letsky E, de Swiet M. The risks of antenatal subcutaneous heparin prophylaxis: a controlled trial. *Br J Obstet Gynaecol* 1983; **90**: 1124–1128.