Policy and Guidelines for Assessment and Management of Adult Patients with Cerebral Venous Thrombosis in Greater Manchester

Version 1.4

Martin Punter, Mark Kellett, April 2014

Summary of Policy

A. Cerebral venous thrombosis should be considered in the following groups of patients

- Patients presenting with new, sub-acute headache suggestive of raised intracranial pressure (ICP)
- Pregnant patients in the third trimester or puerperium who present with new headache suggestive of raised ICP
- Patients with new headache suggestive of raised ICP who have a history of venous thromboembolism
- Patients presenting with progressive neurological decline including any of headache, focal neurological signs, seizures, altered mentation, ENT infection, meningism
- Patients with atypical site of intracerebral haemorrhage (ICH)/multiple sites of haemorrhage
- Patients with ischaemic stroke crossing arterial territories/bilateral stroke

B. Patients in whom cerebral venous thrombosis is considered should undergo urgent imaging of the brain and cerebral venous system guided by local radiologists. In most centres this is likely to be CT brain and CT venogram due to ease of access and quality of venous imaging.

C. Patients in whom the diagnosis of cerebral venous thrombosis is made should undergo initial investigation of aetiology, bearing in mind that most cases have more than one risk factor

- FBC/Renal/Liver/Bone/clotting profiles
- D-Dimer (if pre imaging)
- Full thrombophilia screen (Protein C and protein S, and antithrombin III should be tested after cessation of anticoagulant therapy as results are unreliable in acute thrombosis and with anticoagulation)
- Full drug history, in particular history of taking the oral contraceptive pill
- Inflammatory marker screen
- Lumbar puncture (LP) should be considered and discussed with the neurology team at Salford Royal NHS Foundation Trust (SRFT) prior to initiation of anticoagulation

D. All patients with a confirmed diagnosis of CVT should be discussed with the on-call regional neurology team at SRFT.

- The expectation for confirmed cases discussed with SRFT would be for patients to be transferred to the Greater Manchester Neurosciences Centre (GMNC) Acute Neurology Unit (ANU). If no bed is available then transfer

should be made to the acute stroke unit (ASU) and internal transfer subsequently made to the next available bed on ANU. The neurology registrar on call should liaise with the stroke registrar on call for reasons of bed planning.

- There are no obstetric facilities on the Salford Royal site and patients who are 20 weeks pregnant or more, or immediately post partum, will not be able to access GMNC. If it is felt transfer out of the district general hospital (DGH) is necessary then discussion should be with the on-call neurology team at Lancashire Teaching Hospitals NHS Trust, Preston.

E. The management of patients with CVT would normally be anticoagulation with heparin. The standard of care is usually low molecular weight heparin (LMWH) at the same dose ranges as for treatment of pulmonary embolus.

- Anticoagulation should be started as soon as possible after diagnosis unless LP is indicated.
- In some cases (Large haemorrhage with mass effect, possibility of need for LP, possibility of need for surgical intervention, other active bleeding risk) intravenous unfractionated heparin may be considered more appropriate.

F. Patients with seizures should be treated with appropriate antiepileptic medication as recurrent seizures would risk exacerbating raised ICP

G. Early neurological deterioration can be seen in up to 25% of cases. If deterioration occurs despite optimum anticoagulation then surgical/radiological intervention could be considered and discussed with the appropriate team

H. Only when patients are demonstrated to be improving should they be considered for transfer back to their local hospital for further care/rehabilitation

- Patients should be referred to their local anticoagulation service for on-going management of anticoagulation.
- Usual practice would be to continue heparin until warfarin therapy achieves an INR within the desired range (2-3)
- Patients should be followed up by their local neurologist at least on one occasion
- All patients should undergo follow up brain and venous imaging 4-6 months after commencement of anticoagulation to look for evidence of recanalization
- Duration of anticoagulation will be dependent on aetiology but the following are broad guidelines:
    i. Provoked CVT (associated with a transient risk factor), anticoagulation should be continued for 3 to 6 months, with a target INR of 2.0 to 3.0

ii. Unprovoked CVT, anticoagulation should be continued for 6 to 12 months, with a target INR of 2.0 to 3.0
iii. Recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia, indefinite anticoagulation should be considered, with a target INR of 2.0 to 3.0

Introduction

Aim of the Guideline:

This document aims to provide standards of care for patients with cerebral venous thrombosis throughout Greater Manchester.

Plans for Dissemination of the Guideline:

The agreed final version of the document will be circulated to all Trusts, Health Authorities and Clinical Commissioning Groups throughout Greater Manchester. It will also be made available on SRFT intranet site.

Plans for Updating the Guideline:

After a suitable timeframe the effect of the guideline will be reviewed and amended as necessary.

Key Recommendation:

All patients with proven cerebral venous thrombosis should be referred to, and managed in the Greater Manchester Neurosciences Centre admitting to the Acute Neurology Unit or, if there is no available bed, to the Acute Stroke Unit.

List of abbreviations

AED	Anti epileptic drug
ANU	Acute neurology unit
ASU	Acute stroke unit
CNS	Central nervous system
CRP	C-reactive protein
CT	Computed tomography
CTV	CT Venogram
CVT	Cerebral venous thrombosis
DGH	district general hospital
DVT	Deep vein thrombosis
ENT	Ear, nose and throat
ESR	Erythrocyte sedimentation rate
EVD	External ventricular drain
FBC	Full blood count
GCS	Glasgow Coma Scale
GMNC	Greater Manchester Neurosciences Centre
GRE	Gradient echo
HIV	Human immunodeficiency virus
ICH	Intracranial harmorrhage
ICP	Intracranial pressure
INR	International normalised ratio
LMWH	Low molecular weight heparin
LP	Lumbar puncture
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venogram
NHS	National Health Service
OCP	Oral contraceptive pill
PE	Pulmonary embolus
SRFT	Salford Royal NHS Foundation Trust
SWI	Susceptibility weighted imaging
VPS	Ventriculo-peritoneal shunt
VTE	Venous thromboembolism

Background

Cerebral venous thrombosis (CVT) is a complex disease affecting all age groups. The aetiology is often multifactorial and presentation is varied both in terms of severity and clinical syndrome. The majority (56%) of patients present acutely within 48 hours of symptom onset. A large minority of patients (37%) present in a sub-acute phase (48hrs to 30 days) and a small minority (7%) with a chronic phase (>30 days). The incidence of CVT is variably reported as from 0.5 (Bousser and Ferro, Cerebral venous thrombosis: an aupdate. 2007) to 1.2 (Janghirbani, et al. 2008) per 100,000. For greater Manchester this would translate to 14 to <50 cases per annum. The majority of cases (78%) occurs in the <50 years age group (Canhao, et al. 2005).

Given the broad range of presentations both in terms of syndromes and timescales, and the complexities of management, international guidelines suggest that care in an organised environment is optimal (Saposnik, et al. 2011), and in Greater Manchester this may be most effectively delivered by early access to the Greater Manchester Neurosciences Centre. Organising care in such a centralised way would allow a consistent and high quality care to be provided for each and every patient with this uncommon and difficult to recognise condition.

This document sets out the approach to achieving this aim.

Practice, Evidence and Guideline

1. Recognising patients with cerebral venous thrombosis

1.1. Clinical presentation

1.1.1. Clinical presentation tends to be with one of three types of syndrome

1.1.1.1. Symptoms of raised intracranial pressure (ICP)

1.1.1.2. Focal neurological symptoms

1.1.1.3. Mixed raised pressure and focal symptoms

1.1.2. Symptoms tend to be progressive and diagnostic delay is not uncommon

1.2. Presenting symptoms and signs

1.2.1. Headache is seen in 90% of patients as part of their presentation and is often indicative of raised intracranial pressure (80% of cases). The headache is typically described as diffuse and progresses over days to weeks. 'Thunderclap' headache may also be a presenting feature as can headache with clinical features of migraine. Headache as an isolated symptom has been reported in up to 25% of cases (Patronas, et al. 1981).

1.2.2. Papilloedema is a common finding and represents raised intracranial pressure either from severe venous obstruction, diffuse cerebral oedema, or malignant haemorrhage and infarction and secondary cerebral oedema (associated with lateralising neurological signs).

1.2.3. Diplopia may also be a feature of raised intracranial pressure, a so-called 'false localising sign'

1.2.4. Seizure is frequently seen (approximately 40% of cases) reflecting discrete cortical insult and/or cerebral irritation sometimes demonstrable by electroencephalogram

1.2.5. Other symptoms or combination of symptoms may often give clues as to the location of thrombus.

1.2.5.1. Superior sagittal sinus: Headache, raised ICP, papilloedema, scalp oedema, dilated scalp veins, motor deficits with or without seizures

1.2.5.2. Lateral sinus: Pain in ear/constitutional symptoms if infected, raised ICP, distension of scalp veins, hemianopia, contralateral weakness, aphasia.

1.2.5.3. Deep sinuses: Rapid neurological/conscious deterioration

1.2.5.4. Cortical veins: Rare, typically stroke or seizure

1.2.6. Always check mental state and Glasgow Coma Scale (GCS)

1.2.7. Always check for signs of meningism

1.2.8. Always perform fundoscopy to look for evidence of raised ICP. If ICP is elevated with visual symptoms, close monitoring of visual fields and severity of papilloedema is important (Saposnik, et al. 2011).

1.2.9. Always perform otoscopy to look for evidence of infection

2. Causes of cerebral venous thrombosis

2.1. The causes of CVT are multiple and varied. They often co-exist in the same patient

2.2. Up to 34% of patients have an inherited or acquired prothrombotic condition (Ferro, Canhao and Stam, et al. 2004)

2.2.1. Compared to the general population patients with CVT are more likely to have Protein S/C deficiency (Martinelli, et al. 1998) (Bombeli, Basic and Fehr 2002), antiphospholipid/anticardiolipin antibody (Canhao, et al. 2005), hyperhomocysteinaemia or Factor V leiden deficiency or mutation in the prothrombin G20210A gene (Ventura, et al. 2004)

2.2.2. Late stage pregnancy and early post-partum phase, and oral contraceptive use are also amongst the commoner risk factors in younger women (Martinelli, et al. 1998) (Wilterdink and Easton 2002) (de, et al. 1998)

2.2.3. 7.4% of cases are associated with underlying malignancy (Canhao, et al. 2005).

3. Investigation of suspected cerebral venous thrombosis

3.1. Initial blood screening

3.1.1. Immediate routine blood panel including

3.1.1.1. FBC

3.1.1.2. Renal profile

3.1.1.3. Bone profile

3.1.1.4. Liver profile

3.1.1.5. ESR

3.1.1.6. CRP

3.1.1.7. Clotting studies

3.1.1.8. D-dimer (can be useful if negative unless strong clinical suspicion)

3.1.2. Further blood panel following confirmed diagnosis

3.1.2.1. Thrombophilia screen

3.1.2.2. Antiphospholipid/anticardiolipin antibody

3.1.2.3. Factor V Leiden and prothrombin G20210A mutation

3.1.2.4. Protein S, Protein C and antithrombin III deficiency testing should be delayed until cessation of anticoagulation therapy

3.1.2.5. Homocysteine

3.1.2.6. HIV

3.2. Imaging studies

3.2.1. Imaging of the cerebral venous sinuses should be considered in the following situations

3.2.1.1. Patient with headache preceding stroke

3.2.1.2. Patients with bilateral infarction/haemorrhage

3.2.1.3. Patients with infarction crossing arterial territory

3.2.1.4. Patients with features of raised ICP (headache/papilloedema/VI or III nerve palsy)

3.2.1.5. Progressive/Thunderclap/new atypical headache with known thromboembolic risk

3.2.1.6. Altered mentation where bilateral thalamic lesions are suspected

3.2.2. Imaging should be carried out urgently after the diagnosis of cerebral venous thrombosis is considered

3.2.3. For practical reasons most centres will have easier access to CT brain and CT venogram (CTV) especially during on-call hours. CTV is preferable to plain CT and contrast due to variation in clot density early in the disease (Saposnik, et al. 2011).

3.2.4. Magnetic resonance imaging (MRI) and MR venogram may be preferred in certain instances, such as need to avoid irradiation, need for more sensitive brain parenchymal imaging.

3.2.5. In chronic cases, gradient echo (GRE) or susceptibility weighted imaging (SWI) may be useful to demonstrate low signal in thrombosed sinuses (Saposnik, et al. 2011)

3.2.6. Invasive cerebral angiography/direct venography, by discussion with the vascular Neuroradiologists, is usually only considered where radiological intervention is an option or in the rare instances where CTV/MRV are inconclusive

3.2.7. Follow up imaging in the acute phase is indicated in the following circumstances

3.2.7.1. For patients who are deteriorating despite optimal therapy

3.2.7.2. For patients previously diagnosed who present with symptoms and signs suggestive of recurrence

3.2.8. Most patients (84%) recanalise within 4 months (Baumgartner, et al. 2003)and repeat imaging is indicated within 3-6 months after initiation of anticoagulation (Saposnik, et al. 2011), though recanalization appears to have no bearing on outcome in adult patients (Strupp, et al. 2002)

4. Cerebrospinal fluid analysis

4.1. Lumbar puncture is not typically helpful in the diagnosis of cases with focal neurology and confirmed CVT (Saposnik, et al. 2011). LP may be considered appropriate in some cases, particularly those in whom intracranial infection is considered a possible aetiology

4.2. Lumbar puncture may also demonstrate abnormalities consistent with CNS inflammatory disease as a possible aetiological factor

4.3. If lumbar puncture is performed, opening pressure should always be taken

4.4. Lumbar puncture should be avoided if a large lesion with mass effect is found on imaging or with evidence of severe cerebral oedema with evidence of transtentorial herniation

4.5. Though unrelated to the setting of CVT, the American society of regional anaesthesia and pain medicine has published evidence-based guidelines for anticoagulation during spinal/epiduralragional anaesthesia (Horlocker, et al. 2010). Applying these principles, if lumbar puncture is performed, intravenous unfractionated heparin should be commenced no sooner than 1 hour after completion of LP. Once it is decided no further invasive procedure is necessary this can be converted to sub-cutaneous LMWH

4.6. If repeat lumbar puncture is thought likely to be needed then patients should be given intravenous unfractionated heparin so this can be stopped at short notice

5. Treatment of cerebral venous thrombosis

5.1. Once the diagnosis of cerebral venous thrombosis is secured treatment should be initiated as swiftly as possible

5.2. Organised care is one of the most effective interventions to reduce morbidity and mortality after stroke (Collaboration, Organised inpatient (stroke unit) care for stroke 2007) (Collaboration, How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials 1997) and it therefore seems reasonable to apply this to cerebral venous thrombosis

5.2.1. The Greater Manchester Policy is for all such cases to be transferred to the Greater Manchester Neurosciences Centre.

5.3. Treatment of any acute underling cause should be a priority (e.g. an intracranial infection)

5.4. Anticoagulation therapy

5.4.1. Early anticoagulation is indicated in most cases to prevent clot propagation, promote recanalization and prevent distal thromboembolism

5.4.2. There are only two randomised controlled trials of anticoagulation in CVT and meta-analysis demonstrated a non-statistically significant benefit in terms of death/dependency for anticoagulation (de Bruijn and Stam 1999) (Einhaupl, Villringer and Meister 1991)

5.4.3. Anticoagulation appears safe in this patient group, even in the setting of intracranial haemorrhage (Stam, deBruijm and deVeber 2001)

5.4.4. Low molecular weight heparin (LMWH) is the preferred option in uncomplicated patients (Einhaupl, et al. 2010). A meta-analysis for extracranial venous thromboembolism found a superiority for LMWH with less bleeding risk (Van Dongen, et al. 2004) though there are perceived advantages of UFH for critically ill patients in terms of short bleeding time and reversal.

5.4.5. LMWH should be used during pregnancy (Kearon, et al. 2008) (Saposnik, et al. 2011).

5.5. Thrombolytic therapy

5.5.1. Thrombolytic (mechanical or chemical) therapy may be considered for those patients who are worsening despite adequate anticoagulation. Data are largely anecdotal though suggest more benefit may be achieved in comatose/critically ill patients (Canhao, Falcao and Ferro, Thrombolytics for cerebral sinus thrombosis: a systematic review 2003).

5.5.2. Chemical thrombolysis is not recommended in those who already have ICH or those with impending herniation (Einhaupl, et al. 2010).

5.5.3. Mechanical thrombectomy may be discussed with an interventional neuroradiologist where a patient is worsening despite adequate anticoagulation but there are no randomised controlled trials currently to support its use.

5.6. Management of raised intracranial pressure

Optimum management of raised ICP in the setting of CVT is not known. It may depend on the aetiology of raised ICP (generalised cerebral oedema vs 'malignant' infarction/haemorrhage vs hydrocephalus) but several principles may be followed:

5.6.1. Adequate anticoagulation promotes venous recanalisation and therefore pressure reduction

5.6.2. Lumbar puncture may be considered to reduce ICP

5.6.2.1. There is no randomised controlled evidence to recommend this as standard of practice

5.6.2.2. Performing lumbar puncture may lead to delay in anticoagulation as recommendations are for LMWH starting up to 24 hours after dural puncture (Horlocker, et al. 2010)

5.6.2.3. Repeated LP may be considered for pressure management but this would result in interrupted anticoagulation

5.6.3. Acetazolamide is used for ICP reduction in other conditions but it's role in CVT is not proven by trials (Ferro and Canhao, Acute treatment of cerebral venous and dural sinus thrombosis 2008)

5.6.4. Corticosteroids are not efficacious in CVT and in fact may harm the ischaemic brain (Canhao, Cortesao, et al. 2008)

5.6.5. Anti-oedema therapies may be considered (head elevation, hyperventilation, iv osmotic diuretics (with caution due to impaired clearance in venous outflow obstruction) (26)

5.6.6. Surgical decompressive craniectomy may be considered in certain groups of patients and in a small review of individual cases was associated with a favourable outcome in 86% (Coutinho, et al. 2009)

5.6.6.1. Indication may include large infarction, haemorrhage, or global oedema

5.6.6.2. Decompressive craniectomy is efficacious in select arterial stroke patients with malignant MCA territory infarction and though there is no specific evidence for CVT it may be appropriate to consider in select cases. However, neuronal damage is less pronounced in CVT (Villringer, Mehraein and Einhaupl 1994) and their overall prognosis is better than for acute ischaemic stroke (Vahedi, et al. 2007)

5.6.7. Communicating hydrocephalus may occur in 6.6% of cases of CVT

5.6.7.1. Arachnoid granulations function can become impaired in superior sagittal and lateral dural sinus thrombosis (Wasay, et al. 2008) (Bousser and Russell, Pathology and pathogenesis of venous infarction 1997)

5.6.7.2. In other cases, particularly internal cerebral venous thrombosis, haemorrhage into the ventricles may result in obstructive hydrocephalus.

5.6.7.3. Due to the potentially already high intracranial pressure, early neurosurgical opinion is advised for consideration of clot evacuation/ventriculostomy/EVD/VPS as lesser degrees of ventricular enlargement may be more significant

5.6.8. In refractory cases, VP shunt may be considered

5.6.9. In cases where vision is threatened ophthalmic opinion should be sought and optic nerve fenestration can be considered.

5.7. Management of other complications

5.7.1. Seizures are common in adult patients and up to 40% of cases present with seizures

5.7.1.1. Early seizures are 4 fold more likely with supratentorial parenchymal lesions but a 70% reduction in likelihood of seizure seen in one study (Ferro, Canhao and Bousser, et al. 2008) was not statistically significant, and prophylactic AED therapy is not recommended.

5.7.1.2. AED therapy is recommended in patients with CVT who have suffered a seizure. The duration of AED therapy to recommend is unclear (Einhaupl, et al. 2010).

5.7.1.3. Less than 10% of cases develop late seizures and late seizures are not a predictor of outcome (Ferro, Correia, et al., Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport). Seizures in cerebral vein and dural sinus thrombosis 2003)

5.7.1.4. Late seizures are more common in those with ICH at presentation but almost all occur within the first year (Preter, et al. 1996) (Ferro, Correia, et al., Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT). Seizures in cerebral vein and dural sinus thrombosis 2003)

5.7.2. Headache is a common feature seen in long term follow up in up to 55% of patients

5.7.2.1. Headache tends to be of the migrainous or tension type

5.7.2.2. It may require further vascular imaging or lumbar puncture to exclude recurrent thrombosis or raised ICP, respectively.

5.7.3. Thromboembolism

5.7.3.1. In hypercoagulable states thrombosis may be seen in other sites (limb DVT, vena cava, renal vein, retinal vein) and awareness should prompt appropriate investigation (e.g. worsening renal function)

5.7.3.2. Distal embolism can result in pulmonary embolus

6. Clinical course

6.1. Neurological deterioration can occur in up to 23% of patients ranging from worsening headache to death

6.2. Patients with depressed conscious state on admission are more likely to deteriorate and a third of those who deteriorate will have new parenchymal lesion on brain imaging

6.3. The overall death/dependency rates for patients is approximately 15% in prospective cohort registries and studies

6.3.1. Death in the acute phase of the illness is reported to occur in between 3% and 15% of cases (Dentali, Crowther and Ageno 2006)

6.3.2. The main cause of death in the acute phase is trans-tentorial herniation due to a large haemorrhagic lesion. Multiple lesions/diffuse oedema is the next most frequent cause followed by status epilepticus, medical complications and PE

6.3.3. Death at 30 days occurs in between 3.4% (Canhao, et al. 2005)and 13% (Boncoraglio, et al. 2004)of cases

6.3.4. Deaths after the acute phase are predominantly related to underlying conditions such as malignancy

6.4. Risk stratification scores to predict outcome are available though not used widely (Koopman, et al. 2009)

6.5. The following factors have been reported to be poorer prognostic factors:

6.5.1. Age >37

6.5.2. Male sex
6.5.3. Coma/decreased conscious state
6.5.4. Severity of neurological deficit
6.5.5. Encephalopathy
6.5.6. Intracerebral haemorrhage
6.5.7. Venous infarction
6.5.8. Straight sinus thrombosis
6.5.9. Seizures
6.5.10. CNS infection
6.5.11. Underlying malignancy
6.5.12. Hereditary coagulopathy

6.6. Recurrence of cerebral venous thrombosis

6.6.1. The overall risk of recurrence of any thrombotic event (CVT or systemic) after a CVT is approximately 6.5% (Saposnik, et al. 2011)

6.6.2. The risk of recurrent CVT is between 1.3 to 2.2% within 16 months (Canhao, et al. 2005) (Messe, et al. 2009)

6.6.3. Preventing recurrent CVT

6.6.3.1. Long term anticoagulation for secondary prevention of VTE/CVT should be considered as for other venous thrombo-embolic diseases (Kearon, et al. 2008)

6.6.3.2. Testing for prothrombotic conditions can be beneficial for the management of patients with CVT

6.6.3.2.1. Testing for protein C, protein S, and antithrombin deficiency is generally indicated 2 to 4 weeks after cessation of anticoagulation. There is a very limited value of testing in the acute setting or in patients taking warfarin

6.6.3.3. For patients with provoked CVT (associated with a transient risk factor), anticoagulation may be continued for 3 to 6 months, with a target INR of 2.0 to 3.0

6.6.3.4. For patients with unprovoked CVT, anticoagulation may be continued for 6 to 12 months, with a target INR of 2.0 to 3.0

6.6.3.5. For patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia, indefinite anticoagulation may be considered, with a target INR of 2.0 to 3.0

6.7. Cerebral venous thrombosis and future pregnancy

6.7.1. For CVT associated with pregnancy the risk of recurrence is low

6.7.2. In the absence of other predisposing factors, future pregnancy is not contraindicated

6.7.3. Prophylaxis with LMWH would be reasonable for future pregnancies (Saposnik, et al. 2011)

References

Baumgartner, R W, A Struder, M Arnold, and D Georgiadis. “Recanalisation of cerebral venous thrombosis.” *Journal of Neurology Neurosurgery and Psychiatry*, 2003: 459-461.

Bombeli, T, A Basic, and J Fehr. “Prevalence of hereditary thrombophilia in patients with thrombosis in different venous systems.” *American Journal of Haematology*, 2002: 126-132.

Boncoraglio, G, et al. “Hyperhomocysteinemia and other thrombophilic risk factors in 26 patients with cerebral venous thrombosis.” *European Journal of Neurology*, 2004: 405-409.

Bousser, M G, and J M Ferro. “Cerebral venous thrombosis: an aupdate.” *Lancet Neurology*, 2007: 162-170.

Bousser, M G, and R R Russell. “Pathology and pathogenesis of venous infarction.” In *Cerebral Venous Thrombosis*, by M G Bousser, 20-21. Paris: WB Saunders Company, 1997.

Canhao, J M Ferro, A G Lindgren, M G Bousser, J Stam, and F Barinagarrementeria. “ISCVT Investigators. Causes and predictors of death in cerebral venous thrombosis.” *Stroke*, 2005: 1720-1725.

Canhao, P, et al. “ISCVT Investigators. Are steroids useful to treat cerebral venous thrombosis?” *Stroke*, 2008: 105-110.

Canhao, P, F Falcao, and J M Ferro. “Thrombolytics for cerebral sinus thrombosis: a systematic review.” *Cerebrovascular Diseases*, 2003: 159-166.

Collaboration, Stroke Unit Trialists'. “How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials.” *Stroke*, 1997: 2139-2144.

Collaboration, Stroke Unit Trialists'. “Organised inpatient (stroke unit) care for stroke.” *Cochrane Database Systematic Review*, 2007: CD000197.

Coutinho, J M, C B Majoie, B A Coert, and J Stam. “Decompressive hemicraniectomy in cerebral sinus thrombosis: consecutive case series and review of the literature.” *Stroke*, 2009: 2233.

de Bruijn, S F, and J Stam. “Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis.” *Stroke*, 1999: 484-488.

de, Bruijn S, J Stam, M M Koopman, and J P Vandenbroucke. “the Cerebral Venous Sinus Thrombosis Study Group. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in carriers of hereditary prothrombotic conditions.” *British Medical Journal*, 1998: 589-592.

Dentali, F, M Crowther, and W Ageno. “Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis.” *Blood*, 2006: 2766-2773.

Einhaupl, K M, A Villringer, and W Meister. “Heparin treatment in sinus venous thrombosis.” *Lancet*, 1991: 597-600.

Einhaupl, K, et al. “EFNS guideline on the treatment of cerebrl venous and sinus thrombosis in adult patients.” *European Journal of Neurology*, 2010: 1229-1235.

Ferro, J M, and P Canhao. “Acute treatment of cerebral venous and dural sinus thrombosis.” *Current Treatment Options in Neurology*, 2008: 126-137.

Ferro, J M, M Correia, M J Rosas, A N Pinto, and G Neves. “Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport). Seizures in cerebral vein and dural sinus thrombosis.” *Cerebrovascular Diseases*, 2003: 78-83.

Ferro, J M, M Correia, M J Rosas, A N Pinto, and G Neves. “Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT). Seizures in cerebral vein and dural sinus thrombosis.” *Cerebrovascular Diseases*, 2003: 78-83.

Ferro, J M, P Canhao, J Stam, M G Bousser, and F Barinagarrementeria. “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: 664-670.

Ferro, J M, P Canhao, M G Bousser, J Stam, and F Barinagarretementeria. “ISCVT Investigators. Early seizures in cerebral vein and dural sinus thrombosis: risk factors and role of antiepileptics.” *Stroke*, 2008: 1152-1158.

Horlocker, T T, et al. “Regional anesthesia in the patient receiving antithrobotic or thrombolytic therapy. American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition).” *Regional Anaesthesia and Pain Medicine*, 2010: 64.

Janghirbani, M, M Zare, M Saadatnia, S A Mousavi, M Mojarrad, and E Asgari. “Cerebral vein and dural sinus thrombosis in adults in Isfahan, Iran: freuqncy and seasonal variation.” *Acta Neurol Scand*, 2008: 117-121.

Kearon, C, S R Kahn, G Agnelli, S Goldhaber, G E Raskob, and A J Comerota. “Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical PRactice Guidelines (8th Edition).” *Chest*, 2008: 454S-545S.

Koopman, K, M Uyttenboogaart, P C Vroomen, J van der Meer, J De Keyser, and G J Luijckx. “Development and validation of a predictive outcome score of cerebral venous thrombosis.” *Journal of Neurological Science*, 2009: 66.

Martinelli, I, E Sacchi, G Landi, E Taioli, F Duca, and P M Mannucci. “High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives.” *New England Journal of Medicine*, 1998: 1793-1797.

Messe, S R, L H Sansing, B L Cucchiara, S T Herman, P D Lyden, and S E Kasner. “CHANT Investigators. Prophylactic antiepileptic drug use is associated with poor outcome following ICH.” *Neurocritical Care*, 2009: 38-44.

Patronas, N J, E E Duda, M Mirfakhraee, and R L Wollmann. “Superior sagittal sinus thrombosis diagnosed by computed tomography.” *Surgical Neurology*, 1981: 11-14.

Preter, M, C Tzourio, A Ameri, and M G Bousser. “Long-term prognosis in cerebral venous thrombosis: follow-up of 77 patients.” *Stroke*, 1996: 243-246.

Saposnik, G, et al. “Diagnosis and management of cerebral venous thrombosis: A statement for healthcare professionals from the American Heart Association/American Stroke Association.” *Stroke*, 2011: 1158-1192.

Stam, J, S F deBruijm, and G deVeber. “Anticoagulation for cerebral sinus thrombosis.” *The Cochrane Database of Systematic Reviews*, 2001: CD002005.

Strupp, M, M Covi, K Seelos, M Dichgans, and T Brandt. “Cerebral venous thrombosis: correlation between recanalization and clinical outcome: a lon-term follow-up of 40 patients.” *Journal of Neurology*, 2002: 1123-1124.

Vahedi, K, et al. “DECIMAL, DESTINY, and HAMLET Investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials.” *Lancet Neurology*, 2007: 215-222.

Van Dongen, C J, A G van den Belt, M H Prins, and A W Lensing. “Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism.” *The Cochrane Database of Systematic Reviews*, 2004: CD001100.

Ventura, P, M Cobelli, M Marietta, R Panini, M C Rosa, and G Salvioli. “Hyperhomocysteinemia and other newly recognized inherited coagulation disorders (factor V Leiden and prothrombin gene mutation) in patients with idiopathic cerebral vein thrombosis.” *Cerebrovascular Diseases*, 2004: 153-159.

Villringer, A, S Mehraein, and K M Einhaupl. “Pathophysiological aspects of cerebral sinus venous thrombosis.” *Journal of Neuroradiology*, 1994: 72-80.

Wasay, M, et al. “Cerebral venous thrombosis: analysis of a multicenter cohort from the United States.” *Journal of Stroke and Cerebrovascular Diseases*, 2008: 49-54.

Wilterdink, J L, and J D Easton. “Cerebral ischaemia in pregnancy.” *Advances in Neurology*, 2002: 51-62.

Baumgartner, R W, A Struder, M Arnold, and D Georgiadis. “Recanalisation of cerebral venous thrombosis.” *Journal of Neurology Neurosurgery and Psychiatry*, 2003: 459-461.

Bombeli, T, A Basic, and J Fehr. “Prevalence of hereditary thrombophilia in patients with thrombosis in different venous systems.” *American Journal of Haematology*, 2002: 126-132.

Boncoraglio, G, et al. “Hyperhomocysteinemia and other thrombophilic risk factors in 26 patients with cerebral venous thrombosis.” *European Journal of Neurology*, 2004: 405-409.

Bousser, M G, and J M Ferro. “Cerebral venous thrombosis: an aupdate.” *Lancet Neurology*, 2007: 162-170.

Bousser, M G, and R R Russell. “Pathology and pathogenesis of venous infarction.” In *Cerebral Venous Thrombosis*, by M G Bousser, 20-21. Paris: WB Saunders Company, 1997.

Canhao, J M Ferro, A G Lindgren, M G Bousser, J Stam, and F Barinagarrementeria. “ISCVT Investigators. Causes and predictors of death in cerebral venous thrombosis.” *Stroke*, 2005: 1720-1725.

Canhao, P, et al. “ISCVT Investigators. Are steroids useful to treat cerebral venous thrombosis?” *Stroke*, 2008: 105-110.

Canhao, P, F Falcao, and J M Ferro. “Thrombolytics for cerebral sinus thrombosis: a systematic review.” *Cerebrovascular Diseases*, 2003: 159-166.

Collaboration, Stroke Unit Trialists'. “How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials.” *Stroke*, 1997: 2139-2144.

Collaboration, Stroke Unit Trialists'. “Organised inpatient (stroke unit) care for stroke.” *Cochrane Database Systematic Review*, 2007: CD000197.

Coutinho, J M, C B Majoie, B A Coert, and J Stam. “Decompressive hemicraniectomy in cerebral sinus thrombosis: consecutive case series and review of the literature.” *Stroke*, 2009: 2233.

de Bruijn, S F, and J Stam. “Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis.” *Stroke*, 1999: 484-488.

de, Bruijn S, J Stam, M M Koopman, and J P Vandenbroucke. “the Cerebral Venous Sinus Thrombosis Study Group. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in carriers of hereditary prothrombotic conditions.” *British Medical Journal*, 1998: 589-592.

Dentali, F, M Crowther, and W Ageno. “Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis.” *Blood*, 2006: 2766-2773.

Einhaupl, K M, A Villringer, and W Meister. “Heparin treatment in sinus venous thrombosis.” *Lancet*, 1991: 597-600.

Einhaupl, K, et al. “EFNS guideline on the treatment of cerebrl venous and sinus thrombosis in adult patients.” *European Journal of Neurology*, 2010: 1229-1235.

Ferro, J M, and P Canhao. “Acute treatment of cerebral venous and dural sinus thrombosis.” *Current Treatment Options in Neurology*, 2008: 126-137.

Ferro, J M, M Correia, M J Rosas, A N Pinto, and G Neves. “Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport). Seizures in cerebral vein and dural sinus thrombosis.” *Cerebrovascular Diseases*, 2003: 78-83.

Ferro, J M, M Correia, M J Rosas, A N Pinto, and G Neves. “Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT). Seizures in cerebral vein and dural sinus thrombosis.” *Cerebrovascular Diseases*, 2003: 78-83.

Ferro, J M, P Canhao, J Stam, M G Bousser, and F Barinagarrementeria. “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: 664-670.

Ferro, J M, P Canhao, M G Bousser, J Stam, and F Barinagarretementeria. “ISCVT Investigators. Early seizures in cerebral vein and dural sinus thrombosis: risk factors and role of antiepileptics.” *Stroke*, 2008: 1152-1158.

Horlocker, T T, et al. “Regional anesthesia in the patient receiving antithrobotic or thrombolytic therapy. American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition).” *Regional Anaesthesia and Pain Medicine*, 2010: 64.

Janghirbani, M, M Zare, M Saadatnia, S A Mousavi, M Mojarrad, and E Asgari. “Cerebral vein and dural sinus thrombosis in adults in Isfahan, Iran: freuqncy and seasonal variation.” *Acta Neurol Scand*, 2008: 117-121.

Kearon, C, S R Kahn, G Agnelli, S Goldhaber, G E Raskob, and A J Comerota. “Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical PRactice Guidelines (8th Edition).” *Chest*, 2008: 454S-545S.

Koopman, K, M Uyttenboogaart, P C Vroomen, J van der Meer, J De Keyser, and G J Luijckx. “Development and validation of a predictive outcome score of cerebral venous thrombosis.” *Journal of Neurological Science*, 2009: 66.

Martinelli, I, E Sacchi, G Landi, E Taioli, F Duca, and P M Mannucci. “High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives.” *New England Journal of Medicine*, 1998: 1793-1797.

Messe, S R, L H Sansing, B L Cucchiara, S T Herman, P D Lyden, and S E Kasner. “CHANT Investigators. Prophylactic antiepileptic drug use is associated with poor outcome following ICH.” *Neurocritical Care*, 2009: 38-44.

Patronas, N J, E E Duda, M Mirfakhraee, and R L Wollmann. “Superior sagittal sinus thrombosis diagnosed by computed tomography.” *Surgical Neurology*, 1981: 11-14.

Preter, M, C Tzourio, A Ameri, and M G Bousser. “Long-term prognosis in cerebral venous thrombosis: follow-up of 77 patients.” *Stroke*, 1996: 243-246.

Saposnik, G, et al. “Diagnosis and management of cerebral venous thrombosis: A statement for healthcare professionals from the American Heart Association/American Stroke Association.” *Stroke*, 2011: 1158-1192.

Stam, J, S F deBruijm, and G deVeber. “Anticoagulation for cerebral sinus thrombosis.” *The Cochrane Database of Systematic Reviews*, 2001: CD002005.

Strupp, M, M Covi, K Seelos, M Dichgans, and T Brandt. “Cerebral venous thrombosis: correlation between recanalization and clinical outcome: a lon-term follow-up of 40 patients.” *Journal of Neurology*, 2002: 1123-1124.

Vahedi, K, et al. “DECIMAL, DESTINY, and HAMLET Investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials.” *Lancet Neurology*, 2007: 215-222.

Van Dongen, C J, A G van den Belt, M H Prins, and A W Lensing. “Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism.” *The Cochrane Database of Systematic Reviews*, 2004: CD001100.

Ventura, P, M Cobelli, M Marietta, R Panini, M C Rosa, and G Salvioli. “Hyperhomocysteinemia and other newly recognized inherited coagulation disorders (factor V Leiden and prothrombin gene mutation) in patients with idiopathic cerebral vein thrombosis.” *Cerebrovascular Diseases*, 2004: 153-159.

Villringer, A, S Mehraein, and K M Einhaupl. “Pathophysiological aspects of cerebral sinus venous thrombosis.” *Journal of Neuroradiology*, 1994: 72-80.

Wasay, M, et al. “Cerebral venous thrombosis: analysis of a multicenter cohort from the United States.” *Journal of Stroke and Cerebrovascular Diseases*, 2008: 49-54.

Wilterdink, J L, and J D Easton. “Cerebral ischaemia in pregnancy.” *Advances in Neurology*, 2002: 51-62.

Appendices