CEREBRAL VENOUS THROMBOSIS
Clinical Characteristics and Factors Affecting Outcome

Sini Hiltunen

ACADEMIC DISSERTATION

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CONTENTS

CONTENTS ......................................................................................................................................................... 4
Abstract ............................................................................................................................................................. 7
Tiivistelmä .......................................................................................................................................................... 9
LIST OF ORIGINAL PUBLICATIONS .................................................................................................................... 10
ABBREVIATIONS ............................................................................................................................................... 11
1 INTRODUCTION ............................................................................................................................................ 13
2 REVIEW OF THE LITERATURE ........................................................................................................................ 14
  2.1 Anatomy and functions of the cerebral venous system ........................................................................ 14
  2.2 Pathophysiology of cerebral venous thrombosis .................................................................................. 15
  2.3 Epidemiology of cerebral venous thrombosis ....................................................................................... 17
  2.4 Etiology and risk factors of cerebral venous thrombosis ...................................................................... 17
    2.4.2 Systemic causes of cerebral venous thrombosis ............................................................................ 19
  2.5 Clinical picture of cerebral venous thrombosis ..................................................................................... 22
    2.5.1 Headache ........................................................................................................................................ 23
    2.5.2 Isolated intracranial hypertension ................................................................................................. 23
    2.5.3 Focal syndrome .............................................................................................................................. 23
    2.5.4 Encephalopathy and decreased level of consciousness ................................................................... 23
  2.6 Diagnosis of cerebral venous thrombosis ............................................................................................. 25
    2.6.1 Radiological diagnosis ..................................................................................................................... 25
    2.6.3 Fibrin D-dimer ................................................................................................................................. 29
    2.6.4 Lumbar puncture ............................................................................................................................ 29
  2.7 Treatment .............................................................................................................................................. 30
    2.7.1 General supportive care ................................................................................................................. 30
    2.7.2 Anticoagulation .............................................................................................................................. 30
    2.7.3 Fibrinolytic therapy and mechanical thrombectomy ..................................................................... 31
    2.7.4 Symptomatic treatment ................................................................................................................. 32
  Infectious cerebral venous thrombosis ................................................................................................... 33
  Rehabilitation .......................................................................................................................................... 33
  2.8 Outcome ................................................................................................................................................ 33
    2.8.1 Mortality ......................................................................................................................................... 33
    2.8.2 Recurrence of venous thrombotic events ...................................................................................... 34
    2.8.3 Recanalization .................................................................................................................................. 35
Abstract

Cerebral venous thrombosis (CVT) is a rare cause of stroke, and it is a unique stroke subtype in patient characteristics, causes, clinical course, treatment, and outcome. This disease is also marked for its diversity. Our knowledge on CVT is still limited.

The aim of this study was to investigate clinical characteristics of this disease, risk-factors for CVT, and to gain information on factors associated with poor outcome. For this Thesis project we established retrospectively a detailed database of clinical and radiological data on all consecutive CVT patients treated at the Helsinki University Hospital from 1987 to 2015. To investigate long-term outcome these patients were invited for a follow-up visit, where detailed outcome data was collected. To gain more robust data on CVT we formed an international collaboration with the Academic Medical Centre in Amsterdam, the Netherlands, and Sahlgrenska University Hospital in Gothenburg, Sweden.

We collected data on 243 patients from the Helsinki CVT registry. Patients were aged from 15 to 82 years, with a median age of 42 years (IQR 26-57). The majority of our patients (60%) were women. Symptom duration was acute (less than 2 days) in 50%, subacute (less than 14 days) in 35%, and chronic (over 2 weeks) in 15% of the patients. Three quarters of our patients had headache, and 65% of patients had focal symptoms or disturbances of consciousness. Magnetic resonance imaging was performed in 89% of the patients, and 49% of the patients had parenchymal lesions, either edema or hemorrhage. Almost all of our patients (97%) were treated with anticoagulation in the acute phase. Mortality in the 6 months following CVT diagnosis was 7.5%.

In our study investigating sinus recanalization, 47% of patients (43/91) had complete recanalization, 34% (31/91) had partial recanalization, and 19% (17/91) had no recanalization of the sinuses at follow-up. Poor recanalization was associated with older age, male gender, and absence of known risk factors or causes. Incomplete recovery from CVT (modified Rankin Scale score 1-6) was more common among patients aged ≥37 years, with chronic onset, and in patients with no recanalization. In multivariate analysis recanalization was not independently associated with incomplete functional recovery.

Fibrin D-dimer was measured in 71 out of 138 patients before initiation of anticoagulation. Low D-dimer (<0.5mg/l) was measured in 12.7%, intermediate D-dimer (0.5-2.9mg/l) in 52.1%, and high D-dimer (>3mg/l) in 35.2% of the patients. Levels of D-dimer were lower in patients with longer symptom duration, and higher when more than one sinus was thrombosed. D-dimer levels were not associated with particular risk factors of CVT, parenchymal lesions in imaging, or with clinical presentation of the disease. Patients with lowered level of consciousness had higher D-dimer levels. We found no statistically significant correlation of D-dimer levels to functional recovery.

Hyperglycemia as a risk factor for poor recovery was investigated in 308 patients (169 patients from Amsterdam and 139 patients from Helsinki). Hyperglycemia (plasma glucose >7.8mmol/l) was present in 21%, and severe hyperglycemia (plasma glucose >11.1mmol/l) in 3% of the patients. Patients with hyperglycemia had a more severe clinical picture of CVT; they were older, more often male, had more impaired consciousness, and more hemorrhagic parenchymal lesions. In multivariate analysis hyperglycemia was independently associated with incomplete recovery and mortality. Severe hyperglycemia carried a 33-fold risk of mortality when compared to normoglycemia.

Our study investigating role of cancer as a risk factor for CVT included 594 cases (243 from Helsinki, 224 from Amsterdam, and 128 from Gothenburg) and 6278 controls. Cancer (including both active cancer and history of cancer) was more often present in the CVT cases than controls. Solid cancer was more prevalent (6% vs. 4%), but especially hematological cancer was more often observed in CVT patients (4% vs. 0.2%). In solid cancer the risk of CVT was clearly elevated in the first year after cancer diagnosis, and moderately later. In hematological cancer the risk was very high in the first year, but later no elevated risk for CVT was found.
Our study investigating long-term outcome after CVT included 161 patients, with a mean follow-up of 39 months. Overall mortality in the study period was 11%, with 4% of deaths attributable to CVT. A large majority of our patients (83%) had good functional outcome (modified Rankin Scale score 0-1). Residual symptoms were reported by 68% of patients; 9% had active epilepsy, 20% reported headaches more often than once a week, 21% reported linguistic problems, and 41% reported neuropsychological problems. When tested with Beck Depression Inquiry, 21% had probable depression. In vocational status analysis we included 121 working-aged patients, 23% were unemployed, and 16% were on permanent disability pension. In univariate analysis all reported symptoms except headache were negatively associated with working status. Major stroke symptoms at admission, and low education level (compulsory education only) were associated with both functional outcome and vocational status in age-and sex-adjusted multivariate analysis.

In conclusion, our CVT cases in Helsinki are in demographical aspects similar to other reported CVT series in high-income countries. Recanalization occurred less often in patients with other known factors associated with poor outcome, but the importance of sinus recanalization to clinical recovery is still unclear and requires further studies. Fibrin D-dimer measurements cannot be reliably used to exclude CVT, and thus do not offer a practical diagnostic algorithm. We established admission hyperglycemia as one of the factors affecting outcome in CVT. Hyperglycemia should be treated in the acute phase of the disease, but the effect of tight glycemic control in CVT patients has not been investigated. We confirmed that newly diagnosed cancer is a major risk factor for CVT. Functional outcome after CVT is good in a large majority of the patients, however residual symptoms are common. Most CVT patients are young and of working age, so even mild residual symptoms that affect working ability are of large personal and socio-economic importance.
Tiivistelmä


Tutkiessamme syöpäsairauteen liittyvää sinutromboosiriskiä aineistomme koostui 594 potilaasta (243 Helsingistä, 224 Amsterdamista ja 128 Göteborgista), kontrolliryhmässä oli 6278 potilaista. Syöpäsairaudet olivat sinustromboosisyöpäympäristöä yleisempiä kuin kortrolliryhmässä, etenkin hematologistien syöpien osalta (4% ja 0.2%). Kiinteissä syöptävyissä sinutromboosin riski oli koholla ensimmäisenä vuonna suoraan ja myöhemmin. Hematologiisissa syövissä riski oli erittäin suuri ensimmäisenä vuonna , mutta sen jälkeen riski eikä ollut suurentunut. Tutkimme sinutromboosin jälkeistä pitkäaikaisennustetta 161 potilaalla. Tutkimuksen keskiäikäinen seuranta-aika oli 39 kuukautta. Kokonaiskuolleisuus oli 11% josta 4% sinutromboosii liittyviä. Vaikka suurin osa (83%) potilaista toipui hyvin (mRS pisteet 0-1) jännösoireita raportoi 68% potilaista. Työhönpaluuta tutkittiin 121 työikäisellä, joista 23% oli työttömänä ja 16% oli työkykylläliittävillä. Monimuuttuja-analyysissä työhönpaluun ja toipumiseen liittyvät merkittävät halvausoireet sairauden alkuvaiheessa (NIHSS >2) sekä pelkkä peruskoulun käyminen. Suuri osa sinutromboosipotilaista on työikäisiä, joten lievätkin jännösoireet ovat merkittäviä työhönpaluun kannalta.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals:


In addition, some unpublished data are presented.

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ABBREVIATIONS

ADC  apparent diffusion coefficient
ALL  acute lymphoblastic leukemia
ASA  American Stroke Association
CEVETIS  Cerebral Vein Thrombosis International Study
CI95  95% confidence interval
CNS  central nervous system
CT  computed tomography
CVT  cerebral venous thrombosis
DWI  diffusion-weighted imaging
DVT  deep vein thrombosis
EFNS  European Federation of Neurological Societies
ESO  European Stroke Organisation
FLAIR  fluid-attenuated inversion recovery
GCS  Glasgow Coma Scale
HRT  hormone replacement therapy
ICD-10  International Classification of Diseases Tenth Revision
ICH  intracerebral hemorrhage
IIH  isolated intracranial hypertension
ISCVT  International Study on Cerebral Venous Thrombosis
IQR  interquartile range
LMWH  low molecular weight heparin
LR  likelihood ratio
LS  lateral sinus
MT  mechanical thrombectomy
MEGA study  Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study
MRI  magnetic resonance imaging
mRS  modified Rankin Scale
MRV  magnetic resonance venography
NIHSS  National Institutes of Health Stroke Scale
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tr>
<td>OC</td>
<td>oral contraceptives</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>SDH</td>
<td>subdural hematoma</td>
</tr>
<tr>
<td>SSS</td>
<td>superior sagittal sinus</td>
</tr>
<tr>
<td>TCD</td>
<td>transcranial Doppler ultrasound</td>
</tr>
<tr>
<td>TOF</td>
<td>time of flight</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractioned heparin</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare cause of stroke that occurs when venous circulation of the brain is occluded. This disease is estimated to cause around one percent of all strokes, but in recent years a rise in CVT incidence has been noted. It is probable that CVT has been an underdiagnosed entity due to the wide variability in the clinical presentation of the disease, and requirement of advanced imaging techniques of the cerebral sinuses [1, 2].

Cerebral venous thrombosis is a disease of the young. In published case series, mean age of the patients is around 40, which is largely different from arterial ischemic stroke and intracerebral hemorrhage [3 -7]. CVT shares many common risk factors with venous thromboembolic disease. Factors shifting the blood coagulation homeostasis toward thrombosis are often found in CVT patients; thrombophilia, malignancies, pregnancy or puerperium, and oral contraceptive (OC) usage [3, 4, 8]. Sex-related risk factors in women; pregnancy, puerperium, OC, and estrogen use, are thought to explain the overrepresentation of women in the CVT population, and shift CVT risk to a younger population. In published series 60% to 80% of CVT patients are women [3-6, 9-11].

Cerebral venous thrombosis as a disease is characterized by variability; in both symptoms and radiological findings. Majority of patients experience headache and it can be accompanied by visual disturbances, encephalopathy signs, seizures, or motor or sensory paresis. Clinical presentation can be divided into isolated intracranial hypertension syndrome (headache with or without nausea and visual symptoms), and focal symptoms (sensory or motor paresis, or seizures). Symptoms can develop gradually in a chronic manner, especially in isolated intracranial hypertension syndrome, or symptom onset can be sudden and stroke like [3, 12, 13]. Thrombosis in the cerebral venous circulation can cause general elevation of intracranial pressure, or focal parenchymal changes such as edema, infarction or hemorrhage through a congestive effect [3, 14]. Acute treatment of choice in CVT is anticoagulation, even in the presence of intracerebral hemorrhage. In recent years interventional treatments have also been investigated [15-17].

Outcome after CVT is also very variable, some patients die while others make a full recovery. Short-term mortality in recent studies in developed countries has been less than 10%. Long-term functional outcome after CVT is considered to be good. In published studies a majority of patients have recovered fully, or with only minor symptoms [3-5, 18, 19].

Our knowledge of the clinical picture of CVT is still imperfect, due to the rarity and high variability of this unique disease. Awareness of possible CVT and minimizing delay in diagnosis is essential. Most of our knowledge is based on small-sized single-center series. [3, 4]. Patients with CVT are mostly young and of working age, and thus optimizing recovery has a large socio-economic effect not only on the personal lives of the patients, but also on a larger national scale. Understanding risks, clinical course of the disease, and factors that affect outcome will further our understanding of this disease.
2 REVIEW OF THE LITERATURE

2.1 Anatomy and functions of the cerebral venous system
The essential function of the venous circulation system in the brain is to drain deoxygenated blood from the brain parenchyma towards the jugular veins and the heart. Venous drainage of blood flow from the brain can be divided into two systems; superficial and deep. Anterior and superior parts of the hemispheres drain into superficial cerebral veins that empty into the superior and inferior sagittal sinuses. Lateral and inferior parts of the hemispheres drain into the transverse sinuses. The anastomotic veins of Labbe and Trolard link superior and inferior parts of the superficial system. The deep system comprises of internal cerebral veins and basal veins (of Rosenthal) that unite as the great cerebral vein (of Galen), and drain into the straight sinus. The deep system drains blood from the deep white matter of the brain and basal ganglia. Anatomy of cerebral sinuses is shown in Figure 1.

Cerebral venous sinuses are thin-walled vessels between the periosteal and meningeal layers of the dura, and they lack valves as compared to peripheral veins in the extremities. Superior sagittal sinus (SSS) courses in the superior part of the falx cerebri and terminates in the confluence of sinuses. Inferior sagittal sinus lies in the inferior part of the falx, and it joins with the great cerebral vein (of Galen) to form the straight sinus. Straight sinus lies within the tentorium cerebelli, and joins with the SSS and transverse sinuses in the confluence of sinuses (the torcular herophili).

Anatomy of the confluence of sinuses exhibits great variation, but usually the straight sinus continues as the left lateral sinus (LS), and the SSS ends on the right LS. Small veins from the inferior and lateral parts of the hemispheres drain into LS, and thus most of the venous outflow from the brain passes through these sinuses. The LS continue as the sigmoid sinuses followed by internal jugular veins. The cavernous sinuses are located on both sides of the sella turcica and represent a confluence of extracranial veins and intracranial venous structures. They drain through the great petrosal sinuses into the LS, and the inferior petrosal sinuses drain into the jugular veins. Venous drainage of the cerebellum is mainly drained supratentorially to the great cerebral vein (of Galen) or to the great petrosal sinuses [20, 21].

Figure 1. Anatomy of cerebral sinuses
2.2. Pathophysiology of cerebral venous thrombosis

Pathophysiology of CVT can be divided in two major parts; diffuse process caused by thrombosis in the major sinuses, and local processes caused by thrombosed cerebral veins. In most CVT patients both local and diffuse processes are present simultaneously [13, 22].

Thrombosis in a major sinus (especially the SSS) causes compression of the arachnoid villi and disrupts absorption of cerebrospinal fluid, leading to elevated intracranial pressure. Thrombosis in the lateral sinuses often leads to elevated intracranial pressure, as most venous drainage of the brain parenchyma is through these sinuses. Obstruction of a sinus elevates pressure in local cerebral veins, and the thrombus can propagate from the sinus into a nearby cerebral vein leading to a local pathogenic process [22].

Occlusion of a cerebral vein causes congestion of venous blood, local venous hypertension, and potential diminished arterial blood flow to the area. Vasogenic edema occurs due to disruption of the blood brain barrier and congestion of venous blood, and cytotoxic edema is caused by local ischemia [22]. Both vasogenic and cytotoxic edema are present in CVT [23, 24]. These local disturbances in circulation can cause venous infarction or parenchymal hemorrhages if small vessels are damaged [22]. Brain lesions do not maintain the same anatomy as infarctions caused by arterial occlusion [25].

Pathogenesis of venous thrombosis can be understood according to the classical Virchow’s triad as 1) stasis, 2) changes in the vessel wall, and 3) hypercoagulation. Changes in any element of the triad can convert the normal antithrombotic environment towards thrombosis in the veins. Stasis causes local accumulation of coagulation factors and promotes thrombocyte and leukocyte adhesion. Changes in the vessel wall include trauma, infection, and inflammation. In the formation of cerebral venous thrombus hypercoagulative states play the major role. These states include systemic rise in levels of coagulation factors, states of hyperviscosity, and hereditary or acquired thrombophilia [26, 27] and they may be permanent or temporary.

Clinical signs of CVT are affected by the site of thrombosis, and presence or absence of brain parenchymal lesions. Typical symptoms associated with cortical vein thrombosis are focal deficits. SSS thrombosis causes papillaedema with- or without uni- or bilateral focal symptoms, and isolated left LS thrombosis presents as isolated intracranial hypertension. Cavernous sinus thrombosis is associated with ocular symptoms, and deep venous thrombosis causes severe symptoms such as disturbances in consciousness and bilateral motor symptoms. Presence of parenchymal lesions correlates to focal deficits. Around half of the patients have thrombosis in multiple sinuses, and a majority develop parenchymal lesions. Thrombosis sites reported in large CVT series are shown in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>ISCVT</th>
<th>Narayan et al</th>
<th>Geisbuch et al</th>
<th>Ferro et al</th>
<th>Preter et al</th>
<th>Stolz et al</th>
</tr>
</thead>
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<tr>
<td>N</td>
<td>465</td>
<td>412</td>
<td>143</td>
<td>142</td>
<td>102</td>
<td>79</td>
</tr>
<tr>
<td>Occluded sinus n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sinuses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior sagittal sinus</td>
<td>313 (62)</td>
<td>224 (54)</td>
<td>68 (47)</td>
<td>94 (66)</td>
<td>95 (93)*</td>
<td>57 (72)</td>
</tr>
<tr>
<td>Lateral sinus</td>
<td>536 (115)^*</td>
<td>197 (48)^*</td>
<td>95 (66)</td>
<td>92 (65)</td>
<td>95 (93)*</td>
<td>46 (58)</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>112 (18)</td>
<td>19 (5)</td>
<td>18 (13)</td>
<td>12 (8)</td>
<td>16 (16)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Deep venous system</td>
<td>68 (11)</td>
<td>24 (6)</td>
<td>9 (6)</td>
<td>9 (6)</td>
<td>9 (9)</td>
<td></td>
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<tr>
<td>Cortical veins</td>
<td>107 (17)</td>
<td>14 (3)</td>
<td>.</td>
<td>5 (4)</td>
<td>27 (26)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Jugular veins</td>
<td>74 (12)</td>
<td>14 (3)</td>
<td>.</td>
<td>15 (11)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>8 (1)</td>
<td>10 (2)</td>
<td>.</td>
<td>.</td>
<td>3 (3)</td>
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<tr>
<td>Parenchymal lesions</td>
<td>392 (63)</td>
<td></td>
<td></td>
<td>51 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td>290 (47)</td>
<td>62 (16)</td>
<td>65 (45)</td>
<td>48 (34)</td>
<td>39 (49)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>245 (39)</td>
<td>179 (46)</td>
<td>61 (43)</td>
<td>49 (35)</td>
<td>30 (38)</td>
<td></td>
</tr>
</tbody>
</table>

*Superior sagittal sinus and/or Lateral sinus, ^Left + Right Lateral sinus
2.3 Epidemiology of cerebral venous thrombosis
Cerebral venous thrombosis is a rare cause of stroke, accounting for less than one percent of all strokes [12]. Exact incidence of CVT in adults is still unknown, and has previously been estimated to be 0.3-0.4/100 000 patient years [28]. However, recent studies report higher incidence numbers than previously estimated, mainly because of advances in imaging that facilitate easier detection of the disease disclosing mild cases that previously went undiagnosed [29]. In two non-population based studies in the Middle East, incidence of CVT ranged from 0.34/100 000 to 1.35/100 000 patient years, and in one study made in Hong Kong CVT incidence was 3.4/100 000 patient years [30-32]. In a population-based study done in the Netherlands, CVT incidence was 1.32/100 000 patient years [1], and in a recent population-based study in Australia CVT incidence was 1.57/100 000 patient years. Findings in these population-based studies confirm the assumption that CVT has been an underdiagnosed entity in the stroke field.

Females are overrepresented in the CVT patient population, as approximately 75% of CVT patients are female [3, 8, 11, 33-36]. Female CVT patients also tend to be younger than men [35, 37]. This gender difference is mainly attributable to sex-derived (female-specific) risk factors, estrogen use (OC and HRT), pregnancy, and puerperium [37]. In recent years the number of females in the CVT patient population has been on the rise [9]. In the Dutch study, CVT incidence among women 31-50 years of age was 2.8/100 000 per year, more than twice the incidence of the general population [1]. CVT incidence in children seems to be lower than in adults. A large Canadian study showed a rate of 0.67/100 000 for children [38].

Risk of CVT rises during pregnancy, and most cases occur during the last trimester. However, the risk is highest in the puerperium [37, 39, 40]. Pregnancy-related CVT accounts for around 10% of all CVT cases in high-income countries (5 to 20%) [3, 4, 5, 8, 34], but in low-income countries pregnancy-related CVT plays even a larger role with 10 to 30% of cases attributed to pregnancy [5,33, 39, 41, 42].

2.4 Etiology and risk factors of cerebral venous thrombosis
One of the main characteristics of CVT is the diversity of etiological factors. Risk factors and causes of venous thrombosis include factors that affect any aspect of the Virchow triad; blood stasis, vessel wall, or blood composition. CVT has more risk factors in common with other forms of venous thromboembolism (VTE), namely deep vein thrombosis (DVT) and pulmonary embolism (PE), than with arterial stroke [27].

Most extensive etiological information about CVT is available from the multinational International Study on Cerebral Venous Thrombosis (the ISCVT study, n=624), where 75% of the participating centers did systematic screening for coagulopathies, and in only 12.5% of cases no risk factors were identified [3]. Other large studies providing information on CVT etiology are a US study based on the National Inpatient Sample (n=11400), and the Cerebral Vein Thrombosis International Study (the CEVETIS study, n=706) [8] [4]. Risk factors identified in these studies are shown in Table 2.

Cerebral venous thrombosis is often multifactorial [43]. In the ISCVT cohort, 43% of CVT patients had more than one identified risk factor. Despite extensive investigations, in 10-18% of cases the cause of disease remains unknown [3, 11, 44]. Causes of CVT can be divided into two main categories; local causes and systemic causes.
2.4.1 Local causes of cerebral venous thrombosis

Local infective causes of CVT include bacterial and viral meningitis, infections in the paranasal sinuses, mouth, head, face, and neck [28, 45-47]. Infections in the paranasal sinuses, orbits, and facial skin can cause cavernous sinus thrombosis due to the sinuses connections to facial venous drainage via the ophthalmic veins and pterygoid venous plexus [48]. Otogenic infections, namely mastoiditis, can cause sigmoid or transverse sinus thrombosis, as the LS courses alongside the temporal bone [49]. Most common pathogens reported in a review were staphylococcus aureus (69%), streptococci (17%), pneumococcus (5%), and gram-negative bacilli (5%) [50]. Fungal infections in immunocompromised patients were reported to be the cause in one-third of infectious CVT cases, and were associated with worse outcome than bacterial etiology [51]. Number of infectious CVT has declined dramatically in high-income countries due to the use of antibiotics [12, 52, 53], and is now the cause in less than 10% of cases [3, 4, 6, 36, 44]. In the pediatric CVT population infective causes of CVT are still the most common risk factors found [54, 55].

Any condition causing damage to the walls of the sinus system, alter the blood flow, or affect intrasinus pressure, can in theory cause local thrombosis. Causes that are found in the literature include: CNS malignancy [3], head trauma [56], lumbar puncture [57,58], neurosurgical procedures [59], intracranial mass lesions [60-62], venous catheters [63-65], spontaneous intracranial hypotension [66, 67], epidural-or spinal anesthesia [68, 69], and myelography [70]. Association between dural arterio-venous malformations and CVT has been noted, and malformations are probably a result of chronic CVT and not a risk factor [71-73]. Several cases of patients with multiple sclerosis and CVT have been reported, however, most patients had a previous lumbar puncture or high dose corticosteroids making a causative association of CVT and multiple sclerosis unclear [27, 74].

<table>
<thead>
<tr>
<th>Risk factors for CVT</th>
<th>Nasr et al</th>
<th>CEVETIS</th>
<th>ISCVT</th>
</tr>
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<tbody>
<tr>
<td>n (%)</td>
<td>11 400</td>
<td>706</td>
<td>624</td>
</tr>
<tr>
<td>None identified</td>
<td>312 (44.2)</td>
<td>78 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>59 (8.3)</td>
<td>77 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>150 (1.3)</td>
<td>18 (2.5)</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>1360 (11.9)</td>
<td>290 (41.1)</td>
<td>213 (34.1)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>881 (7.7)</td>
<td>52 (7.4)</td>
<td>46 (7.4)</td>
</tr>
<tr>
<td>Hematological condition*</td>
<td></td>
<td>75 (12)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory disorders</td>
<td>563 (4.9)</td>
<td></td>
<td>30 (4.8)</td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td>12 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy/puerperium</td>
<td>2801 (32.4^)</td>
<td>55 (10.6^)</td>
<td>77 (20.2^)*</td>
</tr>
<tr>
<td>Oral contraceptives or HRT</td>
<td>278 (53.4^)</td>
<td>207 (54.3^)*</td>
<td></td>
</tr>
</tbody>
</table>

*aanemia, polycythemia, thrombocytopenia, of females <50 years of age, of female
2.4.2 Systemic causes of cerebral venous thrombosis

Any factor shifting blood composition towards thrombosis can lead to CVT. In this aspect CVT shares many of the same risk factors as other forms of VTE. Older age, hospitalization, immobilization, and obesity are known risk factors for VTE, but they may not be etiological factors for CVT [27]. Procoagulative states can be transient (such as medication or pregnancy) or permanent (such as genetic thrombophilia or chronic illness).

**Coagulopathies**

Genetic thrombophilia is present in one out of five CVT cases [3, 75]. Most common genetic risks found in CVT patients in Europe are the Factor V Leiden mutation (G169A) [76, 77] and the Prothrombin gene mutation (G20210A) [76, 78]. Deficiencies of Protein C, Protein S, and Antithrombin III are also commonly found in CVT patients. Protein C and Protein S deficiencies may be more frequent and Factor V Leiden mutation is less commonly present in non-European populations [34, 75, 79- 81]. Thrombophilia results reported in CVT studies with over 50 patients are shown in Table 3.

Two meta-analyses investigating genetic thrombophilia and CVT have been published, the first one in 2006 [82] and the second in 2013 [83]. Both studies confirmed that CVT risk is elevated in persons with thrombophilia. The later study reported elevated ORs as follows; Factor V Leiden 2.89 (CI95 2.10-3.97), Prothrombin 20210 mutation 6.05 (CI95 4.12-8.90), Antithrombin III deficiency 3.75 (CI95 1.02-13.82), Protein C deficiency 8.35 (CI95 2.61-26.67), and Protein S deficiency 6.45 (CI95 1.89-22.03) [83].

Studies to investigate novel gene polymorphisms as causes of CVT have been published in recent years, reporting that Factor XII C46T polymorphism is associated with CVT [84], but protein Z, thrombin activatable fibrinolysis inhibitor (TAFI), or plasminogen activator inhibitor 1 (PAI1) polymorphisms were not associated with CVT [76, 85-87]. Results of studies on plasma glutathione peroxidase gene (GPx-3) are conflicting warranting further investigations [88, 89].

Acquired thrombophilia was found in 15% of the cases in the ISCVT cohort. Fasting hyperhomocysteinemia has been associated with CVT, and in the ISCVT cohort the prevalence was 4.5% [3]. In two studies fasting hyperhomocysteinemia was present in 27 to 37% of CVT patients, compared to 10% of controls [80, 90].

Hyperhomocysteinemia was associated strongly with risk of CVT in two meta-analyses with adjusted OR of 4.07 and 2.99, respectively [82][83]. Blood homocysteine levels are affected by both genetic and environmental factors. However, the methylene tetrahydrofolate reductase gene C677T mutation that leads to elevated levels of homocysteine was not itself associated with CVT risk in these two studies [80, 90]. The role of hyperhomocysteinemia in venous thrombosis in general is still controversial, and further investigations are needed to assess the clinical significance and usefulness of treating hyperhomocysteinemia in CVT patients.

Elevated levels of Factor VIII have been reported in 25% to 50% of CVT patients in two small studies. [91, 92]. Other thrombophilia reported in the literature include anticardiolipin antibodies (either as part of antiphospholipid syndrome or systemic lupus erythematosus) [93], and activated protein C resistance without Factor V mutation [80].

Coagulopathies are the most common risk factor found in CVT patients in highly developed countries, and their importance as a CVT risk is clear. Screening for genetic thrombophilia should be included in the investigations of each CVT patient.
Table 3. Thrombophilia reported in CVT studies

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Country</td>
<td>India</td>
<td>India</td>
<td>USA</td>
<td>Middle East/Pakistan</td>
<td>Belgium</td>
<td>USA</td>
<td>Germany</td>
<td>France</td>
</tr>
<tr>
<td>n (% tested for thrombophilia)</td>
<td>612 (94)</td>
<td>428 (100)</td>
<td>182 (NA)</td>
<td>109 (28)</td>
<td>54 (85)</td>
<td>154 (NA)</td>
<td>79 (73)</td>
<td>55 (56)</td>
</tr>
<tr>
<td>Any thrombophilia (% of tested)</td>
<td>109 (19)</td>
<td>114 (27)</td>
<td>20 (65)</td>
<td>17 (37)</td>
<td>19 (33)</td>
<td>10 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>19 (3)</td>
<td>1 (3)</td>
<td>5 (11)</td>
<td>6 (14)</td>
<td>4 (7)</td>
<td>2 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated protein C resistance</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>1 (2)</td>
<td>5 (14)</td>
<td>6 (10)</td>
<td>3 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin gene 21210A</td>
<td></td>
<td></td>
<td></td>
<td>1 (2)</td>
<td>5 (14)</td>
<td>6 (10)</td>
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<td>Antithrombin 3 deficiency</td>
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<td>22 (5)</td>
<td>1 (1)</td>
<td>2 (7)</td>
<td>1 (2)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>50 (9)</td>
<td>39 (9)</td>
<td>3 (3)</td>
<td>2 (6)</td>
<td>.</td>
<td>4 (5)</td>
<td>2 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>28 (5)</td>
<td>53 (12)</td>
<td>4 (3)</td>
<td>3 (8)</td>
<td>5 (11)</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>78 (18)</td>
<td>9 (10)</td>
<td>10 (29)</td>
<td>3 (7)</td>
<td>1 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>7 (8)</td>
<td>2 (6)</td>
<td>1 (2)</td>
<td>4 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>0 (0)</td>
<td>8 (8)</td>
<td>20</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Blood disorders were found in 12% of CVT patients in the ISCVT cohort [3]. Severe anemia (hemoglobin <90mg/l) has been reported as a risk factor for CVT in a case-control setting [94]. Anemia was present in 9% of the ISCVT cohort, but in an Indian cohort its prevalence was much higher with 18% of the patients suffering from anemia. It is probable that anemia is a more significant CVT risk in less developed countries [3, 5]. Diseases underlying anemia include iron deficiency anemia [95, 96], aplastic anemia [97], and hemolytic anemia [98]. In both the ISCVT and Indian cohorts polycythemia or thrombocythemia have been present in 2-3% of patients [3, 5]. Paroxysmal nocturnal hemoglobinuria and sickle cell disease have been reported as a cause of CVT in case reports [34, 99-101].

Malignancy

Malignancies can cause CVT in different ways. Tumors in the central nervous system (CNS) can mechanically compress sinuses, hematological changes or paraneoplastic syndrome can cause a hypercoagulable state, or cancer treatments (i.e. medications, lumbar puncture, surgery) may predispose to CVT [27, 102]. Malignancy was reported in 7.4% of CVT patients in the ISCVT cohort, with similar results from other large cohorts [4, 8, 34]. In the ISCVT cohort solid tumors outside the CNS were present in 3.2% of patients, and 2.9% of patients had hematological malignancies [3]. In a study done in a tertiary cancer center, 0.3% of 7000 cancer patients had CVT as a complication of their disease [102]. Studies of leukemia patients have reported CVT prevalence of 1% to 4% during induction of chemotherapy [103, 104].

Systemic disorders

Vasculitis was the cause of CVT in 3% of patients in the ISCVT cohort, Behcet’s disease and systemic lupus erythematosus are most common types of vasculitis noted [3]. In genetically susceptible populations, Behcet’s disease can amount up to 25% of CVT cases, being one of the major CVT causes [105]. Vasculitis associated with rheumatoid arthritis, Wegener’s granulomatosis, thromboangiitis obliterans, Henoch-Schönlein purpura, and Churg-Strauss syndrome have been reported as causes of CVT in case reports [3, 106-108].

Inflammatory bowel disease can cause CVT due to a prothrombotic state caused by inflammation, dehydration, and anemia [109]. Inflammatory bowel disease was present in 1.6% of the ISCVT patients. Sarcoidosis has also been reported as a cause of CVT in case reports [3, 110].

Thyroid disease was present in 1.7% of ISCVT patients. Hyperthyroidism elevates Factor VIII levels and can be a predisposing factor for CVT [111, 112]. There are also some case reports of hypothyroidism and CVT [113]. Nephrotic syndrome and diabetic ketoacidosis are reported causes of CVT in case reports [3, 114-117].

Systemic infections predispose to CVT as they can cause a prothrombotic environment. In the ISCVT cohort 4.3% of patients had an infection outside the head and neck area [3]. In a smaller European CVT series, general infection was present in 3% of CVT patients [11]. Pathogens reported as causing CVT in case reports include various viruses, bacteria, and parasites [34, 54, 118-122, 119].

Obesity has been suggested as an etiological factor for CVT, and one small study found a procoagulative state in obese women with CVT [123]. A case-control study investigating obesity and CVT found that obesity was not a risk factor in men or in women who were not using OC’s. However, obese contraceptive users were found to have a 30-fold risk for CVT [124]. Dehydration is a risk factor for CVT, noted in around 2% of patients [3, 34]. However, in warm climates dehydration may be a more prevalent risk. The Indian study reported dehydration as the most common risk factor found in a third of all CVT cases [75]. Other procoagulative states that may be linked to CVT include recent surgery and fasting [3, 33, 75, 125].
**Medication**

The most common medication predisposing to CVT is OC use, present in 46% to 55% of all female patients [3, 4, 11, 35, 126]. Oral contraceptive use has multiple effects on blood coagulation factors. It increases the plasma levels of fibrinogen, prothrombin, coagulation factors VII, VIII and X and moderately decreases factor V levels. Oral contraceptives also decrease the level of Protein S and TAFI (thrombin activatable fibrinolysis inhibitor), which leads to relative activated protein C resistance [127]. In one Italian study, up to 93% of female CVT patients under 50 years of age were using OCs [128]. A meta-analysis of OC use and CVT yielded an odds ratio (OR) of 5.59 (CI 3.95-7.91, p>0.001) [82]. Effect of OC use for CVT risk is even more remarked when combined with thrombophilia. One case-control study estimated a 34-fold risk for CVT when OC usage was combined with genetic thrombophilia [129]. Another study noted that OC used with prothrombin 20210 mutation produced an OR of 13.4 (CI 3.5-51.3) for CVT [128]. A case-control study found that obesity in OC users was a major risk factor for CVT, with a marked increase in CVT risk. Authors discussed that the synergic effect of two pro-coagulative states (i.e. OC use and obesity) explained this finding [124].

Estrogen use as hormone replacement therapy (HRT) is often present in post-menopausal women, and is a well-established risk factor for VTE [130]. In the ISCVT cohort 5.8% of women aged over 50 were using hormone replacement therapy, but HRT as a risk factor for CVT has not been confirmed in a case-control setting [3].

L-asparaginase treatment has been linked with CVT, as this cancer treatment lowers circulating antithrombin levels, and VTE is common during treatment. However, discerning L-asparaginase effect from the initial hematological malignancy is challenging [102, 131]. High-dose intravenous corticosteroid treatment has been linked to elevated risk of CVT [132]. Anecdotal reports linking CVT with tamoxifen [133], bevacizumab [134], thalidomide [135], cyclosporine [136], erythropoetin alpha [137], intravenous immunoglobulin [138], clozapine [139, 140], sumatriptan [141], carbamazepine [142], lithium [143], intravenous illicit drug use [34], androgen doping for weightlifting [144], and use of ecstasy [145] have been reported. These numerous etiological factors have been reported in case reports or small series, and thus their clinical significance is still undetermined.

**2.5 Clinical picture of cerebral venous thrombosis**

Clinical symptoms and signs of CVT are extremely diverse, making diagnosis of this disease a challenge. Clinical picture is affected by site of thrombosed sinuses, extension of thrombus, presence of parenchymal lesions, and the age of the patient. Symptoms and signs are grouped into three of the most common patterns: 1) isolated intracranial hypertension syndrome (IIH), including isolated headache as the only symptom of CVT; 2) focal syndrome, presenting as focal neurological deficits, such as paresis, aphasia, or seizures; and 3) encephalopathy with delirium, disturbances in executive functions, or disturbances in consciousness [12, 28]. Other less common presentations of CVT are numerous and include cavernous sinus syndrome, subarachnoid hemorrhage, thunderclap headache, migraine with aura, transient ischemic attacks, tinnitus, isolated psychiatric symptoms, and isolated or multiple cranial nerve palsies [12, 146-149]. Clinical presentation of CVT in major CVT studies is shown in Table 4.

Clinical symptoms of CVT can develop over an extended time-scale, from acute to chronic. Acute onset is defined as symptoms developing in less than 48 hours, subacute 48 hours to 14 days, and chronic in over 14 days. In CVT, gradual worsening of symptoms in a subacute manner over several days is the most commonly reported type of onset [3, 5]. CVT symptoms can, rarely, develop in a hyperacute manner mimicking acute arterial stroke [12]. Patients presenting with seizure, disturbances in consciousness, and parenchymal lesions in MRI had shorter diagnostic delay than patients with IIH syndrome in the ISCVT study [150], and this correlation of IIH syndrome to longer symptom duration has been noted in several other studies as well [7, 148, 151].
2.5.1 Headache
Headache is the most common symptom of CVT, being present in 81% to 95% of CVT patients [3, 5, 6, 11, 152]. In one retrospective multicenter cohort from the United States headache prevalence was only 68% [34]. Headache in CVT can occur in combination with any other clinical symptom or sign. A retrospective study of 136 CVT patients with headache reported diversity in the headache type and localization [153]. Three small prospective studies have investigated headache and CVT reporting severe and continuous headache in the large majority of patients, and vomiting or nausea being present in over half of the cases [148, 151, 154]. Data concerning headache location and site of thrombosis has not yet yielded any clear pattern [151, 153, 154].

A sub-study of the ISCVT cohort noted that patients without headache (n=38, 10% of included patients) were older, more often male, had more often focal symptoms, and had a shorter time from symptom onset to diagnosis. Patients with headache had a more favorable outcome, but headache itself was not an independent predictor of outcome in multivariate analysis [155]. This can be due to the severity of these patients symptoms, as focal symptoms may hinder ability to notice or report headache.

2.5.2 Isolated intracranial hypertension
Isolated intracranial hypertension (IIH) syndrome is a group of symptoms consisting of headache with or without papilledema, visual disturbances, sixth cranial nerve palsy, or vomiting. Visual disturbances include transient visual symptoms, double vision, diminished visual acuity, or diminished visual fields. IIH syndrome is the presenting mode in 20% to 40% of CVT patients [3, 6, 152, 156], and is associated with LS thrombosis [156]. In a study with 195 CVT patients, 62 patients had isolated LS thrombosis. In this subgroup of patients, main clinical presentation was isolated headache (45%) and IIH syndrome (24%) [157]. In the ISCVT cohort elderly patients aged >65 years (n=51) had IIH less frequently than younger patients (7.8% vs 24.3%, p=0.008) [158]. Headache as the only symptom of CVT has been reported in 15% to 30% of patients [148, 151, 154]. Two small prospective studies of CVT patients with isolated headache and no parenchymal lesions in MRI have been published, and LS thrombosis seems to be a common finding (present in 67% and 88% of cases)[148, 151].

2.5.3 Focal syndrome
Focal symptoms in CVT are typically caused by cortical vein thrombosis or thrombosis in the SSS [12, 159]. Paresis in the extremities is present in about 40% of patients in high-income countries [3, 11, 34, 152] whereas aphasia is present in one-fifth of patients [3, 11]. Seizures are present more often in CVT than in other stroke subtypes, and are the presenting syndrome in 28% to 47% of patients [3, 5, 6, 11, 152]. Two studies investigating seizures in CVT reported parenchymal lesions and focal deficits as a risk factor for seizures within the first two weeks after diagnosis [160, 161]. In the ISCVT cohort, risk of early seizures was elevated in presence of supratentorial parenchymal lesions and presenting seizures [162]. Other focal signs are present in around 10% of patients [3, 11].

2.5.4 Encephalopathy and decreased level of consciousness
Diffuse encephalopathy is present in approximately 20% of patients [3, 34] and impaired consciousness in 15% of patients in general CVT patient populations [3, 11, 34]. Elderly patients are more likely to have diffuse encephalopathic symptoms, i.e altered cognition, attentinon and orientation [158]. Presentation with impaired consciousness or coma is highly associated with deep cerebral vein thrombosis [12]. In a study with 32 patients with isolated deep CVT, 72% of patients had Glasgow Coma Scale (GCS) ≤14, and 38% had GCS ≤8 [163].
Table 4. Clinical presentation of cerebral venous thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>ISCVT</th>
<th>Ferro et al</th>
<th>Preter et al</th>
<th>Stolz et al</th>
<th>deBruijn et al</th>
<th>Narayan et al</th>
<th>Wasay et al</th>
<th>Geisbusch et al</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>624</td>
<td>142</td>
<td>102</td>
<td>79</td>
<td>59</td>
<td>428</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td>232 (37%)</td>
<td>30 (29%)</td>
<td>23 (29%)</td>
<td>5 (9%)</td>
<td>61 (14%)</td>
<td></td>
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</tr>
<tr>
<td>Subacute</td>
<td></td>
<td>346 (56%)</td>
<td>48 (47%)</td>
<td>34 (43%)</td>
<td>312 (73%)</td>
<td></td>
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</tr>
<tr>
<td>Chronic</td>
<td></td>
<td>45 (8%)</td>
<td>26 (25%)</td>
<td>22 (28%)</td>
<td>53 (12%)</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>553 (89%)</td>
<td>131 (92%)</td>
<td>58 (73%)</td>
<td>56 (95%)</td>
<td>378 (94%)</td>
<td>129 (71%)</td>
<td>101 (71%)</td>
</tr>
<tr>
<td>IIH syndrome*</td>
<td></td>
<td>143 (23%)</td>
<td>41 (29%)</td>
<td>43 (42%)</td>
<td>.</td>
<td>12 (20%)</td>
<td>29 (16%)</td>
<td>27 (19%)</td>
</tr>
<tr>
<td>Focal symptoms</td>
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<td>57 (40%)</td>
<td>59 (58%)</td>
<td>.</td>
<td>27 (46%)</td>
<td>66 (36%)</td>
<td></td>
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</tr>
<tr>
<td>Paresis</td>
<td></td>
<td>232 (37%)</td>
<td>69 (42%)</td>
<td>45 (57%)</td>
<td>20 (40%)</td>
<td>112 (28%)</td>
<td>66 (36%)</td>
<td>57 (38%)</td>
</tr>
<tr>
<td>Aphasia</td>
<td></td>
<td>119 (19%)</td>
<td>25 (18%)</td>
<td>17 (22%)</td>
<td>11 (20%)</td>
<td>9 (5%)</td>
<td>41 (29%)</td>
<td></td>
</tr>
<tr>
<td>Other focal symptoms</td>
<td></td>
<td>55 (9%)</td>
<td>12 (10%)</td>
<td>.</td>
<td>7 (15%)</td>
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<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td>245 (39%)</td>
<td>52 (37%)</td>
<td>35 (34%)</td>
<td>31 (39%)</td>
<td>28 (47%)</td>
<td>171 (45%)</td>
<td>59 (32%)</td>
</tr>
<tr>
<td>Focal seizures</td>
<td></td>
<td>122 (19%)</td>
<td>.</td>
<td>6 (6%)</td>
<td>.</td>
<td>6 (10%)</td>
<td>73 (17%)</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td></td>
<td>187 (30%)</td>
<td>11 (11%)</td>
<td>.</td>
<td>22 (37%)</td>
<td>98 (23%)</td>
<td>47 (26%)</td>
<td></td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td></td>
<td>87 (14%)</td>
<td>18 (13%)</td>
<td>27 (26%)</td>
<td>29 (37%)</td>
<td>32 (54%)</td>
<td>97 (25%)</td>
<td>27 (15%)</td>
</tr>
</tbody>
</table>

*Isolated intracranial hypertension syndrome
2.6 Diagnosis of cerebral venous thrombosis

2.6.1 Radiological diagnosis

Diagnosis of CVT relies on visualizing the site of occlusion in the venous sinus and thrombus matter. Intra-arterial four-vessel angiography has been the gold standard in the past, but in modern-day clinical practice other non-invasive imaging techniques have mostly replaced it.

**Computed tomography (CT) and venography**

Computed tomography can show signs of CVT. Parenchymal lesions, edema, and especially hemorrhage are visible in CT. Figure 3 depicts parenchymal changes in CT. Hyperdense sinuses, the dense clot sign, can be seen in 25% of CVT patients [164]. In some patients unenhanced CT can show thrombosed cortical vein as the cord sign. In contrast-enhanced CT, thrombus can be seen as a filling defect inside the sinus (the empty delta sign). This may be seen in one third of patients [164]. Visualization of venous thrombus in CT is shown in Figure 2. However, CT scans are normal in 10-30% of patients with diagnosed CVT [165], and sensitivity and specificity of CT are 68% and 52%, respectively. Thus, CT scans alone cannot reliably be used for CVT diagnosis [166].

Computed tomography venography is an effective tool for depicting intracerebral circulation, and it is as sensitive as digital subtraction angiography [167]. Multiplanar reformatted images have a sensitivity of 95%, and specificity of 91% [167]. In establishing CVT diagnosis, CT venography is equivalent to MR venography (MRV), and it is even superior to MRV in visualizing venous structures [168]. Drawbacks of CT are the exposure to ionizing radiation and iodinated contrast materials [169]. Magnetic resonance imaging is superior in imaging the brain parenchyma and cortical veins, so in most cases MRI with MRV is the first choice when suspecting CVT [170].

![Figure 2. Visualization of venous thrombus in a CT scan. Dense clot sign in the right LS (A), and SSS and straight sinus (B). Enhanced CT with the empty delta sign in the left LS (C) and the confluence of sinuses (D).](image-url)
Magnetic resonance imaging (MRI) and magnetic resonance venography

Magnetic resonance imaging combined with venography has replaced conventional angiography and CT angiography in clinical practice, and it is highly reliable in diagnosing CVT. Sensitivity of MRI imaging alone is around 90%, but coupled with venography sensitivity rises up to 100% [171-173]. Venous sinuses visualize as flow void, and thrombus can be seen as an abnormal filling defect in unenhanced MRI. Intraluminal thrombus visualization changes over the age of the clot, depending on hemoglobin degradation products [174]. In the acute stage (0-5 days) thrombus is predominantly isointense in T1-weighted imaging and hypointense in T2-weighted imaging, and it can mimic a normal flow void [175]. In the subacute stage thrombus is hyperintense in both T1- and T2-weighted images. In chronic thrombosis great variability exists in thrombus visualization, but it is typically isointense in T1-weighted imaging and iso- or hyperintense in T2-weighted imaging [175]. Thrombus visualization in MRI is shown in Figure 4. T2*-weighted imaging has more sensitivity in detecting CVT than T1-, T2-weighted, or fluid-attenuated inversion recovery (FLAIR) images [176]. Gadolinium enhancement enables visualizing the empty delta sign, as well as indirect signs of CVT such as meningeal thickening, cortical vein enhancement, and collateral venous pathways [166].

Figure 3. Parenchymal changes in CT. Cord sign in right cortical veins and parietal ischemic lesion (A). Left temporal intracerebral hemorrhage (B). Right-sided hemorrhagic venous infarction (C). Edema depicted in the left thalamus (D).
Figure 4. Visualization of thrombus with MRI. T2 hyperintense thrombus is left LS (A). Left sided cortical vein thrombosis in T2* sequence (B). Flow void in gadolinium enhanced imaging; in the left LS (C), and the SSS and left LS (D).

MRV is the imaging method most widely used in diagnosing CVT. Time of flight (TOF) MRV is more often used than the phase contrast technique. TOF imaging has a short acquisition time, good spatial resolution, and a large covering volume. Phase contrast venography may be better in defining slow blood flow from thrombosis, but it is dependent on operator-defined parameters [169]. In MRV, clot is visualized as lack of signal from a sinus, or the sinus is visualized unevenly in case of partial thrombosis [166]. Venography findings in CVT are shown in Figure 5.

Figure 5. Flow void in MR venography. Occlusion of the left LS (A). Occlusion of straight sinus and both lateral sinuses (B).
Magnetic resonance imaging is better at depicting parenchymal changes than CT [177]. Parenchymal findings in CVT patients are shown in Figure 6. Venous infarctions differ from arterial infarctions in their location. They are often subcortical and do not follow specific arterial territories [166]. T2*-weighted imaging is more sensitive to parenchymal hemorrhagic lesions and subarachnoid hemorrhages than T1- or T2-weighted imaging [176]. Small juxtacortical hemorrhagic lesions seem to be a characteristic finding in CVT [178]. Venous infarction visualization on diffusion-weighted imaging (DWI) differs from arterial infarction, since in arterial stroke apparent diffusion coefficient (ADC) is reduced more than 50%, whereas in venous infarction ADC is often only slightly reduced, or even elevated [166]. Patients without diminished ADC values usually do not have parenchymal sequelae and these DWI lesions may rather represent vasogenic edema from venous congestion [179].

Figure 6. Parenchymal changes in MRI. Bilateral edema of the thalamus in FLAIR sequence (A). Left parietal infarction with hemorrhage and thrombus in the cortical veins in T2* sequence (B). Bilateral hemorrhagic infarction of the thalamus in T2* sequence (C). Left temporal intracerebral hemorrhage in T2* sequence (D).
2.6.2 Transcranial Doppler ultrasound

Heightened flow velocities in the cranial sinuses can be observed in CVT in the acute phase, however, sensitivity of transcranial Doppler ultrasound (TCD) techniques do not allow exclusion of CVT [180, 180]. One study reported positive correlation between normalization of flow velocity and excellent functional recovery [181]. However, the current information about TCD is lacking, and further investigations as to the clinical use of TCD are needed.

2.6.3 Fibrin D-dimer

Fibrin D-dimer measurement is widely used in diagnosis of PE and DVT [182]. D-dimer is a small fragment produced when fibrin in blood clots is degraded by plasmin (fibrin degradation product). D-dimer levels in plasma are low in healthy individuals, but they rise when the coagulation system is activated.

The role of D-dimer in CVT diagnostics has been investigated in a few studies, all being studies with under 50 patients with confirmed CVT. Mean D-dimer levels in patients with CVT are higher than with patients admitted to emergency room with CVT mimics. Mean D-dimer values at admission in confirmed CVT patients before anticoagulation treatment have been 720μg/ml-2052μg/ml [183-187]. Studies investigating predictive value of D-dimer in CVT diagnostics have reported negative predictive value of D-dimer <500μg/ml as 95%-100%, and positive predictive value ranging from 55% to 86% [183, 185, 186, 188]. Patients with false negative D-dimer (confirmed CVT but D-dimer <500μg/ml) have amounted to 0% to 24% in the studies [183-189]. Factors reported related to false negative D-dimer levels were isolated headache [184], time elapsed since onset of symptoms [183, 185, 186], and small number of thrombosed sinuses [185]. In a Chinese study repeated measurements of D-dimer were taken over 6 months, and diminishing values over time were noted. Seven days from symptom onset 100% of patients (n=34) had elevated D-dimer, but at 15 days from onset only 30% had D-dimer >500μg/ml [186].

Meta-analysis of the D-dimer in CVT diagnostics was performed in 2012, including in total 14 studies and 1134 patients. D-dimer measurements had mean sensitivity of 93.9 and mean specificity of 89.7, with a pooled positive likelihood ratio (LR) of 9.1 (CI95 6.8-12.2), and a negative LR of 0.07 (CI95 0.0-0.14). Subpopulations with risk for false negative results were investigated. Mean sensitivity of the measurements with patients with long duration of symptoms was 83.1 (CI95 70.4-92.8), with isolated headache 81.6 (CI95 65.7-93.3), and with single sinus involvement 84.1 (CI95 75.3-91.3) [190].

Recently a meta-analysis was done of d-dimer in low-risk headache patients, i.e. patients with isolated headache, normal neurological examination and normal standard CT scan. In total 636 low-risk patients were found (4 studies), with 45 confirmed CVT cases. Sensitivity of D-dimer in this study was 97.8 (CI95 88.2–99.6), and specificity was 84.9 (CI95 81.8–87.7) [188].

2.6.4 Lumbar puncture

Lumbar puncture is not a useful test in the diagnosis of CVT, with the exception of cases where meningitis is suspected. Patients with CVT often have elevated opening pressure (around 80%), and cerebrospinal fluid can show elevated cell count or protein [3]. Exclusion of CVT with neuroimaging is warranted when elevated opening pressure is noted.
2.7 Treatment

Treatment guidelines for managing CVT have been published by the European Federation of Neurological Societies (EFNS) in 2010 [191], and the American Stroke Association (ASA) in 2011 [192]. The European Stroke Organisation (ESO) guidelines on CVT were published in July 2017 [15].

2.7.1 General supportive care

Goal of supportive care in CVT is to prevent brain neuronal damage due to harmful metabolic changes. Studies investigating supportive care in CVT have not been published, but our knowledge from other stroke types supports treatment in a special stroke unit, with monitoring of consciousness and clinical symptoms, and an active approach to treating hypovolemia, fever, hypoxia, hypo- or hyperglycemia, pain, nausea, and agitation [193].

2.7.2 Anticoagulation

The goal of anticoagulation treatment in CVT is to prevent thrombus progression, to enable natural recanalization of the sinuses, and to prevent DVT and PE. There are two small randomized and blinded placebo-controlled trials investigating anticoagulation in CVT. One trial investigated intravenous unfractioned heparin (UFH) in 20 patients [194], and another study investigated subcutaneous low-molecular-weight heparin (LMWH) in 60 patients [195]. A meta-analysis of these studies did not yield a statistically significant finding favoring anticoagulation, but a positive point estimate was found, with a relative risk of 0.33 (CI95 0.08-1.21) for death, and a relative risk of 0.46 (CI95 0.16-1.31) for death or dependency. Notably, no new intracerebral hemorrhages were noted in the treatment group despite 18 patients with hemorrhagic lesions at baseline, and in the placebo group two PE occurred (one fatal) [196].

A randomized but not blinded trial with 150 patients with puerperal CVT investigated LMWH in comparison to placebo. Investigators noted a statistically significant difference in favor of the treatment group in mortality and in complete recovery [197]. In a study with 142 Portuguese CVT patients, anticoagulation treatment was a predictor of complete recovery [OR 3.8 CI95 1.3-9.6] [11]. A retrospective study investigating CVT patients with intracerebral hemorrhage (ICH) (n=43) noted that patients treated with heparin had a lower mortality than patients who received no heparin treatment (15% versus 69%), and that complete recovery was more common in the heparin-treated patients (52% versus 23%) [194].

There are two randomized controlled studies comparing LMWH to UFH treatment. In the study by Misra et al (n=65), the LMWH group had lower in-hospital mortality (0 vs 6 patients p=0.01), but showed no significant difference in functional recovery [198]. In the other study by Afshari et al (n=52), LMWH and UFH treatment groups did not differ in mortality, functional recovery, or bleeding complications [199]. A nonrandomized analysis on the ISCVT cohort compared patients treated with LMWH (n=119) to patients treated with UFH (n=302). This study found that after adjusting for confounding factors, the patients treated with LMWH were more often independent at 6 months (adjusted OR 2.4, CI95 1.0-5.7). A subgroup analysis of the patients with ICH yielded similar results in favor of LMWH [200].

Use of anticoagulation in treating CVT is based on these small clinical trials, but although scientific knowledge is sparse, use of anticoagulation is the gold standard in CVT treatment, and EFNS, ASA and ESO guidelines recommend treatment with anticoagulants even in the presence of ICH. The most recent ESO guidelines recommend LMWH treatment over UFH in the acute phase [15, 16, 191].

Regarding the use of novel direct anticoagulants in CVT, data are still scarce. In a retrospective study with 16 patients (7 patients treated with rivaroxaban), no difference in functional outcome or bleeding events were noted between warfarin and rivaroxaban treatment groups [201]. In another study with 18 patients (11 patients treated with dabigatran), no comparison between treatment groups were made, but 87% of dabigatran treated patients had good functional outcome (mRS 0-1), and no CVT or VTE recurrences were noted [202]. The ESO guidelines at present do not recommend using direct anticoagulants in the treatment of CVT, especially in the acute phase of the disease [15].
A randomized controlled trial investigating dabigatran versus warfarin in CVT patients (RE-SPECT CVT study) has started in October 2016, and will provide information concerning the role of direct anticoagulants in treating CVT. No studies on acetylsalicylic acid use in treating CVT patients have been published. There are no clinical trials investigating the optimum duration of anticoagulation after CVT, but a cluster-randomized study addressing this issue is currently ongoing (Extending oral anticoagulant treatment after acute Cerebral Vein Thrombosis, EXCOA-CVT). Anticoagulation after CVT is modelled after treatment schemes of DVT and PE [203]. Duration of anticoagulation ranges from 3 months to life-long treatment, depending on the individual risk assessment of each patient [191]. Risk of recurrent VTE is addressed in detail in chapter 2.8.2 (Recurrence of thrombotic events).

2.7.3 Fibrinolytic therapy and mechanical thrombectomy
The goal of fibrinolytic therapy and mechanical thrombectomy (MT) is to achieve rapid recanalization of the thrombosed sinus. Anticoagulation is the standard treatment for CVT, but in recent years interventional treatment options targeted to the subgroup of CVT patients who are in high risk of death or dependency have emerged.

No randomized controlled trials investigating fibrinolytic therapy in comparison to anticoagulation exist, but a multicenter trial is currently underway [204, 205]. Current data on fibrinolytic therapy is based on case reports, small case series, and three systematic reviews. One review was done in 2003 with 72 studies with a total of 169 patients [206], another review in 2010 with fifteen studies and 156 patients [207]. In both reviews the majority of patients were treated with local thrombolysis. Mortality was 5% and 9% respectively, and symptomatic/new ICH was noted in 5% and 7% of treated patients. In the 2010 study patients with large doses of thrombolytic agent and with previous ICH seemed to be in higher risk for major intracranial bleeding complications.

A review of systemic thrombolysis in CVT was done in 2014, and yielded only 16 reports with a total of 26 cases in the literature. 88% of the patients achieved independence, and 2 patients died from intracranial bleeding [208].

The latest review investigating mechanical thrombectomy was published in 2015 including a total of 185 patients [209]. In this review all patients were treated with MT, and 71% with local thrombolysis. AngioJet (40%) was the most commonly used device, followed by a wire (31%), balloon angioplasty (25%), and Penumbra system (7%). In 51% of the patients, more than one device was used. Near to complete recanalization was achieved in 74% of cases, 21% had partial recanalization, and 5% had no recanalization. New or worsening ICH was noted in 10% of the cases. The large majority (84%) of the patients had good functional outcome (mRS 0-2), 4% had poor outcome (mRS 3-5), and 12% died. In subgroup analysis factors related to lower recanalization rate, higher risk of periprocedural complications, and lower chance of good functional recovery were pre-treatment stupor/coma, and the use of AngioJet device. Patients with pre-treatment ICH had lesser chance of good functional outcome. Authors in their discussion note that results concerning the use of AngioJet should be treated with caution, as power of this study did not permit adjusting for confounding factors [209].

One retrospective study with 63 patients deteriorating despite anticoagulation therapy compared local (intrasinusal) thrombolysis to mechanical thrombectomy with or without local thrombolysis. Patients who received mechanical thrombectomy were more often comatose, and had parenchymal hemorrhagic lesions. When adjusted for symptom severity at admission, no significant difference in mortality of functional outcome was noted between patients treated with intrasinusal thrombolysis or thrombectomy [210].

There are no current guideline recommendations concerning thrombolysis or thrombectomy in CVT, but the ESO guidelines suggest not using thrombolysis on patients with low risk of poor outcome (i.e. no coma or mental status disturbance, no deep venous system thrombosis, no ICH) [15].
2.7.4 Symptomatic treatment

Antiepileptic drugs

There are no clinical trials investigating epilepsy medication in CVT. The goal of antiepileptic medication is to prevent seizures, and thus prevent harmful metabolic changes in the brain or the development of epilepsy (recurrent seizures). In the ISCVT cohort, patients with presenting seizures and supratentorial parenchymal lesions were at the highest risk of developing new seizures within the first two weeks of CVT diagnosis. However, this risk was robustly reduced in patients who received antiepileptic drugs (OR=0.006; 95CI 0.001-0.05) [162]. Early seizures are present in 30% to 50% of CVT patients [3, 5, 6, 10, 34, 36, 126, 152], and have been noted as a risk factor for developing post-CVT epilepsy. Epilepsy is diagnosed in 5% to 10% of CVT patients later on at follow-up [7, 126, 160, 162]. Both EFNS and ASA guidelines recommend use of antiepileptic drugs in patients with presenting seizures, but in patients with parenchymal lesions without seizures routine prophylactic antiepileptic drugs are not recommended [16, 191]. The ESO guideline recommends using prophylactic antiepileptic agents in patients with seizures and supratentorial parenchymal lesions [15].

Elevated intracranial pressure

General principles of treating elevated intracranial pressure are commonly applied in treatment of CVT patients (head elevation, hyperventilation, osmotic diuretics, and acetazolamide). There are no RCTs investigating use of acetazolamide or diuretics in CVT patients and no studies investigating therapeutic lumbar puncture. In the ISCVT cohort, steroid treatment did not affect prognosis, and was associated with worse prognosis in patients who had no parenchymal lesions [211]. Analysis of acetazolamide-treated patients in the ISCVT cohort yielded no affect to clinical outcome [212]. In the ISCVT cohort diagnostic or therapeutic lumbar puncture was not harmful to patients, but high herniation-risk cases were already ruled out by clinical decision-making [213]. The ESO guidelines do not recommend using steroids in CVT patients to improve outcome, however, for underlying inflammatory disease (i.e inflammatory bowel disease, systemic lupus erytomatosus) steroids are recommended. Routine use of acetazolamide is not recommended, but it may be considered for secondary isolated intracranial hypertension with severe headaches and threatened vision. No recommendation for use of therapeutic lumbar puncture was made, but it may be considered if there could be potential benefits to visual loss and headache and if the safety profile of the patient is acceptable [15].

Decompressive surgery (hemicraniectomy or hematoma evacuation) in CVT patients is a life-saving operation. The Second International Study on Cerebral Venous Thrombosis (ISCVT2) study combined with systematic literature review reported 69 patients treated with decompressive surgery. The mortality was 15% and 56% regained independence [214]. In a study from the Netherlands, 10 patients underwent hemicraniectomy. Two patients died, six patients had good clinical outcome, and two patients had major neurological sequelae [215]. In a single-center study in India that included 44 CVT patients treated with decompressive hemicraniectomy mortality was 20%, and 61% of the patients achieved mRS 0 to 1 [216]. In one study, 12 patients with malignant CVT were investigated, and 8 patients underwent surgery. All four patients without surgery died during the following 1 to 5 days. From the treatment group, only one patient died of PE. At the end of follow up 6 patients had good recovery (mRS 0-1), and one patient was dependent (mRS 3) [217]. The ESO guidelines strongly recommend use of decompressive surgery to prevent death in patients with parenchymal lesions and impending herniation [15].

Effect of shunting in lowering intracerebral pressure and preventing herniation was examined in a study conducted from the ISCVT cohort and systematic literature review (n=15), including four patients with hydrocephalus. In this report, 25% of the patients died, and 53% regained independence. Patients treated with shunting had a worse prognosis than patients treated with decompressive surgery, but direct comparison between the treatment modalities is not possible [218]. The ESO guidelines do not recommend routine shunting procedures to prevent brain herniation and death [15].
Infectious cerebral venous thrombosis

Infectious CVT is a rare complication of a local infection, and mainly affects the cavernous sinus or LS. It should be noted that in addition to symptoms from local infection, associated bacterial meningitis is present and symptoms of CVT are often less remarked. Intravenous antibiotics should be administered without delay. Antibiotics should be effective against common pathogens found in head, neck, and ear infections. Treatment can be initiated with ceftriaxone 2g x1 together with flucloxacillin 2g x6, or meropenem 2g x3 along with vancomycin 1g x2. Antibiotics should later be adjusted according to cultures from the infection site. Timely surgical procedures to clear the infection focus are essential for recovery [219].

Rehabilitation

The goal of rehabilitation is to adapt, recover, and/or reestablish the premorbid or optimal level of functional independence. There are no clinical studies specifically investigating rehabilitation after CVT. Our knowledge on other stroke types suggests that patients with focal deficits and parenchymal lesions would benefit from multidisciplinary rehabilitation [220].

2.8 Outcome

2.8.1 Mortality

In early reports in the 1950's around half of CVT patients died [221, 222]. Mortality of CVT patients has declined over time. In a systematic review, the year of CVT diagnosis was inversely correlated to mortality (Pearson correlation coefficient -0.72, p<0.001). This trend continued also in studies published after year 1990 (Pearson correlation coefficient -0.51, p<0.001), but was absent after year 2000 [223]. This reduction in mortality can be partly explained by more effective radiological diagnosis of CVT cases with less severe symptoms, and etiological shift from infectious CVT with high mortality to hormone-related CVT with a more benign course. Also general care of stroke patients has improved. Treatment of stroke patients in designated intensive care and stroke units enables prevention of complications and timely treatment by personnel well versed in the care of neurological patients. Routine use of anticoagulation to treat CVT has also reduced occurrence of PE in CVT patients, thus affecting in-hospital mortality.

In a large (n=11 400 CVT patients) study based on the National Inpatient Sample database from the United States in-hospital mortality was only 2% [8]. In the ISCVT cohort mortality in the acute phase was 4.3% [224], and in the CEVETIS study 30-day mortality was only 0.4% [4]. In other CVT patient series mortality in the acute phase ranges from 6% to 10% [5, 11, 36, 41, 152, 225].

In the Venoport-study causes of death were cerebral edema in a majority of the cases (n=7), cerebral anoxia from seizures (n=1), and sudden cardiopulmonary arrest (n=1) [11]. In an Indian study with 428 patients, all in-hospital deaths (n=33) were caused by cerebral herniation [5]. In the ISCVT cohort predominant cause of death was herniation, due to either mass lesion or diffuse edema. Independent predictors of death in ISCVT study were coma, mental disturbance, deep CVT, right intracerebral hemorrhage, and posterior fossa lesion [224]. In the US database study, factors associated independently with mortality were sepsis, malignancy, autoimmune disease, substance abuse, paralysis, intracranial hemorrhage, and hydrocephalus. Factors associated with decreased mortality were male sex and Asian race [8].

Long-term mortality after CVT ranges from 3% to 19% (Table 7). In the ISCVT study CVT caused 56% of deaths, but in other studies only 10% of deaths were attributed to initial CVT, the most common cause of death in the long-term being malignancy [3, 4, 126, 226].
2.8.2 Recurrence of venous thrombotic events

Recurrence of CVT and other venous thrombotic events (i.e. PE, deep or superficial thrombosis in the lower or upper extremities, retinal vein thrombosis, and portal vein thrombosis) is shown in Table 5. Risk of VTE recurrence appears to be lower after CVT than in other types of VTE [227, 228]. Several studies have reported that the majority of VTE recurrences have occurred in the first year after initial CVT diagnosis [6, 226, 229, 230]. Risk factors associated with VTE recurrence have been reported in three studies, and independent factors in multivariate analysis were: personal history of VTE [4], male sex, and thrombocytopenia [229], as well as male sex and severe thrombophilia [230]. In analysis of the ISCVT cohort, the CEVETIS cohort, and a smaller study with 154 patients, warfarin therapy had no effect on risk of recurrence [4, 226, 229]. However, patients’ risk profile in choosing the length of the anticoagulant therapy may have influenced these results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Follow-up mo</th>
<th>CVT/100 patient years</th>
<th>VTE/100 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dentali et al (CEVETIS)</td>
<td>2011</td>
<td>706</td>
<td>40</td>
<td>0.98</td>
<td>2.39</td>
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<tr>
<td>Ferro et al (ISCVT)</td>
<td>2010</td>
<td>624</td>
<td>14</td>
<td>1.50</td>
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</tr>
<tr>
<td>Martinelli et al</td>
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<td>145</td>
<td>72</td>
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<tr>
<td>Maqueda et al</td>
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<td>54</td>
<td>42</td>
<td>0.53</td>
<td>4.23</td>
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<tr>
<td>Gosk-Bierska et al</td>
<td>2006</td>
<td>154</td>
<td>36</td>
<td>2.20</td>
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<td>79</td>
<td>31</td>
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<tr>
<td>Breteau</td>
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<td>55</td>
<td>36</td>
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</tr>
<tr>
<td>Ferro et al</td>
<td>2002</td>
<td>91</td>
<td>12</td>
<td>1.46</td>
<td>4.4</td>
</tr>
<tr>
<td>Preter et al</td>
<td>1996</td>
<td>77</td>
<td>78</td>
<td>2.20</td>
<td>2.2</td>
</tr>
</tbody>
</table>
2.8.3 Recanalization

Sinus recanalization after CVT has been investigated in small studies with under 50 patients. Partial or complete recanalization of sinuses can be observed in a majority of patients, ranging from 70% to 100% in the studies. Complete recanalization of the sinuses is observed in around half of patients [92, 126, 175, 231-236]. In two studies it was noted that the number of patients with recanalization did not change after 6 months in repeated MRI [231, 237]. In a very recent study, time to recanalization while on anticoagulation was investigated in 102 patients. In this study 66% of the patients had complete recanalization and 28% had partial recanalization. This study noted that recanalization rates did not rise after 6 months of anticoagulation. Factors associated with complete recanalization were age <50 years and SSS thrombosis [238]. Two small studies found no correlation between functional outcome and recanalization [232, 237], but a more recent study did find that patients with complete recanalization had better functional outcome than patients with no recanalization. Despite current available information, the role of recanalization in functional recovery remains uncertain.

2.8.4 Functional outcome

Functional outcome in CVT patients is most commonly measured by the modified Rankin Scale (mRS). Modified Rankin Scale is graded from 0 to 6; score 0 is no symptoms at all, score 1 is no significant disability despite symptoms, score 2 is slight disability, score 3 is moderate disability and requiring some help, score 4 is moderately severe disability with requiring help with bodily needs and assistance in walking, score 5 is severe disability with incontinence and constant nursing care, and score 6 is dead. The scale has been developed for stroke research, and is a reliable tool in assessing gross functional outcome after stroke, however, concomitant diseases and socioeconomical factors may influence the rating [239]. Short-term functional outcome measured by the mRS is shown in Table 6.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>mRS 0 (n)</th>
<th>mRS 1 (n)</th>
<th>mRS 2 (n)</th>
<th>mRS 3 (n)</th>
<th>mRS 4 (n)</th>
<th>mRS 5 (n)</th>
<th>Mortality</th>
<th>No follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stolz et al</td>
<td>2005</td>
<td>79</td>
<td>54 (68)</td>
<td>4 (5)</td>
<td>4 (5)</td>
<td>0</td>
<td>12 (15)</td>
<td>5 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISCVT</td>
<td>2004</td>
<td>624</td>
<td>481 (77)</td>
<td>49 (8)</td>
<td>44 (7)</td>
<td>42 (7)</td>
<td>5 (1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>deBrujin et al</td>
<td>2001</td>
<td>59</td>
<td>49 (83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bienfait et al</td>
<td>1995</td>
<td>62</td>
<td>41 (66)</td>
<td>4 (7)</td>
<td>10 (16)</td>
<td>11 (18)</td>
<td>0</td>
<td></td>
<td>12 (3)</td>
<td></td>
</tr>
<tr>
<td>Narayan et al</td>
<td>2012</td>
<td>428</td>
<td>273 (64)</td>
<td>110 (26)</td>
<td>66 (15)</td>
<td>2 (3)</td>
<td></td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ruiz-Sandoval et al</td>
<td>2012</td>
<td>59</td>
<td>43 (73)</td>
<td>12 (24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Short-term functional outcome has been investigated in six studies, of which two were conducted outside Europe [5, 33]. In non-European studies outcome was poorer, with around 25% of patients remaining dependent (mRS score 3-5), compared to the less than 10% in European studies [3, 126, 152]. After CVT 74% of patients achieve independence in 3 months. In one European study [240], outcome was worse than in contemporary European studies, but this can be explained by the early study period (from 1970 to 1990).

Long-term functional outcome with follow-up of 12 months or longer has been reported in 10 studies [3, 4, 6, 7, 10, 34, 36, 126, 152, 234], all except one being performed in mainly European patient populations [34]. Long-term functional outcome was good, with only 5% of patients remaining dependent on help of others, and 70% experiencing only minor residual symptoms, shown in Table 7. The US study by Wasay et.al. reported a higher number of patients remaining dependent (28% versus 5%), but this might be affected since one in three patients were lost to follow-up [34].
Factors related to either poor or good functional outcome have been investigated. In univariate analysis factors related to poor outcome (defined as mRS >2 ) have been: age [3, 10, 11, 34, 126, 152], parenchymal hemorrhage in MRI [3, 10, 11, 34, 51, 126, 152], diminished level of consciousness [3, 5, 11, 34, 36, 41, 126, 152], straight sinus/deep venous system thrombosis [3, 5, 10, 11, 152], parenchymal infarction [10, 126], malignancy [3, 36], CNS infection [3,11], male sex [3], focal deficit [5, 10, 36] , and seizure [5, 11].

Presentation with IIH [10, 36, 152], thrombolytic treatment [3, 34, 11], and partum or postpartum CVT [126] have been associated with good recovery.

A statistical model to predict outcome (mRS >2) of CVT patients was constructed based on the findings of the ISCVT study, and validated in two independent populations. The model has six factors: malignancy (2 points), coma (2 points), thrombosis of the deep venous system (2 points), mental status disturbance (1 point), male sex (1 point), and intracranial hemorrhage (1 point). Using a cut-off point of 3, this model has 96.1% sensitivity and 13.6% specificity for predicting CVT patients with poor outcome [241].

### Table 7. Long-term outcome of CVT patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Follow-up 12 months or longer n (%)</th>
<th>mRS* 0-1</th>
<th>mRS 2</th>
<th>mRS 3-5</th>
<th>Mortality</th>
<th>Lost to follow-up</th>
<th>Follow up (median, mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geisbusch et al</td>
<td>2014</td>
<td>143</td>
<td>mRS 0-2: 80 (74)</td>
<td>8 (6)</td>
<td>20 (19)</td>
<td>35 (20)</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentali et al (CEVETIS*)</td>
<td>2011</td>
<td>706</td>
<td>629 (89)</td>
<td>27 (4)</td>
<td>27 (4)</td>
<td>20 (3)</td>
<td>3 (5)</td>
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</tr>
<tr>
<td>English et al</td>
<td>2009</td>
<td>61</td>
<td>43 (70)</td>
<td>9 (15)</td>
<td>1 (1)</td>
<td>5 (9)</td>
<td>3 (5)</td>
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<td></td>
</tr>
<tr>
<td>Wasay et al</td>
<td>2008</td>
<td>182</td>
<td>26 (27)</td>
<td>43 (45)</td>
<td>27 (28)</td>
<td>24 (13)</td>
<td>62 (34)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Stolz et al</td>
<td>2005</td>
<td>79</td>
<td>50 (63)</td>
<td>2 (3)</td>
<td>4 (5)</td>
<td>14 (18)</td>
<td>8 (9)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Ferro et al (ISCVT*)</td>
<td>2004</td>
<td>624</td>
<td>493 (79)</td>
<td>47 (8)</td>
<td>32 (5)</td>
<td>54 (8)</td>
<td>7 (1)</td>
<td>16</td>
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</tr>
<tr>
<td>Breteau et al</td>
<td>2003</td>
<td>55</td>
<td>mRS 0-2: 45 (82)</td>
<td>3 (5)</td>
<td>7 (13)</td>
<td>0</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferro et al</td>
<td>2002</td>
<td>142</td>
<td>108 (76)</td>
<td>12 (8)</td>
<td>4 (3)</td>
<td>11 (8)</td>
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</tr>
<tr>
<td>de Bruin et al</td>
<td>2001</td>
<td>59</td>
<td>25 (42)</td>
<td>19 (32)</td>
<td>3 (1)</td>
<td>8 (14)</td>
<td>2 (3)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Preter et al</td>
<td>1996</td>
<td>85</td>
<td>66 (77)</td>
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<td>NA</td>
<td>8 (9)</td>
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<tr>
<td>Total</td>
<td>2136</td>
<td>1502 (70)</td>
<td>226 (11)</td>
<td>114 (5)</td>
<td>171 (8)</td>
<td>120 (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Modified Rankin score

Factors related to either poor or good functional outcome have been investigated. In univariate analysis factors related to poor outcome (defined as mRS >2 ) have been: age [3, 10, 11, 34, 126, 152], parenchymal hemorrhage in MRI [3, 10, 11, 34, 51, 126, 152], diminished level of consciousness [3, 5, 11, 34, 36, 41, 126, 152], straight sinus/deep venous system thrombosis [3, 5, 10, 11, 152], parenchymal infarction [10, 126], malignancy [3, 36], CNS infection [3,11], male sex [3], focal deficit [5, 10, 36] , and seizure [5, 11].

Presentation with IIH [10, 36, 152], thrombolytic treatment [3, 34, 11], and partum or postpartum CVT [126] have been associated with good recovery.

A statistical model to predict outcome (mRS >2) of CVT patients was constructed based on the findings of the ISCVT study, and validated in two independent populations. The model has six factors: malignancy (2 points), coma (2 points), thrombosis of the deep venous system (2 points), mental status disturbance (1 point), male sex (1 point), and intracranial hemorrhage (1 point). Using a cut-off point of 3, this model has 96.1% sensitivity and 13.6% specificity for predicting CVT patients with poor outcome [241].

2.8.5 Residual symptoms

Patients seem to recover well from paresis, even though 40% of patients have paresis symptoms in the acute phase (Table 7). Long-term motor or sensory deficits have been observed in only 12% of patients [36, 232, 242], and in one study only 2% of patients reported these symptoms [6].

Post-CVT seizures have been observed in 5% to 16% of patients, and around half of these patients developed post-CVT epilepsy [161, 162]. Risk factors for developing post-CVT seizures are: early seizures (i.e. seizures during the time of initial CVT diagnosis) [126, 161, 162], presence of hemorrhagic parenchymal lesions [161, 162], and venous infarction [126]. In one study all patients with post-CVT seizures had also suffered from early seizures [6].

Long-term papilledema can cause optic atrophy and visual loss. Severe visual loss due to CVT is a rare complication. In the ISCVT study it was noted in 1% of patients [7], and other studies reported severe permanent visual loss in 0% to 3.6% of patients [6, 7, 10, 36, 126]. In a case series with 59 CVT patients with IIH syndrome, 5% developed optic atrophy [156]. In the ISCVT cohort diagnostic delay was associated with disability and visual loss in patients presenting with IIH [150].

---

Table 7. Long-term outcome of CVT patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Follow-up 12 months or longer n (%)</th>
<th>mRS* 0-1</th>
<th>mRS 2</th>
<th>mRS 3-5</th>
<th>Mortality</th>
<th>Lost to follow-up</th>
<th>Follow up (median, mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geisbusch et al</td>
<td>2014</td>
<td>143</td>
<td>mRS 0-2: 80 (74)</td>
<td>8 (6)</td>
<td>20 (19)</td>
<td>35 (20)</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentali et al (CEVETIS*)</td>
<td>2011</td>
<td>706</td>
<td>629 (89)</td>
<td>27 (4)</td>
<td>27 (4)</td>
<td>20 (3)</td>
<td>3 (5)</td>
<td>40</td>
<td></td>
</tr>
<tr>
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<td>2003</td>
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<td>3 (5)</td>
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<td>0</td>
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</tr>
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<td>142</td>
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</tr>
<tr>
<td>de Bruin et al</td>
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<td>18</td>
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</tr>
<tr>
<td>Preter et al</td>
<td>1996</td>
<td>85</td>
<td>66 (77)</td>
<td>NA</td>
<td>NA</td>
<td>8 (9)</td>
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<td>120 (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Modified Rankin score
Sinus thrombosis and the resulting obstruction in venous outflow can cause development of dural arteriovenous fistulas [71]. In CVT case series, arteriovenous fistula development has been reported in 1-3% of patients [6, 7, 126]. In two studies investigating patients with arteriovenous fistula, 39% and 53% of patients had a concomitant CVT [72, 73].

Headache is the most common complaint after CVT, present in around half of patients [7, 18, 36, 152]. Post-CVT headaches can be migraine- or tension-type. One study reported that 29% had migraine-type and 27% had tension-type headache [36]. Severe headache leading to in-hospital treatment has been reported in 10-15% of patients [3, 7]. In one study, central neuropathic pain was diagnosed in 7 out of 43 patients [243].

Presence of neuropsychological and neuropsychiatric problems after CVT has been investigated in small case series. Depression is reported in 20-30% of CVT survivors [18, 242]. In a study with 44 independent CVT patients, 75% self-reported concentration problems and 30% self-reported fatigue. In this study, CVT patients had a lower quality of life than healthy controls [18]. In two studies with robust cognitive testing, cognitive impairment has been noted in one-third of CVT patients [19, 152].

The majority of CVT patients are of working age, however, vocational outcome after CVT is reported in only a few studies. In one study of 59 CVT patients, all participants returned to work [242], but in two other studies 8 out of 34 (24%), and 13 out of 44 (30%) patients did not return to their previous employment [18, 152].

2.8.6 Pregnancy after cerebral venous thrombosis

A large portion of patients with a history of CVT are women of childbearing age. Therefore, the outcome in future pregnancies is of special interest. Recurrence of CVT during pregnancy or puerperium seems to be rare. In a total of 190 reported pregnancies (140 women in 9 studies), there was only one case of recurrent CVT, and 3 cases of other VTE. Of these thromboembolic complications, only one occurred during LMWH treatment. Risk of miscarriage might be elevated in subsequent pregnancies. In these studies, 9% to 31% of pregnancies ended in spontaneous abortion [3, 6, 7, 39, 230, 244-246].

A meta-analysis investigating safety of pregnancies after CVT was published in 2016. In 217 pregnancies there were 2 cases of recurrent CVT and 5 cases of extracerebral VTE. Recurrence rate for CVT was 9/1000 pregnancies, and 13.2/1000 pregnancies for VTE. Compared to pregnancies in the general populations, risk of CVT was 80-fold, and risk of VTE 16-fold. Risk of miscarriage was 17.7%, and rates of miscarriage were higher in women not using prophylaxis (11% vs 19%) [247].
3 AIMS OF THE STUDY

To describe clinical factors affecting recanalization, survey recanalization rates in different CVT patient categories, and investigate whether sinus recanalization correlates with clinical outcome (I).

To investigate if serum D-dimer values reflect type of presentation, radiological features, extent of sinus thrombosis, and outcome in CVT patients (II).

To determine frequency of admission blood hyperglycemia in CVT patient subgroups, and investigate correlation between hyperglycemia and clinical outcome (III).

To assess cancer as a risk factor for CVT in a case-control setting, and determine differences in solid and hematological cancer types (IV).

To investigate long-term sequelae, and factors related to functional outcome and employment as well as to determine risk of VTE, risk of bleeding events, and obstetric outcome after CVT (V).
4 PATIENTS AND METHODS

This study was carried out at the Department of Neurology, Helsinki University Hospital. The study was approved by the institutional review board and by the Ethics Committee (January 7th, 2010, HUS 343/13/03/01/09).

4.1 Data collection to Helsinki CVT registry (I-V)

For the purpose of all these studies within this Thesis Project, we searched all patients aged 15 years or older treated for CVT in the Helsinki and Uusimaa Hospital District from January 1987 to December 2015. This hospital district comprises of 1.6 million inhabitants, and the Helsinki University Hospital (HUH) is the only provider in the area that offers acute neurological care.

Patients were found by a computerized search of our hospitals’ electronic discharge register according to the following criteria: (1) patient living in the defined hospital catchment area, (2) age 15 years or older when diagnosed, (3) discharge diagnosis of cerebral venous thrombosis. Discharge diagnoses included in the computerized search were: ICD-9 code 1.4376A (Nonpyogenic thrombosis of intracranial venous sinus), ICD-10 codes I63.6 (Cerebral infarction due to cerebral venous thrombosis, nonpyogenic) and I67.6 (Nonpyogenic thrombosis of intracranial venous system).

One study researcher (Dr. Hiltunen) retrospectively reviewed records, recorded data elements that are shown in Table 8. National Institutes of Health Stroke Scale (NIHSS), GCS, Barthel Index, and modified Rankin Scale (mRS) were reconstructed from patient records as needed. All brain and vessel imaging were interpreted by neuroradiologists, and assessed post hoc by a senior neuroradiologist, O. Salonen, if needed.

Table 8. Recorded data elements in the Helsinki CVT registry

<table>
<thead>
<tr>
<th>Category</th>
<th>Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic information</td>
<td>sex, age, profession, employment status</td>
</tr>
<tr>
<td>Health history</td>
<td>current medications, previous illnesses</td>
</tr>
<tr>
<td>Risk and etiological factors</td>
<td>family history of PE or DVT, previous DVT or PE, smoking, alcohol use, drug use, bodyweight, pregnancy, puerperium, oral contraceptives, estrogen replacement therapy, malignancies, dehydration, genetic thrombophilia, acquired thrombophilia, thrombocytopenia, anemia, head trauma, surgery, lumbar puncture, infection of the head, face, mouth, neck and CNS, CNS malformations, vasculitis, connective tissue disorders, other systemic disorders</td>
</tr>
<tr>
<td>Symptoms</td>
<td>headache type, headache location and severity, nausea, visual disturbances, paresis, seizures, other focal signs, and time of symptom onset</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>(impaired consciousness, disorientation, motor deficit, sensory deficit, visual disturbances, diplopia, visual field defect, hemianopia, papilledema, aphasia, cerebellar ataxia, cranial nerve paresis, meningismus, NIHSS, GCS)</td>
</tr>
<tr>
<td>Time delays</td>
<td>symptom onset to admission, admission to diagnosis, admission to treatment</td>
</tr>
<tr>
<td>Imaging data</td>
<td>date of imaging studies (CT, CT venography, MRI, MR venography), location of thrombus (SSS, LS, straight sinus, cortical veins, deep venous system, jugular vein, cavernous sinus), hemorrhagic lesion, non-hemorrhagic lesion, SAH, SDH</td>
</tr>
<tr>
<td>Laboratory test results</td>
<td>blood count, C reactive protein, creatinine, blood glucose, international normalized ratio (INR), fibrin d-dimer, homocysteine, laboratory test package for thrombophilia (prothrombin gene mutation, factor V Leiden mutation, levels of protein C, protein S, Antithrombin III, factor VIII, anticardiolipin antibodies, anti-beta-2-glycoprotein antibodies, lupus anticoagulant and activated protein C resistance)</td>
</tr>
<tr>
<td>Treatment of CVT</td>
<td>need and duration of intensive care, anticoagulant therapy, thrombolysis or mechanical thrombectomy, analgesia, antibiotics, antiinflammatories, anticonvulsants, treatments to lower intracranial pressure, hemicraniectomy, date and duration of treatment (UFH, LMWH and oral anticoagulants), bleeding complication during treatment</td>
</tr>
<tr>
<td>Discharge status</td>
<td>GCS, NIHSS, Barthel index, length of hospital stay, need of rehabilitation</td>
</tr>
<tr>
<td>Follow-up 3 to 6 months</td>
<td>current medication, employment status, length of sick-leave, residual symptoms (paresis, epilepsy, vision, neuropsychological), sinus recanalization, NIHSS, Barthel Index, mRS, cause of death</td>
</tr>
</tbody>
</table>
4.2 Recanalization (I)
For this substudy, we included CVT patients treated from 1987 to 2008, who had complete imaging and clinical information available from the follow-up visit (n=91). Rates of recanalization established by MRV (n=88), conventional venography (n=1), and autopsy (n=3) were investigated in different patient subgroups. Recanalization was categorized as complete (uninterrupted blood flow with no residual thrombi), partial recanalization (presence of residual thrombus with narrowing of the lumen or partially interrupted blood flow in at least one primarily thrombosed sinus), or no recanalization (interrupted blood flow in all primarily thrombosed sinuses). All imaging data were interpreted by a neuroradiologist, and reviewed by our study’s senior neuroradiologist Oili Salonen. Correlation of recanalization status to CVT risk factors and functional outcome was investigated.

4.3 D-dimer (II)
For this substudy, we examined patients treated from 1987 to 2010, a total of 138 cases. Patients with D-dimer measured before initiation of anticoagulation treatment were eligible (n=71). Measurement of D-dimer levels were defined as low (<0.5mg/l), intermediate (0.5 to 2.9mg/l), or high (>3.0mg/l), and were measured with accredited photometric immunochemical method (Tina-quant D-Dimer, Roche Hitachi MODULAR, Roche LTD after year 2000, IL Test TM D-Dimer, ACL Futura, and Instrumentation laboratories from 1990 to 2000). Extent of thrombus was recorded as number of thrombosed sinuses. Outcome was measured as mRS and NIHSS score at the 6-month follow-up, and presence of residual symptoms were recorded. We examined if D-dimer levels were associated with sex, age, time elapsed from symptom onset, clinical presentation, risk factors, number of thrombosed sinuses, recanalization status, or outcome.

4.4 Admission hyperglycemia (III)
For this third study, we combined our own CVT database from years 1998 to 2014 with another CVT database from the Academic Medical Centre in Amsterdam, the Netherlands, from years 2000 to 2014. Dutch patients were collected prospectively from July 2006 onwards and retrospectively from 2000 using the International Classification of Diseases Tenth Revision (ICD-10) codes and the Dutch financial coding system for hospital care. Patients with a non-fasting glucose concentration measured within the first 24 hours since CVT diagnosis were included, and patients with a history of diabetes mellitus were excluded.

Blood glucose concentration measurements were done on a Roche Modular P analyzer (Helsinki) and a Roche Cobas 8000 analyzer (Amsterdam). Admission hyperglycemia was defined as blood glucose ≥7.8 mmol/l (141mg/dl), and severe hyperglycemia as blood glucose ≥11.1 mmol/l (200mg/dl).

Correlation of admission hyperglycemia with clinical outcome was investigated. Clinical outcome was measured by mRS during clinical follow-up visits (3 to 6 months), and poor clinical outcome was defined as scoring 3 to 6 points on mRS score. Correlation between mortality and hyperglycemia was also investigated.

4.5 Cancer and risk of cerebral venous thrombosis (IV)
For this study we combined our own CVT database from Helsinki with two other CVT databases; Academic Medical Centre in Amsterdam (the Netherlands), and Sahlgrenska University Hospital in Gothenburg (Sweden). Dutch patients were collected prospectively from July 2006 to December 2015, and retrospectively from 2000 using the International Classification of Diseases Tenth Revision (ICD-10) codes and the Dutch financial coding system for hospital care. Swedish patients were collected retrospectively from 1997 to December 2015 using ICD-10 codes.

Controls were healthy subjects who participated as control subjects of the Dutch Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study. This case-control study included 4956 consecutive patients aged 18 to 70 years with a first DVT of the leg or PE. Control subjects were recruited from
partners of patients and subjects identified by random digit dialing. In total 6297 control subjects (3297 partners and 3000 by random digit dialing) were included. Participants in the control group were between the ages of 18 and 70 years and had no history of venous thrombosis.

We excluded cases (n=1) and controls (n=19) for whom it was unknown if they had a history of cancer.

Cancer was subdivided into solid and hematological malignancies, and further hematological cancer was divided into subtypes (leukemia, lymphoma, myeloma). Non-invasive skin cancers, meningiomas, and myelodysplastic syndrome were not registered as cancer. The following information on cancer was recorded for cases and controls: time from diagnosis, type of cancer, types of treatment, and the presence or absence of known metastases.

4.6 Long-term outcome (V)

For this study, we included all CVT patients treated from January 1987 to August 2013 in the Helsinki University Hospital. All patients were invited to a follow-up outpatient visit, and all included patients provided written informed consent. Data from the time of CVT diagnosis was collected retrospectively according to our CVT database (Table 8). We dichotomized neurological symptoms at admission; NIHSS score 0 to 2 represented minor stroke. Education level was analyzed in three categories: primary (compulsory education of 9 years), secondary (high school or equivalent), and tertiary (university). Primary education only was recorded as low education level. All included patients (n=161) answered two structured questionnaires, with a wide variety of questions. Data collected on the questionnaires are shown in Table 9.

Functional recovery at follow-up was defined as favorable (mRS 0-1) or unfavorable (mRS 2-6). Depression was defined as scoring more than 13 points on the Beck Depression Inventory. Working status was dichotomized to employed or unemployed. Median age derived from the data (38 years) was used as a cut of point in analyses. Patients retired due to old age or illness unrelated to initial CVT were excluded from return-to-work analysis, as were women on maternity leave. Students and persons working 50% or more of standard hours were analyzed as employed.

Table 9. Data collected at long-term follow-up visit

<table>
<thead>
<tr>
<th>Basic information</th>
<th>age, sex, education, working status, current medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual symptoms</td>
<td>epileptic seizures (type, frequency, current and previous medications), headache (type, location, severity), visual disturbances, motor and sensory deficits, memory and concentration problems, fatigue, linguistic problems</td>
</tr>
<tr>
<td>Antithrombotic treatment</td>
<td>treatment duration, medications used (LMWH, warfarin, new oral anticoagulants, Aspirin, other)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>bleeding events (date, type), recurr VTE (date, type), any hospital treatment</td>
</tr>
<tr>
<td>Women</td>
<td>use of oral contraceptives, use of hormonal replacement therapy, subsequent pregnancies (miscarriages, complications, anticoagulation use)</td>
</tr>
<tr>
<td>Additional questionnaires</td>
<td>Beck Depression Inquiry</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>modified Rankin Scale, NIHSS score, Barthel index, blood pressure, body weight</td>
</tr>
</tbody>
</table>
4.6 Statistical methods

In all studies, two-sided values of \( P < 0.05 \) were considered statistically significant (I-V). Chi-square (I, II, and III) and Fisher’s exact (I, III) tests were used to analyze categorical variables in two groups, as were Pearson chi-square (II) and Kruskal-Wallis (II) tests when three groups were compared. Continuous variables were analyzed with Student’s T test (III) and Mann-Whitney U test (III). Analysis on age was done using ANOVA (II). In the studies investigating cancer (IV) and long-term outcome (V), odds ratios (OR), 95% confidence intervals (CI95), and \( P \) values were calculated for each variable. Logistic regression analysis was used in all multivariate analyses (I, III, IV, and V). In the studies investigating recanalization (I), cancer (IV), and long-term outcome (V) variables with \( P < 0.10 \) were used as covariates in multivariate analysis. In the long-term outcome and cancer studies analysis were further adjusted for age and sex. In the study investigating admission hyperglycemia (III), multivariate analyses were adjusted for the potential confounders: age, sex, coma, malignancy, infection, intracerebral hemorrhage, deep CVT, and location of recruitment (Helsinki or Amsterdam).

Statistical software used for data analysis were; SPSS 17.0 (Chicago:SPSS inc) (II), SPSS 20 (Armonk, NY: IBM Corp.) (III), and SPSS 22 (Armonk, NY: IBM Corp.) (IV, V).
5 RESULTS

5.1 Recanalization (I)

5.1.1 Features of the study population

Out of 107 patients treated for CVT we included 91 patients with complete 6 month follow-up data. Mean age of patients was 39.3 years (range 18-75 years), and 70% of patients were female. Seven percent (n=6) of the population were elderly (aged over 65 years). Mode of onset was acute in 42%, subacute in 47%, and chronic in 11% of cases. Most common symptoms and signs were headache (90%), papilledema (25%), seizures (24%), visual disturbances (14%), and motor deficits (14%). The majority of patients (67%) had focal symptoms and signs. Demographic data and recanalization status in different patient age groups is shown in table 10.

Sites of thrombosed sinuses were SSS (64%), right LS (53%), left LS (48%), straight sinus (28%), cortical veins (11%), deep venous system (11%), and jugular veins (18%). Majority (63%) of the patients had thrombosis in multiple sinuses. In 25% of the patients, a parenchymal infarction was noted, and 19% had parenchymal hemorrhage. Anticoagulation treatment in the acute phase was administered to 97% of patients. Despite intensive investigations, risk or etiological factors could not be identified in 11% of cases. In a majority of the patients multiple risk factors were present. Most common identified risk factors were: local infection (22%), other preceding infection (18%), smoking (17%), and anemia 15%. Infections preceding CVT diagnosis were: upper respiratory tract viral infection (n=10), unclear infection focus (n=9), sinusitis (n=8), gastroenteritis (n=8), otitis media (n=4), viral meningitis (n=1), endometritis of the uterus (n=1), alveolitis of the lungs (n=1), glomerulonephritis (n=1), and cellulitis in the leg (n=1). Positive family history for VTE was present in 18% of the cases, and coagulopathies were diagnosed in 16%. Sex-related risk factors were present in majority of women; OC use (53%), HRT (14%), and pregnancy (11%).

Table 10. Demographic data and outcome in different age groups

<table>
<thead>
<tr>
<th>Age&lt;37years</th>
<th>Age 37 to 65 years</th>
<th>Age &gt;66 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>53 (58)</td>
<td>32 (35)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Women</td>
<td>41 (77)</td>
<td>22 (68)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Headache</td>
<td>51 (96)</td>
<td>28 (87)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Focal symptom and/or encefalopathy</td>
<td>34 (64)</td>
<td>22 (68)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Seizure</td>
<td>16 (30)</td>
<td>6 (18)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>IIH</td>
<td>12 (23)</td>
<td>8 (25)</td>
<td>NA</td>
</tr>
<tr>
<td>Number of thrombosed sinuses; median (range)</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Parenchymal oedema/infarction</td>
<td>24 (45)</td>
<td>16 (50)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Parenchymal hemorrhage</td>
<td>6 (11)</td>
<td>1 (3)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>mRS 0-1 at 6 months</td>
<td>43 (81)</td>
<td>25 (80)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Complete recanalization</td>
<td>31 (58)</td>
<td>8 (25)</td>
<td>NA</td>
</tr>
<tr>
<td>Partial recanalization</td>
<td>21 (23)</td>
<td>13 (40)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>No recanalization</td>
<td>5 (9)</td>
<td>6 (18)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>

5.1.2 Recanalization

At follow-up, 47% of the patients achieved complete recanalization, 34% had partial recanalization, and 19% had no recanalization. In univariate analysis, factors associated with poor recanalization were male sex (p=0.030), age ≥37 years (p<0.001), and no identified cause for CVT (p=0.032). Univariate analysis of recanalization status at follow up is depicted in Figure 7. In multivariate analysis the only variable independently associated with no recanalization was increasing age (OR 1.04, CI95 1.01-1.08).
5.1.3. Functional outcome

Functional outcome was assessed at the 6-month follow-up using mRS (Figure 8). Recovery was complete (mRS 0) in 48%, 32% had mild residual symptoms (mRS 1), 14% had moderate residual symptoms (mRS 2), only two patients were dependent or severely disabled (mRS 3 to 5), and 3% of the patients had died (mRS 6). Reported residual symptoms were headache (23%), neuropsychological symptoms (12%), epilepsy (7%), dizziness (6%), and focal neurological or visual deficits (2%).

Incomplete recovery from CVT was more common among patients aged ≥37 years (P<0.001), patients with chronic onset (P=0.034), and in patients with no recanalization (P=0.033). No recanalization at follow-up correlated also to unfavorable outcome (mRS 2-5) (P=0.031). In multivariate analysis, increasing age (OR 1.05, CI95 1.01-1.09) and chronic mode of onset (OR 9.41, CI95 1.02-87.07) predicted incomplete recovery or death (mRS 1-6). In multivariate analysis recanalization status was not independently associated with either incomplete recovery (mRS 1-6), or unfavorable functional outcome (mRS 2-6).
5.2 D-dimer (II)

5.2.1 Features of the study population

In this study we investigated 71 patients with blood fibrin D-dimer levels measured before initiation of anticoagulation treatment. Median age was 35 years, and 76% of the study population was female. Clinical presentations in patients were; focal symptoms (62%), isolated intracranial hypertension (27%), and impaired consciousness (3%). All of our patients received anticoagulant therapy. Median D-dimer was 1.40 mg/L (range 0.05-13.0 mg/L). Distribution of D-dimer measurements are depicted in Figure 9. Nine (12%) patients had low, 37 (52%) patients had intermediate, and 25 (35%) patients had high D-dimer levels.

![Figure 9. D-dimer measurements in the study](image1)

![Figure 10. Association of D-dimer and symptom duration](image2)

5.2.2 Risk factors

D-dimer levels were not associated with particular risk factors; no found risk factors (p=0.201), history of VTE (p=0.567), family history (P=1.00), coagulopathies (p=0.677), malignant disease (p=1.00), smoking (p=0.422), systemic inflammatory disease (p=0.730), medications (p=0.572), dehydration (p=0.284), infection (p=0.425), trauma (p=0.229), and sex-derived risk factors (pregnancy or puerperium (p=0.223) and estrogen use (p=0.631)). Patients with presentation of isolated headache and focal symptoms had similar D-dimer levels, however, higher levels of D-dimer were associated with impaired consciousness (p=0.040). NIHSS score at admission did not correlate to D-dimer. Low D-dimer levels (< 0.5 mg/L) were associated with longer symptom duration (P=0.010), and it is noteworthy that none of the patients with low D-dimer levels had symptom duration less than 2 days (Figure 10).

5.2.3 Radiological findings

D-dimer levels were associated with extent of thrombosis measured by the number of thrombosed sinuses (Figure 11; p=0.044). Presence of parenchymal lesions in MRI imaging did not correlate to D-dimer levels, this was also noted when hemorrhagic lesions and infarction/edema were investigated separately.

5.2.4 Clinical outcome

Clinical outcome was measured at the 6-month follow-up visit with NIHSS score and mRS, and residual symptoms were recorded. D-dimer levels did not correlate to recanalization status or NIHSS score. Neither did we find correlation to presence of residual symptoms (p=0.873); headache (p=0.191), paresis symptoms (p=0.359), or epilepsy (p=0.784). Correlation between favorable functional outcome (mRS 0-1) and D-dimer did not reach statistical significance (p=0.263), but a trend of worse outcome and high D-dimer was observed.
Figure 11. D-dimer and extent of thrombosis
5.3 Admission hyperglycemia (III)

5.3.1 Features of the study population
In this study we included 308 CVT patients. 12 patients were excluded due to known history of diabetes (9 from Helsinki and 3 from Amsterdam) and 60 patients due to missing glucose values (38 from Helsinki and 22 from Amsterdam).

5.3.2 Etiological factors, imaging findings, and treatment
Patient populations in Helsinki and Amsterdam were similar in their age and sex distribution. However, the patients from Amsterdam had more parenchymal lesions \( (P=0.00 \ 43\% \ vs \ 72\% \) and parenchymal hemorrhage \( (P=0.00 \ 18\% \ vs.54\%) \) and were more often treated with endovascular thrombectomy \( (P=0.00 \ 1\% \ vs. \ 21\%) \) and hemicraniectomy \( (P=0.00 \ 1\% \ vs \ 13\%) \).

Admission hyperglycemia was present in 66 CVT patients (21\%), and in 8 patients (3\%) hyperglycemia was severe. Mode of onset, diagnostic delay, and CVT risk factors were similar in patients with and without hyperglycemia. Patients with hyperglycemia had a more severe clinical picture of CVT. There was no difference in infection rate in the study groups \( (P=0.92) \). Baseline data on the study population is shown in Table 11. Patients with hyperglycemia were more often treated at an intensive care unit \( (P<0.001) \), less often received anticoagulation \( (P=0.001) \), and were more often treated with hemicraniectomy \( (P<0.001) \).

5.3.2 Clinical outcome
Follow-up mRS score was available for 96\% of the patients, and information on mortality was available in all patients. Due to the more severe clinical picture of CVT, patients from Amsterdam had more often unfavorable functional recovery (mRS 3 to 6); \( P=0.010, 9\% \ vs 20\% \).

Two patients were diagnosed with diabetes mellitus during the follow-up period. Patients with elevated blood glucose had worse outcome than normoglycemic patients (Figure 12). This association was strong with both unfavorable functional outcome (mRS 0-2 vs mRS 3-6) (10\% vs 34\%, OR 3.1, CI95 1.35-7.12, \( P<0.001 \)) and mortality (21\% vs 5\%, OR 4.13, CI95 1.41-12.09, \( P<0.001 \)). Association of glucose level and functional outcome is shown in Figure 12. When adjusted for confounding factors, increased blood glucose concentration was associated with death and dependency (OR per 1mmol/L increase 1.50, CI95 1.21-1.86), and mortality (OR per 1mmol/L increase 1.73, CI95 1.30-2.31). When we stratified admission hyperglycemia, we noted that severe hyperglycemia was a stronger predictor of poor outcome than mild hyperglycemia, and carries an elevated risk for mortality compared to normoglycemic patients (adjusted OR 33.36, CI95 3.87-287.28).

![Figure 12. Association of glucose level and functional outcome at follow-up](image-url)
Table 11. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Hyperglycemia n=66 (%)</th>
<th>No Hyperglycemia n=242 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female</td>
<td>40 (61)</td>
<td>180 (74%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age mean (SD)</td>
<td>45.6 (15.6)</td>
<td>39.1 (14.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>53 (82)</td>
<td>206 (86)</td>
<td>0.39</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>38 (59)</td>
<td>149 (62)</td>
<td>0.69</td>
</tr>
<tr>
<td>Seizures</td>
<td>23 (35)</td>
<td>74 (31)</td>
<td>0.49</td>
</tr>
<tr>
<td>Coma (GCS &lt;9)</td>
<td>20 (31)</td>
<td>12 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Imaging findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any parenchymal lesion</td>
<td>46 (70)</td>
<td>135 (56)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hemorrhagic lesion</td>
<td>35 (53)</td>
<td>79 (33)</td>
<td>0.002</td>
</tr>
<tr>
<td>Parenchymal edema</td>
<td>19 (29)</td>
<td>78 (32)</td>
<td>0.60</td>
</tr>
<tr>
<td>Superior sagittal sinus</td>
<td>36 (55)</td>
<td>141 (58)</td>
<td>0.55</td>
</tr>
<tr>
<td>Left lateral sinus</td>
<td>32 (48)</td>
<td>116 (47)</td>
<td>0.26</td>
</tr>
<tr>
<td>Right lateral sinus</td>
<td>26 (39)</td>
<td>106 (43)</td>
<td>0.83</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>16 (24)</td>
<td>53 (22)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cortical veins</td>
<td>16 (24)</td>
<td>75 (31)</td>
<td>0.56</td>
</tr>
<tr>
<td>Deep venous system</td>
<td>10 (15)</td>
<td>36 (15)</td>
<td>0.37</td>
</tr>
</tbody>
</table>
5.4 Cancer and risk of cerebral venous thrombosis (IV)

5.4.1 Characteristics of the study and control populations

Our study population consisted in total of 594 cases and 6278 controls. Patient selection and basic demographic data are shown in Figure 13. Cases were younger and more often female than controls, and they more often had a history of cancer. Hematological cancer was markedly present in CVT patients, 4% of our patients had hematological malignancy, and 2.7% had acute lymphoblastic leukemia (ALL). Only 0.2% of controls had hematological malignancy, and only three controls had leukemia (0.05%). Details of cancers in the study and controls populations are shown in Table 12.

At the time of diagnosis 85% (n=580) of our CVT patients had headache, 60% (n=588) had focal deficits, 28% (n=164) had seizures, and 8% (n=49) were comatose. Neuroimaging studies showed intracerebral hemorrhage in 33% (n=193), and parenchymal infarction in 32% (n=189) of the CVT patients.

5.4.2 Solid cancer and risk for cerebral venous thrombosis

In the multivariate analysis after adjustment for age and sex, the risk of CVT was increased in patients with cancer (OR 3.70, CI95 2.71-5.10). The risk was higher in patients with hematological cancer (OR 18.00, CI95 9.15-35.21) than in patients with solid cancer (OR 2.46, CI95 1.69-3.58).

Fifteen patients had solid cancers diagnosed within the last year (2.5% of all CVT patients), whereas only 25 controls had a new cancer diagnosis (0.4% of controls). Diagnosis of solid cancer in the last year carried a clearly elevated risk for CVT (OR 10.40, CI95 5.35-20.23). Solid cancer diagnosis made more than one year previously carried a moderate risk for CVT (OR 1.63, 1.02-2.63).
5.4.3 Hematological cancer and risk for cerebral venous thrombosis

Hematological cancer carried a larger risk for CVT than solid cancer (OR 18.00 vs OR 2.46). Patients with ALL were at highest risk (OR 67.83, CI95 15.37-299.39), but hematological malignancy was still a risk factor for CVT even if patients with ALL were excluded from the analysis (OR 9.43, CI95 3.85-23.13).

New hematological cancer diagnosis was present in 20 cases (3.4%), but in only 2 controls (0.03%). We noted a very high risk for CVT in the first year since diagnosis of hematological cancer (OR 89.68, CI95 20.74-387.85), but we found no association after the first year of hematological cancer (OR 2.52, 95% CI 0.56-11.32).

<table>
<thead>
<tr>
<th></th>
<th>Patients, n=594 (%)</th>
<th>Controls, n=6278 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of cancer</strong></td>
<td>59 (10)</td>
<td>232 (4)</td>
</tr>
<tr>
<td><strong>Hematological cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active chemotherapeutic treatment</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Leukemia, unspecified</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Solid cancer</strong></td>
<td>36 (6)</td>
<td>217 (4)</td>
</tr>
<tr>
<td>Active chemotherapeutic treatment</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Breast (only women)</td>
<td>8 (2)</td>
<td>69 (2)</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (0.8)</td>
<td>4 (0.06)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4 (0.7)</td>
<td>18 (0.3)</td>
</tr>
<tr>
<td>Gynecologic (only women)</td>
<td>3 (0.8)</td>
<td>3 (0.09)</td>
</tr>
<tr>
<td>Prostate (only men)</td>
<td>0</td>
<td>21 (0.7)</td>
</tr>
<tr>
<td>Bladder</td>
<td>2 (0.3)</td>
<td>20 (0.3)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 (0.1)</td>
<td>14 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (2)</td>
<td>32 (0.5)</td>
</tr>
</tbody>
</table>

Table 12. Details of cancers in the study and control populations
5.5 Long-term outcome (V)

5.5.1. Characteristics of the study population
Out of 195 consecutive CVT patients, we included 161 for this study. Nine patients declined participation in our study, and four cases were excluded (1 had moved abroad, 1 had incorrect initial diagnosis, and 2 due to missing data). Twenty one patients died during the follow-up period. Participation rate was 93%. Median follow-up time was 39 months (IQR 14-95 months) with a total of 818 patient-years. Majority of our patients (67%, n=106) were women, and median age at onset was 38 years (IQR 24 to 54).

In vocational status analysis, we included 121 working-aged patients (under 65 years of age) of whom 70% (n=86) were women. From vocational analysis, we excluded retired patients (26 due to old age, and 9 due to non CVT-related underlying illness), and women on maternity or nursing leave (5 patients). Students (7 cases) and part-time workers (2 cases) were treated as employed.

At admission 85% (n=136) of our patients had headache. Over half of the patients (52%, n=94) had focal symptoms, and one-third of our patients (31%, n=50) had presentation of IIH. Ten patients (9%) had impaired consciousness, and 31 patients (19%) suffered from major stroke symptoms (NIHSS score ≥ 2 points). Anticoagulation treatment was administered for 157 patients (97.5%), 3 patients were treated with local thrombolysis, and two patients were treated with hemicraniectomy. Imaging findings at admission are shown in Table 13.

5.5.2 Mortality
Overall mortality during follow-up was 11% (n=21), with 7 cases attributable to index CVT. Six deaths occurred in the first month after CVT diagnosis, five of them attributable to index CVT. All these early deaths were due to brain herniation. Other causes of death were malignancy (n=7), coronary artery disease (n=2), pulmonary fibrosis (n=1), dementia (n=1), and in 3 cases the cause of death remained unknown.

5.5.3 Reproductive health
Out of 24 pregnancies (in 21 women), 5 ended in spontaneous miscarriage and 19 pregnancies occurred with no thrombotic events or complications. Antithrombotic medication was prescribed in a majority of the pregnancies; in 19 cases LMWH, and in 2 cases Aspirin. In only two pregnancies no medications were used.

Table 13. Imaging findings at admission

<table>
<thead>
<tr>
<th>Neuroimaging findings (n=161)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus sagittalis superior</td>
<td>87 (54)</td>
</tr>
<tr>
<td>Lateral sinus, left</td>
<td>81 (50)</td>
</tr>
<tr>
<td>Lateral sinus, right</td>
<td>71 (44)</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>33 (21)</td>
</tr>
<tr>
<td>Cortical veins</td>
<td>43 (27)</td>
</tr>
<tr>
<td>Jugular vein</td>
<td>40 (25)</td>
</tr>
<tr>
<td>Deep cerebral vein thrombosis</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Parenchymal infarction/edema</td>
<td>34 (21)</td>
</tr>
<tr>
<td>Parenchymal hemorrhage</td>
<td>22 (14)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>
5.5.4 Adverse events during follow-up and anticoagulation use

At follow-up, 71% of our patients used antithrombotic drugs, and 62 patients (39%) were prescribed life-long anticoagulation treatment. Three patients used direct oral anticoagulants (Figure 14). During follow-up there were 9 cases of recurrent VTE, 3 superficial vein thromboses, 5 deep venous thromboses of the legs, and 2 PE yielding VTE incidence of 1.1/100 patients years. Patients reported 10 bleeding events requiring medical help: 3 nose bleeds, 1 gynecological bleeding, 1 hematuria, and 5 potentially life-threatening subdural hematomas. Incidence of hemorrhagic events requiring medical help was 1.3/100 patient years (Table 15).

**Figure 14.** Use of thrombotic drugs at follow-up

![Bar chart showing use of thrombotic drugs at follow-up]

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at CVT Onset</th>
<th>Adverse event</th>
<th>Time since index CVT</th>
<th>Precipitating factors</th>
<th>Medications in use</th>
<th>INR†</th>
<th>Thrombophilia</th>
<th>Medications after event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>36</td>
<td>DVT+PE*</td>
<td>7 mo</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Protein C deficiency</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>PE</td>
<td>12 mo</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>DVT</td>
<td>3 years</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>DVT</td>
<td>8 years</td>
<td>Gastrointestinal surgery</td>
<td>LMWH† prophylaxis</td>
<td></td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>CVT</td>
<td>11 mo</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Aspirin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>DVT</td>
<td>12 mo</td>
<td>Neurosurgery</td>
<td>-</td>
<td></td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>DVT</td>
<td>4 years</td>
<td>Monoclonal gammopathy</td>
<td>Clopidogrel</td>
<td></td>
<td>Warfarin</td>
<td>Warfarin and Aspirin</td>
</tr>
<tr>
<td>Male†</td>
<td>36</td>
<td>SDH²</td>
<td>12 years</td>
<td>-</td>
<td>Warfarin 3.6</td>
<td></td>
<td>Protein C deficiency</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Female</td>
<td>49</td>
<td>SDH</td>
<td>4 mo</td>
<td>Essential thrombocthemia</td>
<td>LMWH and Warfarin</td>
<td>3.1</td>
<td>Antiphospholipid syndrome</td>
<td>LMWH and Aspirin</td>
</tr>
<tr>
<td>Male</td>
<td>66</td>
<td>SDH</td>
<td>4 mo</td>
<td>Head trauma</td>
<td>Aspirin 100mg</td>
<td>1.2</td>
<td>-</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>SDH</td>
<td>9 mo</td>
<td>Head trauma</td>
<td>Warfarin 2.6</td>
<td>2.1</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>SDH</td>
<td>0.5 mo</td>
<td>-</td>
<td>Warfarin 2.1</td>
<td>2.1</td>
<td>-</td>
<td>Warfarin 6 months</td>
</tr>
</tbody>
</table>

† International Normalized Ratio, ‡ Same patient, *Deep vein thrombosis, †Pulmonary embolism, ‡Low-molecular-weight heparin, ²Subdural hematoma
5.5.5 Residual symptoms
Residual symptoms were reported by 68% of the patients. Symptoms reported included self-reported neuropsychological problems (41%), self-reported linguistic problems (21%), headache more often than once a week (20%), impaired vision (9%), and motor/sensory deficit (6%). Depression (tested with Beck Depression Inquiry) was noted in 19% of the patients, and antidepressants were used by 11% of the patients. Epileptic seizures were common. 35% had had seizure(s) at some point in their disease, and 9% had active epilepsy (i.e. suffered from seizures in the last year). Epilepsy medication was used by 21% of the patients at the time of the follow-up visit.

5.5.6 Functional outcome
Good functional outcome (mRS 0-1) was achieved by 83% of our patients, and only two patients were dependent (Figure 15). Male sex, low education level, estrogen use in females, presence of focal symptoms at admission, major stroke symptoms, and hemorrhagic parenchymal lesion in MRI were associated with unfavorable outcome in univariate analysis. In age- and sex-adjusted multivariate analysis major stroke symptoms (OR 5.8, CI 95 2.2-15.6) and low education level (OR 4.8, CI 95 1.3-17.4) were independently associated with unfavorable outcome. Functional outcome according to clinical and neuroimaging characteristics is shown in table 14.

5.5.7 Vocational outcome
Vocational outcome analysis included 121 working aged patients, of whom 23% were unemployed at the time of follow-up, and 16% were on permanent disability imbursement due to CVT. Patients residual symptoms were associated with unemployment; motor/sensory deficit (OR 4.53, CI 95 1.13-18.20), self-reported linguistic problems (OR 9.33, CI 95 3.57-24.27), self-reported neuropsychological problems (OR 10.48, CI 95 3.93-27.93), impaired vision (OR 4.00, CI 95 1.27-12.65), active epilepsy (OR 29.33, CI 95 3.42-251.42), and depression (OR 3.54, CI 95 1.31-9.56). Headache more than once per week was the only residual symptom not associated with unemployment (OR 1.01, CI 95 0.23-4.44). Residual symptoms and vocational outcome is depicted in Figure 16. Vocational outcome according to clinical and neuroimaging characteristics is shown in table 14. Other univariate factors with association were male sex, age >38 years, low educational level, coagulation disorder, major stroke symptoms, and estrogen use in women. In age- and sex-adjusted multivariate analysis, low education level (OR 4.8, CI 1.0-21.2) and major stroke symptoms (OR 3.2, CI 1.1-10.9) were associated with unemployment.
Figure 16. Residual symptoms and vocational outcome
<table>
<thead>
<tr>
<th>Table 14. Functional and vocational outcome of the study population according to clinical and neuroimaging characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Age &gt;38 years</td>
</tr>
<tr>
<td>Low education level</td>
</tr>
<tr>
<td>Risk Factors</td>
</tr>
<tr>
<td>Local infection</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Any systemic disorder</td>
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<tr>
<td>Any coagulation disorder</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>No known risk factor</td>
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<tr>
<td>OC* or HRT^ (women only)</td>
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<tr>
<td>Clinical findings at admission</td>
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<tr>
<td>Focal symptoms ± encephalopathy</td>
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<tr>
<td>Headache or (IH) only</td>
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<tr>
<td>GSC° 12 or lower</td>
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<tr>
<td>NIHSS² &gt;2 points</td>
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<tr>
<td>Neuroimaging at admission</td>
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<tr>
<td>Infarction</td>
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<tr>
<td>Intracerebral hemorrhage</td>
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<tr>
<td>Deep cerebral vein thrombosis</td>
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<tr>
<td>Hydrocephalus</td>
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*Oral contraceptives, *Hormonal replacement therapy, *Isolated Intracranial Hypertension Syndrome, °Glasgow Coma Scale, **National Institutes of Health Stroke Scale
6 DISCUSSION

6.1 General discussion

Cerebral venous thrombosis is a rare disease, and because of this most CVT data derive from modestly sized study populations. For this Thesis project we collected a retrospective CVT registry covering all in-hospital CVT patients from 1987 and onwards, and for long-term outcome evaluation all survivors were invited for a follow-up visit. During this project we managed to collect one of the largest single-center CVT cohorts. For more accurate data analysis multicenter co-operation is essential considering the rarity of the disease. We managed to collect a very notable European CVT database when our CVT database was combined with the large and detailed CVT databases from the Academic Medical Centre in Amsterdam (the Netherlands) and Sahlgrenska University Hospital in Gothenburg (Sweden).

6.2 Recanalization (I)

The main findings of this study were that poor recanalization was associated with older age, male gender, and absence of known risk factors or causes. In our study almost half of the patients had complete recanalization, 34% had partial recanalization, and 19% had no recanalization of the sinuses. Our findings of complete sinus recanalization in around half of the patients is in line with previous smaller studies [92, 126, 175, 231-234] [235, 236]. A recent Mexican study reported higher recanalization rates, with 66% of the patients achieving complete recanalization and only 6% with no sinus recanalization at 6 months. In this study all 102 patients received anticoagulation [238]. Anticoagulation was given to almost all of our own CVT patients as well (97%), so compared to this new study our recanalization rates were low. Part of the differences in recanalization rates may be explained by differences in patient populations. In the Mexican series, women, young age, and pregnancy related CVT were more prevalent. This difference may also be explained by the shorter length of our follow-up, as some of our patients had follow-up imaging before 6 months had passed (minimum of 4 months to follow-up). Recanalization of the sinuses seems to occur in the first 6 months after diagnosis, and recanalization rates do not rise in further repeated imaging studies [231, 237] [238].

In the univariate analysis, we found that male sex, older age, and absence of risk factors or causes for CVT were associated with poor recanalization. In the multivariate analysis, increasing age was the only variable independently associated with recanalization status, but the relatively small number of patients in our study has to be taken into account when assessing these results. In the Mexican study, factors affecting recanalization were SSS thrombosis, defined cause of CVT, and patient age of <50 years [238]. Many studies have noted that older CVT patients have worse outcome [3][10][11][126][152][34]. Due to differences in etiological profile in different age groups, younger patients, especially women, have more transient risk factors [37]. In both our own study and the Mexican study, a defined cause of CVT was noted to correlate with recanalization. This strengthens the notion that a treatable or preventable cause for thrombosis improves sinus recanalization.

We found no independent correlation between recanalization and functional outcome in multivariate analysis, despite a trend noted in univariate analysis. However, patients with no recanalization had more often headaches. In one previous study patients with no recanalization suffered more often from headaches, but in two other studies no correlation between recanalization and outcome was observed [232, 237] [237]. The Mexican study found that patients with complete recanalization had better functional outcome, but correlation to residual symptoms was not observed [238]. Thus the data of recanalization and how it affects outcome after CVT is still unclear, and studies with larger sample sizes are warranted to investigate this issue.
6.3 D-dimer (II)

In this study we noted that D-dimer levels in CVT patients correlated with extent of thrombosis and time elapsed from symptom onset. D-dimer was elevated in 87% and negative in 13% of the patients (9 out of 71 patients). In previous small studies, false negative D-dimer measurements were noted in 0% to 24% of the patients [183-187][188, 189]. A meta-analysis investigating D-dimer in CVT was published in 2012. In this meta-analysis false negative D-dimer was measured in 6% of suspected CVT cases, with whom the diagnosis was later confirmed (10 out of 155 patients). In this meta-analysis, D-dimer measurements had mean sensitivity of 93.9 (CI95 87.5-97.1) and mean specificity of 89.7 (CI95 86.5-92.2). It should be noted that in patients with factors associated to false negative measures, D-dimer sensitivity was well below 90 [190]. In a recent meta-analysis investigating D-dimer in low CVT-probability headache patients (i.e. normal neurological status and normal standard CT scan) sensitivity of D-dimer was 97.8 and specificity was 84.9 [188].

We noted that D-dimer levels correlated to extent of thrombosis (i.e. number of thrombosed sinuses), a fact reported in previous studies of D-dimer in both CVT and DVT [183, 185, 186, 248]. We also noted a correlation to time elapsed since symptoms onset, a finding reported in previous retrospective studies [183, 185], and investigated thoroughly with repeated imaging and D-dimer measures in 2014 [186]. D-dimer levels in our study did not correlate to clinical presentation, presence of parenchymal lesions, or outcome. Our findings in multivariate analysis could have been affected by the study’s retrospective design that led to quite a large exclusion rate and thus limiting our patient numbers. One study previously reported that patients with isolated headache have lower D-dimer levels [185], but this finding might be confounded by longer diagnostic delay in patients presenting with isolated headache [150].

D-dimer alone is not a reliable way to exclude CVT. However, in low CVT probability patients with acute or subacute symptoms, D-dimer may in the future function as one way to exclude CVT without need for MRI. No other potential biomarkers have yet been studied in detail in CVT settings. Future studies with large numbers of participants should focus on studying various biomarkers in the early phase and also study combinations of biomarkers to search for a quick, easy, and inexpensive way of excluding CVT and other thrombotic events without the need of invasive or costly investigations.

6.4 Admission hyperglycemia (III)

Our study is the first investigation into hyperglycemia in CVT. At admission one in five patients had elevated blood glucose levels. We found out that hyperglycemic patients were older, and they had a more severe manifestation of the disease with higher numbers of ICH, hemicraniectomy, and intensive care unit treatment. The effect of hyperglycemia on outcome was investigated in multivariate analysis, and we found a clear dose-dependent correlation to poor outcome and death.

Hyperglycemia is well-known to be associated with poor prognosis in both ischemic and hemorrhagic stroke patients [249-252], but does hyperglycemia has a causative effect on CVT outcome? Hyperglycemia has been suggested to work as a secondary marker of stroke severity, levels rising due to stress hormone release [249][251]. Many mechanisms concerning how hyperglycemia affects stroke outcome have been reported. High glucose has a negative effect on ischemic brain parenchyma. It has been linked with hematoma volume, hemorrhagic transformation, loss of penumbral tissue, diminishing recanalization and reperfusion, and elevated risk of [251]reperfusion injury [249, 250, 253]. Hyperglycemia also has a systemic effect shifting coagulation homeostasis towards thrombosis [254]. Probably these same mechanisms noted in other stroke types are also implicated in CVT.

In CVT patients, symptom presentation is diverse. Thus, blood glucose measurement time from ictus varies from patient to patient. We had to exclude 16% of our patients from this study due to unrecorded glucose measurements. Nevertheless, baseline characteristics of included and excluded patients were similar, except for a lower rate of ICH in the excluded patients. Undiagnosed diabetes has also been suggested as a confounding factor in stroke and myocardial infarction studies [255]. However, in our CVT population this
probably does not play a major role, as CVT patients are generally younger harboring smaller diabetes risk, and only two of our patients (0.6%) were diagnosed with diabetes in the following 6-month period.

Our conclusion is that a causal relationship of admission hyperglycemia and poor outcome exists in CVT. This conclusion is based on the strength of the association we found, the presence of a concentration-response effect, and the consistency with observations in other conditions. Efficient blood glucose control might improve outcome in CVT patients, however, so far there are no existing clinical trials. Data on tight glycemic control in ischemic stroke patients is conflicting, some studies showing benefit, and some showing even harm. Therefore, further studies are needed to determine the most beneficial approach [253].

6.5 Cancer and risk of cerebral venous thrombosis (IV)

In this study we noted that cancer raises CVT risk around 4-fold. This association has previously been noted in DVT and PE, and seems to be of similar magnitude [256][257][258]. However, CVT is a more rare complication, so the absolute risk for the individual is lower.

In PE and VTE studies, hematological and solid cancers seem to carry a similar risk for thrombosis, but based on our findings this seems not to be the case with CVT. Hematological cancers carried a much larger risk than solid cancer (OR 18 vs OR 2.5). This increased risk of CVT in hematological types of cancer was largely but not fully attributable to acute lymphoblastic leukemia (ALL). When we excluded these patients, we still found that hematological cancer increased the risk of CVT approximately 10-fold. Previous studies have suggested that patients with ALL are especially prone to developing CVT, and our study confirms this finding [103, 104]. Suggested mechanisms behind CVT in ALL induction therapy include L-asparaginase caused antithrombin deficiency and the use of intrathecal methotrexate. All of our patients except for one underwent this therapy at the time of CVT.

We found out that risk for CVT was highest in the first year after cancer diagnosis. Similar elevation of risk has also been noted in studies investigating VTE [256-258]. The theory is that both prothrombotic changes initiated by active cancer cells and prothrombotic risks of cancer therapies (surgery and chemotherapy) accumulate in this time period [258, 259]. It is likely that the same mechanisms play a role in CVT patients.

In conclusion, cancer is an important risk factor in CVT, especially in the first year after cancer diagnosis and specifically in hematological malignancies.

6.6 Long-term outcome (V)

In this study we noted that functional outcome after CVT is generally good, with 11% mortality rate, and 80% of patients recovering with mild residual symptoms (mRS 0-1). Venous thrombotic events and bleeding complications were rare, and pregnancies occurred without complications. However, residual symptoms were very common, and they affected ability to return to employment.

Our findings regarding functional outcome and mortality after CVT are in line with the largest CVT outcome study, as were our findings regarding predictors of poor outcome (male sex, age, intracerebral hemorrhage), and good outcome (presentation with IIH) [3, 260]. Interestingly, we observed that low education level and an NIHSS score over two points strongly associated with both incomplete functional recovery and diminished working ability. Education level may correlate with the patient’s motivation, or can hinder finding a suitable employment. The NIHSS score works well in arterial stroke correlating with outcome and the size of parenchymal damage [261]. Our findings that the NIHSS score also correlates with outcome in CVT suggests that the NIHSS score could prove useful in CVT.

Neuropsychological problems were often reported and depression was fairly common. Both these findings have previously been noted in smaller CVT cohorts, but have not yet been investigated in any of the larger CVT studies [18, 19, 242, 262]. Unfortunately our study did not include neuropsychological testing, but is
relying on patient self-reported symptoms. Paresis symptoms and epilepsy were both present in one out of ten patients, and these findings are similar to other CVT cohorts [3, 36, 160].

Incidence of VTE (1.1/100 patient years) in our study was considerably lower than what has been reported in two large CVT cohorts (ISCVT and CEVETIS); VTE incidence 4.1 and 2.35/100 patient years, and CVT incidence 1.5 and 0.98/100 patient years, respectively. This difference in recurring thrombotic events may be explained by the larger proportion on permanent anticoagulation in our study. 40% of our patients used anticoagulants, and in the two other studies only 20% of the patients used anticoagulants. These studies also found no correlation between permanent anticoagulation use and VTE recurrence [4, 229]. Patients on permanent anticoagulation are in clinical practice also the ones with the highest risk for recurrent thrombosis, so caution should be used when assessing efficacy of continuous anticoagulation. Differences in institutional practices in using anticoagulation may explain this difference in medication. In our study 25% of the patients were using aspirin. No guidelines regarding aspirin use in CVT patients exist, but in our center treating physicians often prescribe aspirin to patients with no obvious or transient risk factors. Aspirin use may in part explain the low incidence of VTE recurrence in our patients, as aspirin moderately reduces the risk for venous thrombosis [263]. Despite the high number of patients using anticoagulation medication, occurrence of bleeding events were low. The relatively young age of CVT patients may explain this finding. Notably, subsequent pregnancies after CVT were uneventful, with no thrombotic complications. Our findings are in line with those of previous studies emphasizing that a history of CVT should not prevent future pregnancies [244, 245].

In our study, 25% of working-age CVT patients were unemployed at the end of the follow-up period, and 16% received permanent disability pension. All recorded residual symptoms except headache correlated to employment status. Only small studies have previously explored working ability after CVT. In one study all of the patients recovered without functional disability and resumed their work [14]. In two other studies, 20–40% of the CVT patients failed to resume full-time employment [13, 18]. Of course, non-medical issues, such as general economic climate and national sick retirement benefits and rules, may also affect employment rates.

In conclusion, CVT patients had a good outcome, with minor neurological symptoms, and a small risk for recurrent VTE. Neurological symptoms affecting working ability were common, and in this young patient population importance of mild residual symptoms should not be underestimated.

6.7 Strengths and limitations
Strengths of our study include collection of consecutive patients in a very detailed data registry, and our registry represents a whole population diagnosed with CVT in the Helsinki and Uusimaa area, and thus selection bias in our registry is low. The Helsinki CVT database has been collected retrospectively based on ICD-10 diagnosis numbers from hospital records, so it is possible that some patients have been missed due to wrong diagnosis coding. Retrospective study design has inherent problems. Patient data initially recorded by numerous clinicians may vary, and some data has not been initially recorded accurately in the patient records causing missing or flawed data. Study V had a prospective arm were patients were invited for a follow-up visit. Caution should be used in assessing our findings on self-reported cognitive symptoms, as recall bias and psychological reactions to CVT diagnosis probably affects patients perception of their individual symptoms.

For studies III and IV we used a combined database from three CVT centers, and the possibility of differences in population, selection of patients, patient characteristics, treatment strategies, and data recording has to be taken in to account when assessing our findings.
6.8 Future perspectives

Cerebral venous thrombosis remains an entity still under investigation. Most of our knowledge is derived from other stroke subtypes or is gathered from small patient series. For further CVT investigation it is vital to increase international collaboration in gathering large patient series of this rare disease. Regular collaborator meetings enable planning, designing, and executing of study networks with large numbers of patients worldwide. Support of good quality CVT studies in low-income countries is important, as our knowledge of CVT in still sadly lacking. Genetic investigations enable us to discover novel predisposing factors for CVT. Studying diagnostic and prognostic blood biomarkers may ease CVT diagnostics, and determining prognosis in the future. Larger international multicenter studies with large patient numbers enables reliable testing of novel treatment approaches and discovering underlying causes and risks of CVT.
SUMMARY AND CONCLUSIONS

Cerebral venous thrombosis is a rare cause of stroke in adults with a wide spectrum of symptoms and causes. Clinical outcome of patients with CVT is variable. Less than one in ten CVT patients die in the acute phase. A majority of the patients recover well with good functional recovery. Patients with CVT are mainly young and working-aged, thus, factors affecting risk of this disease and clinical outcome should be of special interest.

Sinus recanalization is less common in patients with known factors of poor outcome. Data suggest that complete recovery and sinus recanalization are linked, but the independent effect of recanalization in clinical outcome still needs to be studied more extensively.

Fibrin D-dimer levels in CVT patients were affected by the extent of thrombus in cerebral sinuses and the time elapsed from symptom onset. D-dimer measurements alone are neither sensitive enough to rule out CVT nor to predict outcome of CVT patients. At the moment clinical usefulness of D-dimer measurement is unclear.

Admission hyperglycemia is more common among CVT patients with a more severe clinical picture and it appeared to be an independent predictor of patient outcome. Thus, it is worth to monitor CVT patients’ blood glucose levels and probably worth treating in the acute phase of the disease. The effect of tight glycemic control in CVT should be investigated in large and randomized future trials.

Cancer elevates the risk of CVT, especially in the first year after cancer diagnosis. Solid malignancies elevate the risk 4-fold, while hematological malignancies carry a higher 10-fold risk. Should a patient with newly diagnosed cancer and ongoing chemotherapy develop new neurological symptoms or signs, especially new-onset headache, he/she should be investigated for CVT.

Long-term outcome after CVT is good compared to other stroke subtypes. 80% of the patients recover well, and only one patient out of ten dies. Venous thrombosis recurrence is rare and subsequent pregnancies are safe. Self-reported mild residual symptoms are very common, and working ability after CVT was quite often affected. Patients should be informed of the good outcome associated with CVT. However, in working-aged patients, special care in treating depression, pain, and neuropsychological symptoms should be taken in order to facilitate full recovery and return to previous life including the same employment.
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ORIGINAL PUBLICATIONS