

Evidence and clinical judgment*: Treatment of cerebral vein thrombosis

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Cerebral vein thrombosis (CVT) is an unusual cerebrovascular disease that is estimated to account for about 0.5% of all strokes (1). CVT presents with a remarkably wide spectrum of clinical signs and symptoms that lead, according to their grouping, to four main patterns: isolated intracranial hypertension, focal syndrome, cavernous sinus syndrome, and subacute encephalopathy (2). The clinical picture is usually more severe when the deep cerebral venous system is extensively occluded and when parenchymal lesions occur (3). CVT is generally considered a more benign disease than thrombosis of the cerebral arteries, with lower mortality rates and lower rates of residual disability (4). In addition, recurrences appear to occur less frequently than in patients with venous thrombosis in more usual sites, such as the lower extremities. These observations could be explained, in part, by the fact that patients with CVT are usually younger and more frequently present one or more transient, reversible risk factors.

Most patients with objectively diagnosed CVT are treated with anticoagulant drugs, usually unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed by a vitamin K antagonist (VKA). The use of thrombolytic therapy is usually limited to selected patients with a more severe clinical presentation. International guidelines recommend the use

of either UFH or LMWH during the acute phase of illness and the use of VKA therapy for 3–12 months as secondary prevention for recurrent disease (5–8). Because limited evidence from clinical studies is available to support recommendations, clinical guidelines do not address a number of practical issues, some of critical importance, that clinicians encounter in everyday clinical practice.

The Italian Society for Thrombosis and Haemostasis (SISSET) has proposed a new format for its guidelines, named “Evidence and Clinical Judgment”. The aim of these documents is not to provide a traditional guideline based on graded recommendations, but to address specific and clinically relevant questions that are not addressed by usual clinical practice guidelines, but are important to assist physicians in areas where best clinical practice is uncertain. In this paper, we will try to offer evidence and clinical judgments for the optimal treatment of patients with CVT.

Methods

A working group (WA, FD, and AS) was nominated by SISSET and invited to define clinical questions on the treatment of CVT and to perform a systematic review of the literature using the following data sources: electronic databases (MEDLINE, from 1966 to August 2009, EMBASE, from 1980 to August 2009, and the Cochrane Library), reference lists of selected papers and narrative reviews, editorials, guidelines and direct consultation with field experts. Two reviewers performed study selection independently, with disagreements resolved through discussion and by the opinion of a third reviewer, if necessary. Detailed information on search strategies and results are available upon request. Selected articles

were ranked according to a hierarchy of evidence levels, including systematic reviews, controlled clinical trials, uncontrolled clinical trials and case series.

Finally, all available evidence was summarised in evidence tables (Tables 1–3). Because it was anticipated that for each of the selected questions very low levels of evidence could be available, unmet clinical questions were subsequently addressed to internationally recognized experts in the field (JD, TB, MGL, MP), in order to obtain an “evidence-based clinical judgment”. International experts were selected based on their expertise: two neurologists with a large experience in the management of stroke patients (MGL and MP) and two internists/haematologists with considerable experience in the management of venous thromboembolism (VTE) and use of anti-coagulant drugs (JD and TB). To avoid intellectual bias, we selected experts who were not directly involved in any of the main studies retrieved in the literature.

We identified four clinical questions on the treatment of patients with CVT. The first question was on the use of either LMWH or UFH for the initial treatment of CVT; the second question was on the duration of administration of either LMWH or UFH in the acute phase treatment of CVT and on the optimal timing for starting treatment with VKAs; the third question was on the role for thrombolysis in the acute treatment of patients with CVT; the fourth question was on the optimal duration of secondary prevention with VKAs (Table 4). Selected experts were requested to review the summary of the evidences provided by the working group and to briefly answer each of the proposed ques-

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Reference	Study type	Treatment	Patients, N	Inclusion criteria	Exclusion criteria	Endpoint	Results
de Bruijn, 1999 (10)	Double blind RCT	LMWH (Nadroparin 180 anti-factor Xa units/kg per 24 hours) and matching placebo for 3 weeks (double-blind part of trial), followed by 3 months of oral anticoagulants for patients allocated to nadroparin (open part).	59	Patients with clinically suspected CVT confirmed by cerebral angiography or by MRI (including MR angiography) were eligible.	Age <18 years, pregnancy, indications for (leg-vein thrombosis or pulmonary embolism) or contraindications (bleeding disorders, thrombocytopenia <100x10 ⁹ /l, hepatic or renal dysfunction, diastolic pressure >110 mm Hg, or recent gastrointestinal haemorrhage) to heparin, conditions with a poor prognosis unrelated to sinus thrombosis, papilloedema with impaired vision that required lumbar punctures or cerebrospinal fluid shunting, or recently performed lumbar puncture or surgical procedure.	<ul style="list-style-type: none"> Primary endpoint: Poor outcome defined as Barthel Index of 15 or less, or death assessed at day 21 after randomisation. Secondary endpoints: OHS after 12 weeks (not blinded) dichotomised between death or (partial) dependence (grade 3 to 5) and minor handicap or better (grade 0 to 2). 	<ul style="list-style-type: none"> 6/30 (20%) in the nadroparin group and 7/29 patients (24%) in the placebo group had a poor outcome (risk reduction, -4%; 95%CI, -25, 17%). After 12 weeks, 4/30 (13%) in the nadroparin group and 6/29 (21%) in the placebo group had OHS of >=3 (risk reduction, -7%; 95% CI, -26% to 12%). There were no symptomatic ICH. One patient in the nadroparin group had a major gastrointestinal haemorrhage, and one patient in the placebo group died from clinically suspected PE.
Einhaupl et al, 1991 (9)	Double blind RCT	Intravenous high-dose UFH, 25,000 - 65,000 IU/day (after a bolus of 3,000 IU, heparin dose was adjusted to obtain a aPTT value of at least twice the pre-treatment value, and maximally 120 sec) or placebo (saline infusion).	20	Patients in which the diagnosis of CVT was made by intra-arterial contrast angiography.	Contraindication to heparin.	<ul style="list-style-type: none"> Primary outcome: Clinical condition at 3 months assessed with a composite CVT severity scale (items for headache, focal signs, seizures, and level of consciousness). Secondary endpoint: ICH diagnosed by CT scan. 	<ul style="list-style-type: none"> 8/10 heparin-treated patients had a complete recovery and two had slight neurological deficits. In the placebo group, only 1/10 had a complete recovery, six patients had neurological deficits, and three patients died (p < 0.01). Two patients had with new ICHs in the control group, and 0 in the heparin group.
Stam et al, 2002 (11)	Meta-analysis of RCTs	UFH or LMWH (followed by anticoagulant treatment for 3 months) vs placebo.	79	Patients with CVT documented by MRI or conventional angiography (including patients with CVT and ICH documented prior to anticoagulant treatment) in which neurological outcome and death were documented.	Trials including patients where CVT was diagnosed by CT scan alone.	<p>Primary outcome:</p> <ul style="list-style-type: none"> Death or dependency at the end of the follow-up. Death from any cause at the end of follow-up. <p>Secondary outcome:</p> <ul style="list-style-type: none"> Confirmed PE within the treatment or follow-up period. Symptomatic fatal or non-fatal ICH that was documented by CT or MRI scanning, or at autopsy, and that caused clinically manifest neurologic deterioration. Major extracranial haemorrhage, defined as any bleeding that required transfusion or significant surgical intervention, or that caused permanent disabling deficit (e.g. intra-ocular bleeding causing blindness). 	<ul style="list-style-type: none"> Meta-analysis shows a non-significant RR of 0.46 (95% CI 0.16, 1.31) in death or dependency associated with anticoagulant therapy. The ARR in the risk of death or dependency at follow-up was -13% (95% CI -30%, 3%). Anticoagulant treatment was associated with a RR of death of 0.33 (95%CI 0.08, 1.21). The ARR in the death risk was 13% (95%CI -27%, 1%). There were no confirmed PE. No new symptomatic ICHs were diagnosed after anticoagulant therapy (one study reports two patients in the control group with new ICHs, but without clinical details). One patient on nadroparin treatment in one study suffered a major non-fatal gastrointestinal haemorrhage. With a pooled RR of 2.9 (CI 0.12 to 68.5), and an ARR of +2% (95%CI -6, 11).

RCT, randomised controlled trial; LMWH, low-molecular-weight heparin; CVT, cerebral vein thrombosis; OHS, Oxford Handicap Scale; RR, relative risk; ICH, Intracranial Haemorrhage; aPTT activated partial thromboplastin time; CT, computed tomography; MRI, magnetic resonance imaging; PE, pulmonary embolism.

Table 1: Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for the treatment of cerebral vein thrombosis (CVT).

tions. Experts were contacted via e-mail and were blinded to the answers provided by their peers. Based on the clinical judgment provided by the experts, we formulated some practical suggestions aimed to assist practicing clinicians in their daily activity. No formal method for the grading of recommendations was applied.

Results of the literature review

Two randomised controlled studies (RCTs) and one meta-analysis that have addressed the efficacy and safety of UFH and LMWH in the acute treatment of CVT were identified (9–11). The meta-analysis of the two clinical trials found a reduction in death or dependency with the use of UFH or LMWH, but this was not statistically significant, likely because of the very small number of patients enrolled in the studies. The use of anticoagulant treatment was not associated with an increased risk of symptomatic intracranial haemorrhage (ICH). No direct comparisons between UFH and LMWH are available. Results are summarised in ► Table 1.

One Cochrane review and one meta-analysis that have evaluated the role of thrombolytic drugs in the acute treatment of CVT were identified (12, 13). There are no RCTs that have evaluated thrombolytic therapy in this setting, and the results of the available studies, when combined, suggest a non-negligible risk of bleeding complications. Results are summarised in ► Table 2.

Finally, no clinical studies have specifically addressed the issue of the optimal duration of secondary prevention of VTE with anticoagulant therapies in patient with CVT. We have identified one systematic review of the literature that has assessed the long-term clinical history of patients with CVT and has estimated recurrence rates (14). The rate of

patients who are death or dependent after long-term follow-up appears to be substantially low, suggesting that in most cases the disease is more benign than it was previously thought. Recurrence rates are also substantially low, but the mean follow up after oral anticoagulant treatment is withheld is short and does not allow meaningful conclusions. There are insufficient data to allow identification of patients at increased risk of recurrences in this patients population. After few months from the acute events, the majority of patients show complete recanalisation of the venous thrombosis. Results are summarised in ► Table 3.

Practical suggestions based on “evidence and clinical judgement”

The questions are listed in ► Table 4.

Question 1

Despite the lack of direct comparisons in clinical trials, UFH and LMWH should be considered equivalent for the initial treatment of CVT and physicians should select between LMWH and UFH based on their usual practice in most cases.

Question 2

Although no clinical studies have assessed whether extended duration of heparin treatment, regardless of the timing of introduction of warfarin, improves clinical outcome as compared to shorter duration, treatment with either UFH or LMWH in patients with CVT should be administered for longer than the usual 5–7 days. The initiation of warfarin should be delayed until the patient is clinically stable, mainly for safety concerns.

Question 3

In the absence of RCTs and with some evidences of an increased risk of major bleeding complications, the use thrombolysis

should be restricted to very selected, high-risk patients.

Question 4

Secondary prevention of CVT should follow the same rules applied for patients with deep-vein thrombosis (DVT) or pulmonary embolism (PE). Patients should be carefully evaluated for the presence of underlying risk factors and treatment should be individually tailored as much as possible. In comparison with DVT, CVT occurs at a younger age, is less commonly unprovoked and more frequently secondary to a transient risk factor, and, probably, has a lower incidence of recurrences. Thus, it seems acceptable to stop oral anticoagulant treatment after 3–6 months in most CVT patients with transient risk factors. In all other, patients, the duration of secondary prevention should be reassessed periodically, and life-long treatment should be considered in the presence of permanent risk factors or recurrent events.

Areas of agreement or controversy in clinical judgment

On the basis of the available evidence and of the clinical judgments provided by the four international experts, we have tried to address questions that can be clinically relevant for the practicing clinician dealing with CVT patients and to provide clinicians with some practical recommendations. Some heterogeneity among expert opinions reflects current knowledge gaps, but may also reflect the different backgrounds of the interviewed clinicians. Overall, most answers were actually quite consistent and do truly provide additional, useful suggestions for the management of this uncommon, but potentially severe disease.

All four experts agreed that UFH and LMWH should be considered as equivalent agents for the initial treatment of CVT. Reasons to support equivalence included: the signal of benefit from currently available RCTs; the relative safety of the use of LMWH and UFH in patients with CVT;

Table 2: Thrombolysis for the treatment of cerebral vein thrombosis (CVT).

Reference	Study type	Treatment	Patients, N	Inclusion criteria	Exclusion criteria	Endpoint	Results
Ciccone et al, 2004 (12)	Meta-analysis of RCTs and of quasi randomised trial	<ol style="list-style-type: none"> (1) thrombolysis versus placebo or open control; (2) thrombolysis versus full dose anticoagulation (unfractionated heparin or low-molecular weight heparin followed by oral anti-coagulants); (3) thrombolysis versus less intense anticoagulant (low-dose heparin, given subcutaneously); (4) thrombolysis versus antiplatelet treatment; (5) thrombolysis versus 'standard therapy' (i.e. a potentially confounded therapy). <ul style="list-style-type: none"> • Any clot dissolving (thrombolytic) agents, regardless of duration, dosage and route of administration – either via selective catheterisation of the occluded sinus or by peripheral intravenous injection or combined – were accepted for the treatment group. 	-	<ul style="list-style-type: none"> • RCTs of thrombolytic agents in acute cerebral vein and dural sinus thrombosis recognised within 15 days of symptom onset. • Patients over 18 years of age with definite CVDST (a symptomatic clinical condition with the demonstration of vein/sinus thrombosis by MR venography, intraarterial venography or CT venography,) within 15 days of symptom onset. 	<ul style="list-style-type: none"> • Trials including patients. • Diagnosed by brain computerised tomography (CT) scan alone. • Cases of involvement of the cortical veins alone, without sinus thrombosis. 	<ol style="list-style-type: none"> (1) The number of patients who recovered completely (modified Rankin Scale 0 or 1) at the end of the scheduled follow-up. (2) Death from any cause at the end of the follow-up. (3) The number of patients with symptomatic fatal or non-fatal intracranial haemorrhage (any new intracranial haemorrhage or haemorrhagic transformation of a cerebral infarct that developed after randomisation, that is documented by CT or MR scanning, or at autopsy, and that caused clinically manifest deterioration of the neurological condition). (4) The number of patients with any major extracranial haemorrhage (any bleeding that requires transfusion or significant surgical intervention, or that causes permanent disabling deficit; e.g. intraocular bleeding causing blindness). <ul style="list-style-type: none"> • Any available information about safety in both the thrombolytic and control groups. 	No published, ongoing or planned RCTs were identified.
Canhao et al, 2003 (13)	Systematic review	Thrombolysis	169	Patients with CVDST	-	To assess the efficacy and safety of thrombolysis in patients with CVDST.	<ul style="list-style-type: none"> • No randomised clinical trial (RCT) was found. Seventy-two studies (169 patients) were included. • At discharge, 10 patients (7%; 95% CI 3–12%) were dependent and nine patients (5%; 95% CI 2–9%) died. • Intracranial haemorrhages occurred in 17% of cases. In 5% they were associated with clinical deterioration. Extracranial haemorrhages occurred in 21%, but only 2% required blood transfusion.

Table 3: Clinical history and long-term risk of recurrent venous thromboembolic events in patients with cerebral vein thrombosis (CVT).

Reference	Study type	Patients, n	Inclusion criteria	Exclusion criteria	Endpoint	Results	Notes
Dentali et al, 2006 (14)	Systematic review of observational studies	1,488	(1) Diagnosis of CVT was objectively confirmed (with DSA or conventional angiography, MRI, or MRA, computed tomography venography, at surgery or with autopsy); (2) patients ≥ 18 years; (3) studies included ≥ 10 patients; (4) a follow-up of at least 3 months; (5) information on one or more of the following data: mortality and disability rates, clinical or radiological predictors of poor outcome, recanalisation, or recurrence of CVT or of other VTE.	Studies in which the diagnosis of CVT was exclusively clinical without objective imaging, and all the studies in which residual disability was not measured with a commonly accepted score (i.e. modified Rankin Score, Glasgow Outcome Scale).	(1) Mortality (2) Residual disability (3) Recanalisation (4) Recurrence (5) Potential radiological and clinical predictors of poor outcome.	<ul style="list-style-type: none"> Mortality rate during peri-hospitalisation period is 5.6% (range, 0%-15.2%) and 9.4% (range, 0%-39%) at the end of follow-up period. 88% of surviving patients recover completely or have only a mild functional or cognitive deficit. 66% of patients recanalized within the first few months after presentation. 2.8% of patients (range, 0%-11.7%) had objectively confirmed recurrence. 3.7% of patients (range, 0%-8.6%) had a VTE other than CVT during follow up. 	<ul style="list-style-type: none"> Duration and type of treatment is different in the original studies. Duration of follow-up varied widely between studies, ranging from 12 to 145 months.

and the proven efficacy of these drugs in other VTE disorders. However, experts expressed different preferences for their own clinical practice. LMWH was preferred by some experts because of its practical advantages (e.g. easier administration, no need for monitoring). UFH was preferred by other experts because of the availability of a continuous monitoring of the activity of the drug, and because of the easier reversibility of UFH in case of bleeding complications or in case patients require invasive procedures. Thus, UFH might be the right choice in all patients at increased risk for bleeding complications because of the severity of presentation or because of underlying, predisposing conditions.

There was full agreement and easy consensus among experts on the indication to delay the introduction of VKAs treatment, mostly to ensure a better safety profile until patient clinical condition becomes stable, but also because of the preference for the extended use of UFH or LMWH to ensure a consistently adequate anticoagulant effect for the first 7–14 days since early introduction of warfarin is believed to provide periods of inadequate anticoagulation.

A consensus was also found on the indications to thrombolytic therapy in patients with CVT. All experts recommended to severely restrict the use of lytic therapy for CVT and to use it as a last resort. They suggested the use of lytic therapy for patients who have extensive CVT that is likely to be fatal and for those patients who do not respond to conventional anticoagulation. One expert suggested the use of intra-arterial thrombolysis for the treatment of CVT in instances where the patient continues to deteriorate neurologically as a result of venous ischaemia and venous stasis despite therapeutic anticoagulation, if appropriate expertise is available and the use of systemic thrombolysis in patients with clinical deterioration despite therapeutic anticoagulation in centres where catheter-directed thrombolysis is not available. Of course, thrombolysis is not indicated when neurological deterioration is caused primarily by ICH in the setting of CVT.

Finally, all experts suggested a minimum duration of anticoagulation of 3–6 months for the secondary prevention of CVT. There were some differences among

Question 1: Are LMWH and UFH both effective and likely equivalent for the initial treatment of CVT? Do you have any preference?

1	There is no plausible biological or other reason why treatment efficacy should differ between UFH and LMWH for CVT. Would use UFH if a patient is hospitalised or considered to be at higher risk for bleeding, in whom rapid reversal would be warranted.
2	LMWH is effective and likely equivalent to UFH. Preference is for LMWH.
3	LMWH and UFH are both effective for the initial treatment of CVT.
4	There is no difference in effectiveness between LMWH and UFH. Prefer to begin with UFH because it is possible to immediately reverse or at least reduce its anticoagulant effect.
Summary	Consensus that LMWH and UFH are both effective and likely equivalent for treatment of CVT. Disagreement in terms of preferred agent.
Recommendation	Use of either LMWH or UFH for the initial treatment of CVT.

Question 2: Would you recommend that the same treatment regimens used for the therapy of deep vein thrombosis (i.e. heparins for approximately 5–7 days and warfarin possibly started on the first treatment day) can be safely and effectively applied to patients with CVT or would you suggest different treatment durations/regimens?

1	Extend the use of UFH/LMWH for patients with more severe venous thromboembolism (non-thrombolysed) to ensure a consistently adequate anticoagulant effect for 7–14 days; early introduction of warfarin may provide periods of inadequate anticoagulation.
2	Same treatment regimen as for the treatment of DVT, but delay introduction of warfarin in critically ill patients.
3	Recommends against initiation of warfarin on the first treatment day. Initiate warfarin treatment when the patient's clinical condition has been stable on therapeutic dose anticoagulation for at least 48 hours.
4	Begin with warfarin after 3-5 days to monitor any potential early haemorrhagic complications.
Summary	Consensus on the indication to delay the introduction of VKA treatment. No substantial disagreement.
Recommendation	Treatment with either UFH or LMWH should be administered for longer than the usual 5 to 7 days, and the initiation of warfarin should in most cases be delayed

Question number 3: Is there a role for thrombolysis for the treatment of CVT, and if so, when would you consider to use thrombolytic agents in patients with CVT?

1	Severely restrict the use of lytic therapy for CVT.
2	Use thrombolysis as a last resort only.
3	Use intra-arterial thrombolysis when the patient continues to deteriorate neurologically despite therapeutic anticoagulation, if appropriate expertise is available. Consider systemic thrombolysis in patients with clinical deterioration despite therapeutic anticoagulation in centers where catheter-directed thrombolysis is not available.
4	Use thrombolysis only within controlled trials.
Summary	Consensus on the recommendation to restrict the use of lytic therapy for CVT. Disagreement in the routine use of thrombolysis for selected, high-risk patients.
Recommendation	The use thrombolysis should be restricted to very selected, high risk patients.

Question number 4: What is the optimal duration of VKAs therapy after a first episode of CVT and what factors would take into account to decide treatment duration?

1	Duration of anticoagulation should follow the same principles as non-CVT venous thrombosis.
2	Treat patients for six months initially and then assess.
3	Treat patients with VKA therapy for 3–6 months following a first episode of CVT and in the absence of a severe and chronic hypercoagulable state. This should be followed by therapy with an antiplatelet agent indefinitely.
4	Treat most patients from 3–6 months.
Summary	Consensus on a minimum duration of anticoagulation of 3 to 6 months. Disagreement in the selection of patients for whom longer term therapy is required and in the use of antiplatelet therapy after anticoagulant treatment is stopped.
Recommendation	Secondary prevention of CVT should follow the same rules applied for patients with DVT or PE.

Table 4: Summary of the questions, expert opinions, and recommendations.

experts in the selection of patients for whom longer term therapy is required. In general, all experts suggested to consider whether pathogenic factors are reversible, known but permanent or unknown. In the presence of reversible risk factors the suggested duration of treatment ranged between three and six months, whereas life-long treatment was suggested in the presence of recurrence, malignancy or severe thrombophilia. In patients with unprovoked events, a minimum of six months was generally suggested, and the possibility to subsequently base the decision of prolonging or stopping treatment with monitoring of clot resolution and evaluating clinical conditions was proposed by one of the experts. Of great importance, it is reminded to always consider patient preference when deciding whether or not oral anti-coagulant therapy should be stopped.

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