Summary and general discussion
Cerebral venous thrombosis (CVT) is a distinct type of stroke that was described for the first time almost 200 years ago. In contrast to arterial stroke, most adult patients with CVT are in their thirties or forties and less than 10% are over the age of 65. Because of gender specific risk factors (pregnancy, puerperium and oral contraceptives), the condition affects women three times more often than men. Headache is the most common symptom, present in 90% of patients. Other frequent signs and symptoms are papilledema, seizures and focal neurological deficits. A venous infarct, often hemorrhagic, is found in approximately half of all patients. Anticoagulation with therapeutic dose of heparin is the primary treatment. This thesis describes the results of studies we performed on the epidemiology, diagnosis and treatment of CVT.

Part I: Epidemiology and diagnosis of cerebral venous thrombosis

In chapter 2 we present new evidence about the incidence of CVT among adults. Until now, estimates of the incidence ranged from 0.2 to 0.5 per 100,000. These figures were based on an extrapolation of old mortality data and therefore inaccurate. We performed a retrospective cross-sectional study among all 19 hospitals located in 2 Dutch provinces, serving 3.1 million people. By hand searching the medical records of potential patients, we identified adult CVT cases admitted during 3 years (between January 1st 2008 and December 31st 2010). Patients who did not live in one of the provinces, or in whom the diagnostic confirmation did not meet our predefined standard were excluded. Among 9270 potential cases, we identified 94 new cases of CVT in three years. This gives an incidence of 1.32 per 100,000 person-years (95% CI 1.06 to 1.61). Our study shows that the incidence of CVT among adults is higher than previously believed.

In chapter 3, we used data of the international study on cerebral vein and dural sinus thrombosis (ISCVT), a multi-center prospective observational study, to study gender specific differences in clinical presentation, etiology and outcome of CVT. 465 out of a total of 624 patients were women (75%). A gender specific risk factor (GSRF: oral contraceptives, pregnancy, puerperium or hormonal replacement therapy) was present in 65% of women. Women were significantly...
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younger, more often had headache at presentation and had a better prognosis than men (complete recovery 81% vs. 71%, p=0.01). The latter was caused by a better outcome in female patients with a GSRF (complete recovery 85% vs. 72% for women with and without a GSRF, respectively). Logistic regression analysis confirmed that the absence of a GSRF is an independent predictor of poor outcome in women (odds ratio 3.7, CI 1.9-7.4). Possible explanations for this observation include a younger age and different risk factor profile of women with a GSRF.

Intracerebral hemorrhages occur in 40% of patients with CVT. In chapter 4, we examined whether small juxta cortical hemorrhages (JCH) are characteristic for CVT and studied their radiological and pathological properties. We identified all patients with CVT and an intracerebral hemorrhage at baseline admitted to our hospital between 2000 and 2010 (prospectively from July 2006). A JCH was defined as a small hemorrhage (diameter < 20 mm), located in the white matter just below the cortex. To determine the specificity of JCHs for CVT, we examined the frequency of JCHs in a control group of patients of similar age with an intracerebral hemorrhage not related to CVT. 53 of the 114 patients with CVT had an intracerebral hemorrhage. One or more JCHs were present in 14/53 (26%) of them. The remaining 39 had other kinds of hemorrhages. Papilloedema was more common among patients with a JCH compared to patients with other types of hemorrhages (44% vs. 9%, p=0.01). All patients with a JCH except one (93%) had thrombosis of the superior sagittal sinus, compared to 49% of patients with CVT and other kinds of hemorrhages (p=0.004). Re-analysis of the cerebral imaging results showed that JCHs are confined to the juxta cortical white matter, near the U-fibers, and that they follow the curvature of the cortex. This feature results in a cashew-nut or round appearance, depending on the location of the JCH. We confirmed these findings by histopathologic analysis of the brain of a patient with CVT and JCHs. Among the 196 control patients (spontaneous intracerebral hemorrhage, not caused by CVT) only three patients had a JCH. One of these three controls appeared on re-examination of the imaging results to have had CVT, which had been missed before. The location and the shape of JCHs and their association with thrombosis of the superior sagittal sinus suggest that these hemorrhages probably originate in the arcuate segment of the subcortical vein of the superficial venous system. We concluded that small juxta cortical hemorrhages are a characteristic feature of cerebral venous thrombosis and are rarely encountered in other conditions.
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Chapter 5 is a review of isolated cortical vein thrombosis (ICVT), a subtype of CVT in which there is thrombosis of a cerebral vein without concurrent thrombosis of a major sinus. Due to the rarity of ICVT, little is known of its clinical and radiological manifestations. We performed a systematic review of published data on ICVT. Out of 140 potentially relevant studies, 40 were included in the analysis, with data of 104 patients. All studies were retrospective case reports and case series. Mean age was 40 and 68% were female. The most common symptoms were headache (71%), seizures (57%) and focal neurological deficits (58%). Papilledema was not reported in any patient and increased cerebrospinal fluid pressure was found in only 2 out of 11 patients in whom this was measured. Most cases (71%) were diagnosed with MRI, but conventional angiography was also performed in 45%. Imaging showed a parenchymal brain lesion in 83% and in 21% subarachnoid hemorrhage. 79% of all patients were treated with anticoagulation. The mortality at discharge was 7%. These data show that signs of increased intracranial pressure are less common in ICVT compared to CVT. MRI and in some cases conventional angiography are the most frequently used diagnostic modalities and, similar to CVT, anticoagulation is the most widely used therapy. The mortality is similar to published figures for patients with CVT.

In chapter 6 we examined the apparent decline in mortality of patients with CVT over time in a systematic review of the literature. Studies with 40 patients with CVT or more that reported mortality at discharge or follow-up were eligible. We ranked studies according to the year halfway the period of patient inclusion. Out of 4,585 potentially eligible studies, 74 fulfilled the selection criteria. The number of patients per study varied from 40 to 706 (median 76). Data from 8,829 patients with CVT, included between 1942 and 2012, were analyzed. The average age was 32.9 years and 64.7% were women. There was an inverse correlation between mortality and year of patient recruitment (Pearson’s correlation coefficient -0.72, p<0.001). In a sensitivity analysis the correlation remained statistically significant after exclusion of studies published before 1990, retrospective studies, or single-center studies. The frequency of focal neurological deficits and coma also decreased significantly over time (correlation coefficient -0.50 and -0.52, respectively). These data confirm that there is a clear trend in declining mortality among patients with CVT over time. Possible explanations are improvements in treatment, a change in risk factors, and, most importantly, the identification of less severe cases by improved diagnostic methods.
Part II: Treatment of cerebral venous thrombosis

Chapter 7 is a narrative review of the different treatment options for CVT. Due to the paucity of controlled trials, treatment decisions for these patients often have to be made in the absence of sound evidence. Heparin is considered the mainstay of treatment, supported by data from 2 small trials. Besides anticoagulation, no other aspects of the treatment of CVT have thus far examined in a randomized trial. More invasive treatment options are endovascular thrombolysis and – in some severe cases – decompressive hemicraniectomy. 35-50% of patients suffer from seizures during the acute phase and these should be treated promptly with anti-epileptic drugs. Late seizures usually occur within 6-12 months, mostly in patients who had seizures in the acute phase. Increased intracranial pressure is common in the acute phase, but unless the patient’s vision is threatened, treatment to reduce the pressure is rarely required. Oral anticoagulation with vitamin K antagonists is indicated after the acute phase, for a period of 3 to 12 months. Rarely, in the case of a recurrent thrombosis or some forms of genetic thrombophilia, a longer – or even lifelong – period of treatment is justified.

In chapter 8 we report the results of an international survey of treatment variations in CVT. Ninety-one out of 165 invited physicians (55%) completed our online survey. Ninety-two percent considered heparin the primary therapy and most (64%) used unfractionated, intravenous heparin. Forty-three percent had used endovascular thrombolysis in selected cases, with rt-PA as the most frequently used drug. Our survey showed there is considerable practice variation between physicians in the duration of anticoagulation. Most prefer 6 months, but a significant minority favors a shorter or longer duration. This area of uncertainty is the rationale behind the design of the EXCOA-CVT study (EXtending oral antiCOAgulant treatment after acute Cerebral Vein Thrombosis). EXCOA-CVT is a cluster randomized trial that compares standard (3-6 months) to extended (12 months) duration of anticoagulation. The frequency of recurrent venous thrombotic events is the primary efficacy endpoint and major hemorrhagic complications the principal safety endpoint of the trial. The trial is expected to start in January 2014 (excoa-cvt.com).
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Anticoagulation

Chapter 9 is our recent update of the Cochrane meta-analysis about the effectiveness and safety of anticoagulant therapy in patients with CVT. Unconfounded randomized controlled trials in which anticoagulant therapy was compared with placebo or open control were eligible for inclusion in the meta-analysis. CVT had to have been confirmed by MRI-venography, CT-venography or conventional angiography. We included two small trials involving 79 patients. One trial (20 patients) examined the efficacy of intravenous, adjusted dose unfractionated heparin. The other trial (59 patients) examined high dose, body weight adjusted, subcutaneous, low-molecular weight heparin (nadroparin). Two trials were excluded from the meta-analysis: one because it has been published only as an abstract and the other because the diagnosis of CVT was not established by the predefined criteria. Anticoagulant therapy was associated with a pooled relative risk of death of 0.33 (95% confidence interval (CI) 0.08 to 1.21) and of death or dependency of 0.46 (95% CI 0.16 to 1.31). The absolute reduction in the risk of death or dependency by heparin treatment was 13% (95% CI 30% to -3%). No new intracerebral hemorrhages were observed in patients treated with heparin. Instead, in the trial by Einhaupl, follow-up imaging showed new intracerebral hemorrhages in 3 of the 10 patients in the placebo arm, although the paper fails to report if these were symptomatic.1 Two patients in the placebo arms (one in each trial) had a diagnosis of probable pulmonary embolism (one fatal). Before the use of heparin, pulmonary embolism was a well known complication of CVT2, but nowadays it is rarely reported.3

Based upon the limited evidence available in the meta-analysis, anticoagulant treatment for CVT appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency. Although the estimated pooled risk reductions did not reach statistical significance, patients and doctors may be reluctant to embark upon a new trial in adult patients that includes a placebo group. International guidelines recommend the use of heparin in patients with CVT, regardless of the presence of baseline intracerebral hemorrhagic lesions.4,5 Most physicians concur with these guidelines and consider heparin the primary treatment for CVT6. Some have questioned7,8 or downright criticized this strategy, stating there is insufficient evidence for its efficacy and safety.9,10
Which type of heparin to choose?
Neither the guideline of the European Federation of Neurological Societies nor that of the American Stroke Association gives an explicit recommendation on which type of heparin to use: low-molecular weight heparin (LMWH) or unfractionated heparin (UFH). Most neurologists appear to favor UFH (chapter 8). Data from large randomized trials in deep vein thrombosis, however, have unequivocally shown that LMWH is more effective and – more importantly in the case of CVT – results in less hemorrhagic complications than UFH. In chapter 10 we examined the effect on clinical outcome of each type of heparin in patients with CVT who were included in the ISCVT study. Patients not treated with heparin (n=107) and those who sequentially received both types of heparin (n=99) were excluded from the analysis. The primary endpoint was functional independency at 6 months (Rankin score ≤ 2). Secondary endpoints were complete recovery (Rankin 0-1), mortality, and new intracranial hemorrhages. 119 patients received LMWH (28%) and 302 UFH (72%). Significantly more patients treated with LMWH were functionally independent after 6 months, both in univariate analysis (OR 2.1, CI 1.0-4.2) and after adjustment for prognostic factors and imbalances (OR 2.4, CI 1.0-5.7). LMWH was associated with less new intracerebral hemorrhages (adjusted OR 0.29, CI 0.07-1.3), especially in patients with intracerebral lesions at baseline (adjusted OR 0.19, CI 0.04-0.99). There was no difference in complete recovery and mortality.

These results suggest a better efficacy and safety of LMWH over UFH in patients with CVT, although the uncontrolled design of this study has obvious limitations. Recently a randomized trial which directly compared LWMH to UFH in patients with CVT was published. In this open-label study, 66 patients were randomized between fixed dose LMWH (n=34) or adjusted dose intravenous UFH (n=32). Mortality at discharge was significantly higher in UFH treated patients (18.8% vs. 0%, p=0.01). This study, however, did have methodological flaws and the trial was not enrolled in any trial registry prior to start of the study. Also, the difference in outcome is very large; much bigger than one would expect based on data from previous studies, even studies from developing countries. This may partly be explained by the fact that patients in the UFH arm were in a worse clinical condition (lower Glasgow coma scale and more often thrombosis of the deep venous system).
In conclusion, based on the available data in patients with CVT, in combination with data from larger randomized trials in extracerebral venous thromboembolism, a plausible pathophysiological basis and obvious advantages of LMWH in daily practice, we believe that LMWH is preferable above UFH for the initial treatment of patients with CVT. The only patients we still treat with UFH are those with contra-indications for LMWH (e.g. renal failure) and patients who are expected to require decompressive surgery within the next 48 hours, since UFH has a shorter half-life and can be antagonized with protamine sulfate in acute situations.

Endovascular thrombolysis
Over the past few years, various researchers concluded that the scanty evidence for the efficacy and safety of endovascular thrombolysis for CVT warrants a randomized trial.\textsuperscript{15-17} To this end we launched the TO-ACT trial (Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis). The rationale and design of this study are addressed in chapter 11. TO-ACT is a prospective, randomized, open-label, blinded endpoint (PROBE) trial. Patients with CVT are eligible if they have a high probability of poor outcome and if the responsible physician is uncertain if endovascular thrombolysis or standard anticoagulant treatment is better. A high risk of poor outcome is defined by presence of one or more of the following factors: mental status disorder, coma, intracranial hemorrhagic lesion or thrombosis of the deep cerebral venous system. Inclusion of 164 patients (82 in each treatment arm) provides a power of 80\% to detect a 50\% relative reduction of poor outcomes. Patients are randomized to receive either endovascular thrombolysis or standard therapy (therapeutic doses of heparin). Endovascular thrombolysis consists of local application of rt-PA or urokinase within the thrombosed sinuses and/or mechanical thrombectomy. The primary endpoint is the modified Rankin score (mRS) at 12 months, with a score $\geq 2$ defined as poor outcome. Secondary outcomes are 6 months mRS, mortality and recanalisation rate. Major intra- and extracranial hemorrhagic complications within one week after the intervention are the principal safety outcomes. Results will be analyzed according to the “intention-to-treat” principle. Blinded assessors (physicians or research nurses) not involved in the treatment of the patient will assess endpoints with standardized questionnaires.
The first patient in the TO-ACT trial was randomized in September 2011 and currently 27 patients have been included. There are 11 active centers (5 in Portugal and 6 in the Netherlands) and 2 additional hospitals (Inselspital, Bern, Switzerland and Xuan Wu, Beijing, China) will join shortly. The steering committee is committed to recruit other centers, but due to limited funding and bureaucratic hurdles, this process has been difficult. If we extrapolate the current speed of recruitment, the first interim analysis (after recruitment of 55 patients) is expected in the beginning of 2015. Additional information about the TO-ACT trial is available at www.to-act-trial.org.

Decompressive surgery
Chapters 12, 13 and 14 focus on the efficacy of decompressive hemicraniectomy for patients with severe CVT and impending cerebral herniation. In chapter 12, we report the clinical outcomes of the first 3 CVT cases treated with decompressive surgery in our hospital. Two patients had an excellent outcome. The third patient, who had been comatose for at least twelve hours prior to surgery, died despite the intervention. Chapter 13 is an extension of this project and reports the outcomes of 10 patients, at the time the largest prospective study of this intervention for CVT. The median age of the patients was 41 years (range 26-52). Five patients were comatose before surgery. All patients except one had space-occupying intracranial hemorrhagic infarcts. The median preoperative midline shift was 9 mm (range 3-14). Two patients died from progressive cerebral edema and expansion of the hemorrhagic infarcts. Of the remaining patients, 6 had a good clinical outcome (no disability in 5; minor disability in 1). Chapter 14 describes an international retrospective registry of patients treated with decompressive surgery in 22 centers and a systematic review of all published cases. In total, 69 patients were included, 38 from the registry. Decompressive craniectomy was performed in 45 patients, hematoma evacuation in 7 and both interventions in 17 patients. Eleven patients (15.9%) had died. At last follow up (median 12 months) 39 patients (56.5% of total, 67% of survivors) had a mRS of 0-2 (no or minor disability). Three of the 9 patients with bilateral fixed pupils recovered completely. Only 7% of surviving patients remained severely disabled (mRS 4 or 5). This result is much better than in patients with arterial stroke who need hemicraniectomy. In the pooled analysis of randomized trials for decompressive surgery for ischemic stroke, 45% of the surviving patients in the surgery arm were severely disabled (mRS 4 or 5) at follow-up.18 In conclusion, decompressive
hemicraniectomy can be life-saving and can result in an excellent outcome in patients with severe CVT and impending cerebral herniation.

Of course a randomized controlled trial would offer the highest level of evidence for the benefit of hemicraniectomy for severe CVT. For various reasons, we believe such a trial is not feasible. Only 5 to 10% of patients with CVT would be eligible for randomization. This makes recruitment of a sufficient number of patients almost impossible. In addition there are ethical concerns. Transtentorial herniation is the most frequent cause of early death in patients with CVT\textsuperscript{19, 20} and most patients with clinical and radiological signs of herniation will die if they are not operated.\textsuperscript{21, 22} Compared to this gloomy outlook, the outcome of patients who undergo surgery appears to be so much better that we believe withholding patients this therapy is unethical. The data from chapter 14 provide no ground for the concern that surgery would decrease mortality at the cost of severe disability among the survivors. To acquire more data on decompressive surgery for CVT, an international prospective registry was launched (DECOMPRESS-2, principal investigator Prof J.M. Ferro). Participating centers record clinical and radiological information of consecutive patients with CVT treated by decompressive hemicraniectomy or hematoma evacuation. Clinical recovery and quality of life is measured at 6 and 12 months. The DECOMPRESS-2 registry aims to include 100 patients in the coming years. The first patient was included in January 2012 and as of November 2013 15 patients from 9 hospitals have been included.

Other ongoing research projects
Since 2006, more than 160 patients with CVT have been admitted to the Academic Medical Centre, most of whom were referred in the acute phase by other hospitals. Data on baseline characteristics, radiological findings and clinical recovery of these patients are recorded in a prospective database. Since 2012 we also ask consent from each patient to store citrate plasma and DNA. In addition we collect clinical information and blood from patients who are suspected to have CVT, but in whom this condition was ruled out by CT or MRI venography. Several ongoing research projects are based on these databases. The aim of one of these projects is to identify biomarkers which can help exclude CVT without the need to perform expensive and laborious radiological investigations. The first biomarkers that will be examined are D-dimer – which was already the
focus of several other studies$^{23}$ – and factor XIII activation peptide. This project is a joint effort with colleagues from the Inselspital hospital in Berne, Switzerland (P.I. Prof. Dr. Marcel Arnold) and the department of experimental vascular medicine of the Academic Medical Centre (Prof. Dr. J.C. Meijers). The aim of another study is to identify candidate genes associated with CVT through exome sequencing of a large number of CVT cases and controls. This so-called “BEAST study” (Biorepository to Establish the Aetiology of Sinovenous Thrombosis), is a collaboration of a group of international researchers, chaired by Prof. Dr. Pankaj Sharma (Imperial college, London).$^{24}$ Preliminary results of the first 500 patients are expected beginning of 2014.
Chapter 15

References


