Cerebral Venous Thrombosis

Complications and Outcomes

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ABSTRACT

Cerebral venous thrombosis (CVT) is a relatively rare cause of stroke, which predominantly affects working-aged adults and particularly women. The clinical course is highly miscellaneous. Data from large cohorts are scarce and knowledge on CVT complications and outcomes are limited. The overarching aim of this thesis was to investigate prognostic factors affecting clinical outcome after CVT. We investigated adult patients consecutively diagnosed with CVT from a local registry, the Sahlgrenska CVT Registry (*study I*), and from a newly established large international cohort from, in total, 17 hospitals, the International CVT Consortium (*study II-V*).

Among 62 working-aged adults included from the Sahlgrenska CVT Registry, functional outcome was good as 87% were independent at long-term follow-up. However, 29% were unable to return to work and merely 19% were asymptomatic (*study I*). In study II-V, patients were included from the International CVT Consortium. Acute symptomatic seizure(s) occurred in 441/1,281 (34%) patients, predicted by variables related to parenchymal injury adjacent to the cerebral cortex (*study II*). Of 123/1,127 (11%) experiencing a first late seizure (>7 days after diagnosis), seizure recurrence rate was 70% (*study III*). A dural arteriovenous fistula was detected in 29/1,218 (2.4%) patients, most commonly concomitant or subsequently to the diagnosis of CVT (*study IV*). Acute symptomatic seizures, status epilepticus in the acute phase and dural arteriovenous fistulas were not associated with worse functional outcome (*study II and IV*). From risk factors affecting clinical outcome, we developed the combined SI_2NCAL_2C risk score to calculate individual risks of dependency or mortality at 6 months, mortality at 30-days and mortality at 1 year. The model showed promising performance in internal validations (*study V*).

This thesis indicates that although most patients recover well and achieve independency after CVT, residual symptoms are frequent and one-quarter of working-aged adults are unable to return to work. Seizures frequently complicate the acute phase and every tenth patient experiences late seizures after CVT. The high risk of late seizure recurrence supports the diagnosis of epilepsy at time of a first late seizure. Dural arteriovenous fistulas are infrequent and mostly appear simultaneously or after CVT. The SI_2NCAL_2C risk score can be used with information available in routine clinical practice, to predict dependency or mortality at 6 months, mortality at 30-days and mortality at 1 year, but warrant external validation prior to implementation in clinical practice.

Keywords: Cerebral venous thrombosis, complications, return to work, seizure, follow-up, dural arteriovenous fistula, outcome

SAMMANFATTNING PÅ SVENSKA

Cerebral ventrombos (även kallat sinustrombos eller CVT) innefattar bildandet av en venös blodpropp i hjärnans durala sinus och/eller kortikala vener. Omkring 1-2 per 100 000 personer drabbas per år. Ungefär 0,5-1% av all stroke beräknas bero på CVT, men till skillnad från arteriellt orsakad stroke drabbas en avsevärt yngre population med en medelålder på ca 40 år och företrädelsevis kvinnor (60-70%). Neurologiska, kognitiva och emotionella följdsymptom är vanligt förekommande, liksom kronisk huvudvärk och krampanfall, och kan få stora konsekvenser både för individen och för dess anhöriga. Till följd av relativt låg förekomst är CVT underbeforskat, och kunskap om sjukdomen baseras i huvudsak på data från fallserier eller mindre patientgrupper. Data från större internationella grupper av patienter är sällsynt, i synnerhet från studier som undersöker komplikationer och utfall.

Det huvudsakliga syftet med denna avhandling var att undersöka faktorer som kan påverka kliniskt utfall efter CVT. Vi presenterar data från vuxna patienter som drabbats av CVT och behandlats på Sahlgrenska universitetssjukhuset i Göteborg mellan 1996 och 2021. Delarbete II-V innefattar även patienter från en stor internationell kohort, the International CVT Consortium, ett nyetablerat samarbete som inkluderar vuxna patienter med CVT från totalt 17 akademiska center runt om i världen.

I delarbete I undersöktes, i en svensk population, prevalens av och faktorer associerade med återgång till arbete efter CVT. Det kliniska utfallet var gott såtillvida att 87% av de deltagande 62 personerna återhämtade sig väl och var inte beroende av hjälp i sin vardag. Trots detta kunde totalt 29% av patienter i arbetsför ålder inte återgå till arbete inom uppföljningsperioden (median 135 månader). Kvinnligt kön och skada i hjärnvävnaden i samband med CVT innebar lägre chans att kunna återgå i arbete. Endast 19% rapporterade att de inte hade några kvarvarande symptom.

I delarbete II undersöktes förekomst av och riskfaktorer för akutsymptomatiska krampanfall (inom 7 dagar efter CVT diagnos) och dess påverkan på kliniskt utfall. Sammantaget drabbades 441 av 1281 (34%) patienter av akutsymptomatiska krampanfall. Riskfaktorer för akutsymptomatiska krampanfall inkluderade tillstånd som är associerade med vävnadsskada i eller nära hjärnbarken. Akutsymptomatiska krampanfall var inte associerade med försämrat kliniskt utfall.

I delarbete III undersökte vi förekomst och riskfaktorer för sena krampanfall som inträffat minst 7 dagar efter diagnos av CVT. Av de 1127 inkluderade patienterna drabbades 123 (11%) av sena krampanfall. Sena krampanfall var förknippade med bland annat akutsymptomatiska krampanfall och riskfaktorer som är associerade med en permanent hjärnskada. Sju av tio patienter med sena krampanfall drabbades av ytterligare ett anfall, vilket berättigar diagnos av epilepsi redan efter ett första sent krampanfall.

I delarbete IV undersöktes sambandet mellan CVT och uppkomsten av durala arteriovenösa fistlar (dAVF, en typ av kärlmissbildning i hjärnan), samt hur denna kombination påverkar kliniskt utfall. En eller flera dAVF kunde påvisas hos 29/1218 (2.4%) undersökta patienter. Vanligen påvisades dAVF samtidigt som, eller vid en följande undersökning efter, påvisandet av CVT. Kombinationen av CVT och dAVF var inte associerat med försämrat kliniskt utfall jämfört med patienter som ej hade dAVF.

I delarbete V utvecklade vi en prognostisk algoritm för att utifrån information som finns tillgänglig vid diagnos av CVT, kunna identifiera patienter med ökad risk för död eller för att bli beroende av andras hjälp i vardagen. Vi undersökte faktorer som tidigare rapporterats ha ett samband med försämrat kliniskt utfall efter CVT, och utvecklade en kombinerad kalkylator kallad SI_2NCAL_2C. Kalkylatorn kan användas för att beräkna individuell risk för död eller hjälpberoende vid 6 månader, mortalitet inom 30 dagar och mortalitet inom 1 år efter CVT.

Sammantaget bidrar denna avhandling med ny och viktig kunskap om CVT från en stor internationell patientpopulation. Vi har visat att en relativt stor andel av överlevande patienter i arbetsför ålder inte kan återgå till arbete efter CVT och att kvarvarande restsymptom är vanliga. Krampanfall är en vanlig komplikation i akutskedet, och var tionde patient drabbas av sena krampanfall. Den höga risken för återkommande sena krampanfall motiverar diagnos av epilepsi, och därmed krampförebyggande behandling, redan vid ett första krampanfall. Kärlmissbildningen dAVF är en ovanlig komplikation till CVT. Varken akuta krampanfall eller dAVF var associerade med försämrat kliniskt utfall. Resultaten i denna avhandling bidrar till ökad kunskap om hur olika tillstånd påverkar kliniskt utfall efter CVT, vilket förhoppningsvis kan vara av betydelse för patienter som i framtiden drabbas av CVT.

LIST OF ORIGINAL PUBLICATIONS

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

I. Erik Lindgren, Katarina Jood, Turgut Tatlisumak.
Vocational outcome in cerebral venous thrombosis: Long-term follow-up study.
Acta Neurol. Scand. 2018:137(3):299-307.

II. Erik Lindgren,* Suzanne M. Silvis,* Sini Hiltunen, Mirjam R. Heldner, Fabiola Serrano, Michele de Scisco, Johan Zelano, Susanna M. Zuurbier, Mayte Sánchez van Kammen, Maryam Mansour, Diana Aguiar de Sousa, Sara Penas, Saleem Al-Asady, Esme Ekizoglu, Petra Redfors, Awet Ahmed, Nilüfer Yesilot, Masoud Ghiasian, Miguel A. Barboza, Valencia Arnao, Paolo Aridon, Martin N.M. Punter, José M. Ferro, Timothy Kleinig, Antonio Arauz, Turgut Tatlisumak, Marcel Arnold, Jukka Putaala, Jonathan M. Coutinho,** and Katarina Jood.**
Acute seizures in cerebral venous thrombosis.
Neurology. 2020:95(12):e1706-e1715.

III. Mayte Sánchez van Kammen,* Erik Lindgren,* Suzanne M. Silvis, Sini Hiltunen, Mirjam R. Heldner, Fabiola Serrano, Johan Zelano, Susanna M. Zuurbier, Maryam Mansour, Diana Aguiar de Sousa, Patrícia Canhão, Saleem Al-Asady, Esme Ekizoglu, Petra Redfors, Nilüfer Yesilot, Masoud Ghiasian, Miguel A. Barboza, Valentina Arnao, Paolo Aridon, Martin N.M. Punter, José M. Ferro, Antonio Arauz, Turgut Tatlisumak, Marcel Arnold, Jukka Putaala, Katarina Jood,** and Jonathan M. Coutinho.**
Late seizures in cerebral venous thrombosis.
Neurology. 2020;95(12):e1716-e1723.

IV. Erik Lindgren, Alexandros Rentzos, Sini Hiltunen, Fabiola Serrano, Mirjam R. Heldner, Susanna M. Zuurbier, Suzanne M. Silvis, Maryam Mansour, William Allingham, Martin N. M. Punter, Blake F. Giarola, Jeremy Wells, Mayte Sánchez van Kammen, Eike I. Piechowiak, Nicole Chiota-McCollum, Carlos Garcia-Esperon, Christophe Cognard, Timothy Kleinig, Masoud Ghiasian, Jonathan M. Coutinho, Marcel

Arnold, Antonio Arauz, Jukka Putaala, Katarina Jood, Turgut Tatlisumak: the International CVT Consortium.
Dural arteriovenous fistulas in cerebral venous thrombosis: Data from the International Cerebral Venous Thrombosis Consortium.
Eur J Neurol. 2022;29(3):761-770.

V. Erik Lindgren,* Katarzyna Krzywicka,* Maria A. de Winter, Mayte Sánchez van Kammen, Mirjam R. Heldner, Sini Hiltunen, Diana Aguiar de Sousa, Maryam Mansour, Patrícia Canhão, Esme Ekizoglu, Miguel Rodrigues, Elisa M. Silva, Carlos Garcia-Esperon, Valentina Arnao, Paolo Aridon, Naaem Simaan, Suzanne M. Silvis, Susanna M. Zuurbier, Mine Sezgin, Andrey Alasheev, Andrey Smolkin, Daniel Guisado-Alonso, Nilüfer Yesilot, Miguel A. Barboza, Masoud Ghiasian, Ronen R. Leker, José M. Ferro, Antonio Arauz, Marcel Arnold, Jukka Putaala, Turgut Tatlisumak, Jonathan M. Coutinho,** Katarina Jood.**
A scoring tool to predict mortality and dependency after cerebral venous thrombosis.
Manuscript.

* Authors contributed equally as first authors.
** Authors contributed equally as senior authors.

Studies II and III were subject to an editorial,
"Distinguishing early from late seizures in cerebral venous thrombosis: cinderepilepsy."
Neurology, 2020;95(12):513-514

The original publications are appended at the end of the thesis. Reprints were made with permission from the copyright holders.

CONTENT

ABBREVIATIONS

AED	Anti-epileptic drug
aOR	Adjusted odds ratio
ASS	Acute symptomatic seizures
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
CVT	Cerebral venous thrombosis
CVT-VITT	Cerebral venous thrombosis with vaccine-induced immune thrombotic thrombocytopenia
dAVF	Dural arteriovenous fistula
D-FIS	Daily Fatigue Impact Scale
DOAC	Direct oral anticoagulants
DOAC-CVT	Direct Oral Anticoagulants in the Treatment of Cerebral Venous Thrombosis
DVT	Deep venous thrombosis
EQ-5D	European Quality of life Five Dimensions
EXCOA-CVT	Extending Oral Anticoagulation Treatment after Acute Cerebral Vein Thrombosis
HAD	Hospital Anxiety and Depression scale
HR	Hazard ratio
HRT	Hormone replacement therapy
ICD-10	International Classification of Diseases Tenth Revision

ICH	Intracerebral hemorrhage
IQR	Interquartile range
ISCVT	International Study on Cerebral Venous and dural Thrombosis
Lisat-11	Life Satisfaction Questionnaire-11
LMWH	Low-molecular weight heparin
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
PE	Pulmonary embolism
PRIORITy-CVT	Prediction of Infarction and Recanalization in Cerebral Venous Thrombosis
RE-SPECT CVT	A clinical trial comparing efficacy and safety of dabigatran etexilate with warfarin in patients with CVT and dural sinus thrombosis
RTW	Return to work
SE	Status epilepticus
SECRET	Study of Rivaroxaban in Cerebral Venous Thrombosis
TO-ACT	Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1 INTRODUCTION

1.1 HISTORICAL PERSPECTIVE

The primary reports on cerebral venous thrombosis (CVT) date back to the first half of the 19th century. In 1825, the French physician Dr. Ribes described a patient presenting with severe headache and seizures.[1] A few years later, the English physician Dr. Abercrombie published a case report of a 24-year old woman who developed headaches and a fatal status epilepticus during her postpartum period.[2] In both patients, autopsies revealed thromboses in the cerebral sinuses and veins. Over the 20th century, radiologic imaging techniques evolved and radiologic visualization of the dural sinuses and veins either by catheter cerebral angiography, computed tomography (CT) venography or magnetic resonance imaging (MRI) venography has since played a key role in the diagnosis of CVT. The diagnosis, however, has remained challenging due to the rareness of the disease and the heterogeneity of symptoms at presentation which span from mild, chronic headache, to focal neurologic deficits, severe seizures, coma, transtentorial cerebral herniation and death.[3] During the latter part of the 20th century, diagnosis of CVT has been more widely acknowledged, as various case reports and case series were published from single centers. The first larger prospective study on CVT, the International Study on Cerebral Venous and Dural Thrombosis (ISCVT), was published in 2004 and comprised data on 624 patients with CVT.[4] Multicenter and international collaborations have since emerged, allowing for an increase in the amount of comparatively larger patient cohorts.[5-8]

In part due to the relative rarity of the disease and due to few patients seen in individual centers, the entities of CVT are not well-investigated. For example, in approximately 15% of patients diagnosed with CVT, no underlying etiological risk factor can be established.[4] Large cohort studies on CVT are scarce, and still, most of our knowledge on CVT originates from observational data and relatively small single center studies. Clinical features and symptoms of CVT are highly variable. Evidence is lacking on prognosis, complications in the acute phase and long-term follow-up. Most CVT patients have otherwise long and healthy life expectancy, as apart from children, mainly working-aged adults and predominantly women are affected.[3,4] It is therefore of particular importance to investigate factors influencing the outcome, not only for the affected individuals themselves, but also for their families, and socioeconomically for the society at large.

2 REVIEW OF THE LITERATURE

2.1 ANATOMY AND PHYSIOLOGY

The cerebral venous system constitutes of a network of cerebral veins and dural sinuses. Its main function is to drain deoxygenated blood and cerebrospinal fluid from the brain, for further transport extracranially through the jugular veins to the heart. Cerebral venous sinuses are formed by the meningeal and periosteal dural layers. Cerebral venous sinuses and veins, as opposed to peripheral veins, possess no valves nor vessel wall muscles. As a result, the cerebral venous system is physiologically mainly passive, and is thereby influenced by extravascular factors such as surrounding intracranial pressure and total cerebral blood flow. Cerebral venous pressure varies depending on the positioning of the individual, being approximately +1mm Hg in horizontal position and -3mm Hg in vertical position. In vertical position, venous blood flow is relatively constant around 600-700ml per minute, merely slightly varying with arterial pulsations. The precise cerebral venous blood velocity is not completely understood, but varies from 30 to 50cm per second in the internal jugular veins.[9-11]

The cerebral venous circulation can be divided into the superficial venous system and the deep cerebral venous system, connecting in the confluence of sinuses (Figure 1).

The superficial venous system drains the superficial parts of the large cerebral hemispheres including the cerebral cortex. Venous capillaries within the parenchyma assemble in venules and form cortical veins upon the cerebellar convexity. The cortical veins empty into bridging veins that pass through the subarachnoid space to the dural sinuses. Veins of the lateral surface anastomose with veins of the medial surface before they join the prominent superior sagittal sinus, which harbors the major part of the superficial venous drainage. The superior sagittal sinus terminates posteriorly in the confluence of sinuses, joining together with the inferior sagittal sinus and the deep cerebral venous system. In approximately 60% of individuals, the superior sagittal sinus ends by becoming the right transverse sinus. Consequently, the lateral sinuses (transverse sinuses and sagittal sinuses) most commonly drain the superior sagittal sinus asymmetrically, and equally in merely 20% of healthy individuals.[10-13]

The transverse sinuses pass bilaterally from the confluence of sinuses attached to the tentorium cerebelli. The transverse sinuses receive blood from the

temporal, parietal and occipital lobe and follow the posterior cranial fossa, forming the sigmoid sinuses on each side, leaving the intracranial space as the internal jugular veins. The right transverse sinus is usually prominent in comparison to the left side, and receives the larger amount of drainage from the superior sagittal sinus. In almost 20% of individuals, the transverse sinus of either side is hypoplastic or even absent. The cavernous sinuses drain parts of the frontal lobe and orbital areas, and consist of venous plexus located anteriorly and superiorly to sella turcica, with a close connection to important anatomical structures such as the internal carotid artery as well as the, oculomotor-, trochlear-, ophthalmic-, and abducens nerves.[10-14]

The deep territories of the brain, including the thalami, the internal capsule and parts of the basal ganglia, are drained through the deep cerebral veins (internal cerebral veins, the great cerebral vein of Galen, and the basal vein of Rosenthal) anteriorly to the cavernous sinus, or posteriorly into the straight sinus, which further empty into the confluence of sinuses.

The superior anastomotic vein (vein of Trolard) connecting the superior sagittal sinus and the superficial medial cerebral vein in the Sylvian fissure, and the inferior anastomotic vein (vein of Labbé) connecting the superficial medial cerebral vein and the sigmoid sinus, together facilitate alternative venous drainage paths of particular importance in case of vein and/or sinus occlusion. The veins of Trolard and Labbé are typically presented reciprocally on each side - when one is large, the other is usually small. When present, the vein of Labbé is more frequently occurring on the left side, and conversely the vein of Trolard is more frequently situated on the right side.[9-14]

The glymphatic (glia-lymphatic) system has gained a lot of attention during the last decade. The glymphatic system is believed to facilitate resorption of cerebrospinal fluid and metabolic waste products from the parenchymal extracellular space, primarily during sleep.[15,16] Proposedly, from the periarterial space of penetrating arterioles (Virchow-Robin spaces), cerebrospinal fluid is transported to the parenchymal extracellular space by Aquaporin-4 water channels, gradually pulsating towards venous perivascular and perineural spaces, meningeal lymphatic vessels and arachnoid granulations.[15] Enlargement of perivascular spaces has been reported in patients with small vessel disease and lacunar infarcts, but the clinical relevance of the glymphatic system in relation to different subtypes of stroke is yet to be determined.[17]

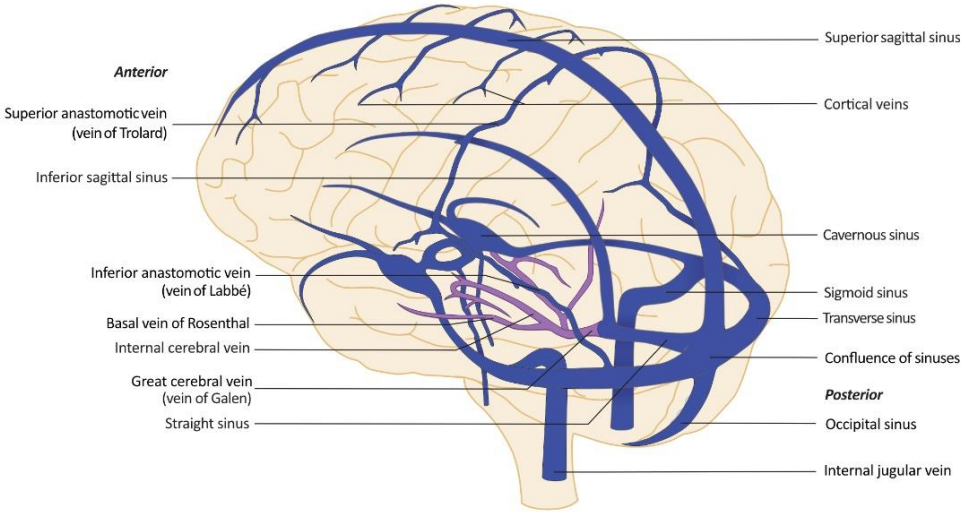

Figure 1. *Anatomy of the cerebral venous system. Image adapted by Judith Klecki, with kind permission from the author and the copyright holder.*[18]

2.2 PATHOPHYSIOLOGY

Thrombi are formed locally in cerebral sinuses and veins by factors influencing any entity of the Virchow's Triad - stasis of blood flow, damage to the vessel wall or relative hypercoagulability. Obstruction or stagnation of venous blood flow leads to thrombus formation by accumulation of coagulation factors, thrombocytes and leukocyte adhesion. Damage to the vessel wall causes exposure and release of coagulation factors. Imbalance in the natural prothrombotic and thrombolytic equilibrium may cause relative hypercoagulability.[3]

The pathophysiology of CVT can be described as two separate entities, although regularly occurring simultaneously; i) thrombosis of the cerebral veins and ii) thrombosis of the major sinuses. Thrombosis of the cerebral veins cause stagnation of venous blood flow backwards towards the parenchyma. Typically, the extended anastomotic venous system and collaterals present alternative routes for the blood. However, in case of inadequate compensation, the venous pressure gradually increases and both cytotoxic and vasogenic edema can occur. Progression of increased pressure and inhibition of blood flow gradually transforms edema to a venous infarction and/or eruption of capillaries leading to intracerebral hemorrhages.[19-22] Cytotoxic edema is

caused by ischemia and leads to cellular swelling. Vasogenic edema is formed by eruption of the blood-brain barrier, leading to leakage of blood plasma into the interstitium. The latter may be reversible by treating the underlying condition and restoring drainage.[3,21,23] Hemorrhagic or non-hemorrhagic parenchymal lesions are common and occur among 60% of patients with CVT. As compared to arterial lesions, venous lesions are characterized as lesions not limited by the traditional arterial anatomical territories and more often have hemorrhagic components (around 40% of patients in most published CVT cohorts).[3-5,7,8,24-26] Further, due to a higher ratio of vasogenic edema,[14] venous lesions are to a larger extent radiologically and clinically reversible compared to arterial lesions.[23] However, in severe cases multiple lesions, hemorrhage and edema all contribute to a substantial increase of the intracranial pressure. These patients are at risk of cingulate- or transtentorial herniation. Transtentorial herniation is the most frequently reported cause of acute death among patients with CVT.[27]

Thrombosis of the major sinuses decreases regional venous blood flow and also hinders the circulation of cerebrospinal fluid by obstruction of arachnoid villi. Thereby, thrombosis of the major sinuses may lead to generally increased intracranial pressure with clinical symptoms and signs such as headache and papilledema, and in severe cases to compression of parenchyma and cerebral transtentorial herniation.[3,28,29]

A recent report suggested that patients achieving early recanalization within the first week of anticoagulation treatment, have a higher chance of early radiologic regression of non-hemorrhagic parenchymal lesions as compared to those with persistent occlusion.[30] However, substantial knowledge gaps persist in understanding the underlying pathophysiology of CVT, mechanisms of brain injury and the potential benefit from treatments aiming at recanalization.[31]

2.3 EPIDEMIOLOGY

CVT is a fairly uncommon disease, believed to account for 0.5-1% of all strokes.[3,32] Early studies based on autopsy series suggested an incidence of 0.1-0.2 per 100 000 individuals annually.[33] In more recent population-based studies, reported incidence have been higher, ranging from 1.2 to 2.0 per 100 000 individuals annually.[24,32,34-38] These population-based studies show a trend towards an increase in incidence during the last decades, and it has been hypothesized that this increase mostly is attributable to improvements in non-invasive radiological techniques that allow for earlier diagnosis and less severe cases to be detected.[39,40] This hypothesis is also supported by the gradual

decrease in mortality over the same time period. A systematic review[40] showed decreased case-fatality from studies published prior to the millennium shift, whereafter reported mortality rates amount to 5-10%.[36,39,40] The mortality rate is lower than in other causes of stroke, but patients affected by CVT are significantly younger with a mean onset age around 40 years old.[4] For example, in the prospective ISCVT cohort, 78% of CVT cases occurred in patients <50 years of age,[4] compared to arterial ischemic stroke and intracerebral hemorrhage where around 30% of the cases occur in patients younger than 65 years.[41] Moreover, the distribution between sexes differs from arterial stroke. In adults, CVT predominantly affects women with a frequency of 60-80% in most published CVT patient cohorts.[3-5,7,8,42,43]

2.4 ETIOLOGY AND RISK FACTORS

Predisposing causes of CVT are multiple and often combined. Risk factors can theoretically be explained as affecting any of the categories of Virchow's Triad - stasis of blood flow, damage to the vessel wall or relative hypercoagulability.[3] Associated conditions primarily resemble risk factors for more common types of venous thromboembolism (VTE) such as deep venous thrombosis (DVT) or pulmonary embolism (PE), rather than those of arterial stroke.[44] As a consequence of the relatively low incidence of CVT, evidence on risk factors is limited to small case-control studies, prevalence in cohort studies, small case series and case reports.[45] The most commonly associated conditions and prevalence in large CVT cohorts are summarized in Table 1.[4-8,24-26,46-53]

Associated conditions for CVT can be divided into chronic risk factors (hereditary thrombophilia,[4,54] malignancy,[4,55] myeloproliferative neoplasms,[4,56] inflammatory diseases such as inflammatory bowel disease[4,57] or Behçet's disease,[38,58] antiphospholipid syndrome,[48,59] obesity,[60] dural arteriovenous fistula [dAVF][4]) and transient risk factors (female sex-specific risk factors,[61-63] infections,[4,8,64,65] mechanical precipitants including iatrogenic causes during neurosurgical procedures,[66] head trauma,[4,8,67] dehydration[4,5,8], anemia[4,6,68]).[3] For patients with an underlying predisposition for CVT, additional risk factors may result in a multiplicative effect on the risk of developing CVT, which for example have been reported for oral contraceptive use in women with obesity or in women with concomitant hereditary thrombophilia.[60,61]

The prevalence of risk factors varies by gender and age. Women of child-bearing age possess a threefold increased risk of CVT as compared to men.[3,4,42] However, the skewed ratio is equalized when adjusting for female hormone-related risk factors. These are termed female sex-specific risk factors and

include oral contraceptive drug use, pregnancy, postpartum period or hormone replacement therapy (HRT).[3] Median age at onset is around 40 years old and men are slightly older at onset as compared to women.[42,43] The most common risk factors for CVT in the elderly are malignancies, hereditary thrombophilia and hematological conditions.[69]

The prevalence of risk factors also varies between geographical regions.[53] A recent study which included patients mainly from India and Pakistan, all tested for genetic thrombophilia, reported anemia in approximately 50% of the cases.[6] In the same cohort, frequency of oral contraceptive drug use was notably lower as compared to previous studies from Europe[4], North America,[7,47] and South America.[53] The prevalence of infectious causes has declined over time in high-income countries while use of antibiotics has improved, but infections are still a frequent cause in low and middle income countries.[4,6,8,53,70] The inflammatory Behçet's disease is more common in the Eastern Mediterranean area and in regions along the Silk Road.[5,38]

Table 1. *Conditions associated with cerebral venous thrombosis*

	Risk factor	Prevalence in CVT cohorts‡
Chronic risk factors	None identified	6-44%
	Hereditary thrombophilia	9-46%
	Factor V Leiden mutation	3-27%
	Prothrombin G20210A mutation	2-19%
	Antithrombin deficiency	<1-7%
	Protein S deficiency	1-12%
	Protein C deficiency	1-9%
	Hematological condition‡‡	4-20%
	Cancer	1-11%
	Inflammatory disorders	4-5%
	Behçet's disease	<1-9%
	Dural arteriovenous fistula	1-2%
Transient risk factors	Female sex-specific risk factors‡‡‡	3-68%
	Oral contraceptive drug use	5-54%
	Pregnancy or postpartum	1-31%
	HRT	1-5%
	Infection (local or systemic)	2-22%
	Trauma	<1-3%
	Anemia	2-18%
	Dehydration	<1-27%

Abbreviations: CVT – cerebral venous thrombosis; HRT – hormone replacement therapy.
‡Preter 1996, Ferro 2002, Ferro 2004, Gosk Bierska 2006, Wasay 2007, Khealani 2008, Martinelli 2010, Dentali 2012, Narayan 2012, Nasr 2013, Pai 2013, Geisbüsch 2014, Duman 2017, Alet 2020, Bagan 2021.
‡‡Hematological condition – either of anemia, polycytemia vera, essential thrombocytopenia.
‡‡‡ Among women <50y.

2.4.1 CHRONIC RISK FACTORS

Hereditary thrombophilia

Hereditary predisposing factors for venous thrombosis have been associated with CVT in case-control series.[71] The association of hereditary thrombophilia and increased risk for CVT has been established in three meta-analyses.[54,56,72]

Data from the most recent meta-analysis, by Green et al, show increased risk for CVT in patients with Factor V Leiden mutation/G1691A (odds ratio [OR] 2.51, 95% confidence interval [CI] 1.93-3.27), prothrombin/G20210A mutation (OR 5.53, 95% CI 3.98-7.69), and anticoagulation protein deficiencies (protein S [OR 5.68 95% CI 1.44-22.40], protein C [OR 10.74, 95% CI 3.07-37.65], antithrombin [OR 3.75, 95% CI 1.02-13.82]).[72] Thrombin activatable fibrinolysis inhibition factor and plasminogen inhibitor 1 gene polymorphisms were not associated with CVT.[72]

The prevalence of hereditary thrombophilia in large CVT patient cohorts varies from 9-46% depending on patient selection, geographical region and percentage of patients tested (Table 1). Factor V Leiden and prothrombin G20210A mutations are more common in Europe, while anticoagulation protein deficiencies are more frequent in non-European countries.[73] In northern Europe, the prevalence of Factor V Leiden mutation and prothrombin G20210A mutation in general populations is 10-15% and 2%, respectively.[74-76]

Only one recent multicenter study has comprehensively investigated genetic variants associated with CVT using a genome-wide association analysis.[77] In this study, single nucleotide polymorphism within the 9q34.2 region was strongly associated with CVT in comparison with controls, with an OR of 2.65 (95% CI 2.21-3.20). The 9q34.2 region is associated with coding of the ABO blood group system, and patients with A, B or AB had 2.85 times (95% CI 2.32-3.52) increased risk of CVT compared to patients with blood type O. Similar results were reported in a case-control study.[78] The frequency of blood type O was significantly lower (25% vs. 45%), and non-O blood types were higher (75% vs. 56%) in the 77 patients with CVT, as compared to the 4272 healthy blood donors. Consequently, having a non-O blood type was associated with a 2.4-fold increased risk of CVT (OR 2.44, 95% CI 1.42-4.26).[78]

As patients with CVT are typically relatively young[3,4] and consequently have low exposure to environmental factors, genetic markers associated to CVT may play an important role in the development of the disease, in particular in combination with other risk factors. Screening for genetic thrombophilia should be considered in all patients with CVT, and particularly in patients with unknown etiology. However, as risk factors for CVT often are multiple with potential multiplicative or additive effects, potential genetic thrombophilia should also be considered in patients with confirmed non-genetic risk factors.[45]

Other chronic pro-thrombotic conditions

In the ISCVT cohort, 16% of the patients with CVT had diagnosed underlying acquired thrombophilia which included, among others, hyperhomocysteinemia (5%), nephrotic syndrome (1%) and antiphospholipid antibodies (6%).[3] Although the most recent meta-analysis shows an association between hyperhomocysteinemia and CVT with OR 3.53 (95% CI 2.50-4.96),[72] the association remains debatable. For example, mutation in the methylene tetrahydrofolate reductase gene (MTHFR/C677T) which leads to elevated levels of homocysteine has not previously been associated with CVT in case-control studies.[79,80] Results are conflicting, as in the recent meta-analysis from Green and coworkers, the MTHFR/C677T gene was indeed associated with CVT (OR 2.11, 95% CI 1.35-3.32), although only after the exclusion of two studies with outlying results from studies that were considered heterogenic.[72] An alternative explanation of the association is that homocysteine is an acute phase reactant, rather than a risk factor for CVT itself.[45]

Inflammatory and autoimmune diseases

No controlled studies are available, but several case reports and case series acknowledge a potential association between inflammatory bowel diseases (i.e. ulcerative colitis and Crohn's disease) and CVT.[57] In the ISCVT, inflammatory bowel disease was reported in 1.6% of the patients.[4] Inflammatory bowel diseases affect the gastrointestinal tract and may cause a pro-thrombotic state through abnormal levels of factors related to inflammation and coagulation (Factor V, factor VIII, fibrinogen, antithrombin) as well as potential anemia and dehydration.[81] Further, acute relapses are often treated by high dosages of corticosteroids.[82]

Vasculitis are inflammatory diseases which affect the vessel wall connective tissue. Associated vasculitis related to CVT in case reports and case series include the previously mentioned Behçet's disease,[58] systemic lupus erythematosus,[83] granulomatosis with polyangiitis,[84] Sjögren's disease[85] and Churg-Strauss syndrome.[86] Activation of pro-thrombotic antiphospholipid antibodies have been reported in inflammatory systemic diseases such as in the antiphospholipid syndrome, in systemic lupus erythematosus or in Behçet's disease.[87]

Nephrotic syndrome has been reported among children with CVT in approximately 5% of the cases, but it is a rare associated condition among adults.[88,89]

Thyroid disease, both hyperthyroidism with thyrotoxicosis[90] and hypothyroidism,[91] has been suggested to be associated with CVT.

Cancer

Tumors of the central nervous system (CNS), systemic malignancies and solid tumors outside the CNS can cause CVT. Pathophysiological mechanisms, apart from direct mechanical compression of sinuses, include accumulation of tumor pro-coagulants, inflammatory cytokines, inflammation and cell proliferation.[92-94] Data from cohort studies suggest a prevalence of hematological and solid malignancies of 7-15% among patients diagnosed with CVT.[4,8,47,53,95] One case-control study reported increased prevalence of malignancy among patients with CVT (53/594, 8.9%) as compared to controls (160/6278, 2.5%) despite younger age among cases.[55] Further, cancer treatment, in particular L-Asparaginase and intrathecal chemotherapy are highly suspected to be associated with CVT by lowering of antithrombin levels, although it is challenging to distinguish from the increased risk of the underlying hematological cancer.[96]

In the case-control study by Silvis et al,[55] cancer types with highest risk of CVT were lung cancer (adjusted odds ratio [aOR] 32.4), hematological cancer (aOR 25.1), gastrointestinal cancer (aOR 5.8), and breast cancer (aOR 2.6). The association to CVT was particularly high within the first year after diagnosis of cancer. Another study from the same researchers showed that while history of cancer was found in 9.3% of CVT patients younger than 55 years, it was 24.4% for those aged 55 years or older.[97]

The high prevalence of cancer among patients with CVT should alert physicians to evaluate cancer as a potential underlying factor, especially in older patients with CVT of unknown etiology.[69] Efficacy of malignancy screening has not been systematically tested in the setting of CVT patients, and is thus not routinely recommended in the available guidelines.[71,98] The occurrence of malignancies, however, is higher among male patients and in the absence of headache.[99] Clinicians may, therefore, be more inclined to investigate patients with CVT without general risk factors for CVT, or with potential symptoms of cancer, and in particular with increasing age.

Myeloproliferative neoplasms

Myeloproliferative neoplasms including polycythemia vera and essential thrombocytosis, reportedly increase risk of venous thrombus formation at unusual locations.[100] The association to CVT is still uncertain, but prevalence in cohort studies span from 2 to 3%.[4,48]

Dural arteriovenous fistulas

The relationship between dAVFs and CVT has remained enigmatic for several decades. Whether dAVFs cause the CVT or vice versa has not been

determined. In available case series, dAVFs have been diagnosed prior to, simultaneously or subsequently to CVT.[4] The relationship between dAVFs and CVT and possible pathophysiological mechanisms are discussed in chapter 2.7 in this thesis.

2.4.2 TRANSIENT RISK FACTORS

Female-specific risk factors

In young women, the most frequent risk factors are estrogen-related and include oral contraceptive use, pregnancy and the postpartum period.[4,43,60,101] The prevalence of female-specific risk factors in large CVT patient cohorts from Europe amounted to 64-79% but was notably lower in a study from India and Pakistan, probably due to less frequent use of oral contraceptives in the general population.[4,6,8] The risk of CVT during oral contraceptive use has been reported in two case-control studies and in a recent meta-analysis. The pooled OR was 5.59 (95% CI 3.95-7.91).[56,61,101] The relative risk increase is particularly high among women with genetic thrombophilia and obesity, nevertheless the absolute risk increase remains low.[60,101] Although the underlying mechanism for the elevated risk is uncertain, oral contraceptive use influences factors that are involved in the hemostasis (prothrombin, factor V, VII, VIII and X, fibrinogen, prothrombin fragment I and II, activated protein C resistance).[102,103]

During pregnancy and the postpartum period, increased procoagulants such as factor VIII and fibrin, and decreased physiological anticoagulants such as protein S could alter the hemostasis.[104] Further, acquired activated protein C resistance is increased while fibrinolytic activity is reduced.[105,106] Consequently, risk of venous thrombus formation increases manifold during pregnancy, and the risk seems to be particularly high during the last trimester or the puerperium.[42,62,63,107,108] In a case-control study, the increased risk of CVT in the group of pregnant or postpartum women was all attributable to the postpartum period (aOR 10.6, 95% CI 5.6-20.0), and was particularly high in the first 6 weeks after childbirth (aOR 18.7, 95% CI 8.3-41.9).[62] In case reports CVT has been associated with in vitro fertilization.[109]

Hormone replacement therapy is a well-documented risk factor PE and DVT. Among patients with CVT, however, the relationship has only been described in uncontrolled CVT patient cohorts and anecdotal reports among post-menopausal women.[4,42,72,110-112] The association to CVT is yet to be tested in a case-control setting.[3,72,110]

Hematological disorders

Anemia is frequently reported in CVT patient cohorts (Table 1), and was particularly common in a study from southern Asia (51%).[4,6] The large variation in occurrence may be explained by regional differences or that measurement of hemoglobin has not been mandatory in all studies.[68] Based on two case-control studies and a meta-analysis, anemia has been suggested as a risk factor for CVT with a pooled OR of 4.04 (95% CI 2.07-7.89).[68,72,113] It has been speculated that anemia, in particular when caused by iron deficiency, may lead to thrombocytosis and thereby increase the risk of venous thrombosis.[114]

Conversely, high hemoglobin levels with increased blood viscosity, have been suggested as a potential predisposing factor for CVT in case reports and a case series evaluating CVT occurring at a high altitude.[115]

Infections

Infections can alter the hemostasis systemically, but more commonly, local infections in the CNS or the head and neck area cause relative hypercoagulability in part by recruitment of inflammatory cells to the sinuses. Cerebral venous thrombosis as a complication to invasive otitis, mastoiditis, sinusitis and meningitis, where the infection has advanced to the adjacent transverse, sigmoid or cavernous sinuses, has been reported repeatedly.[116-118] Over time, the importance of bacterial infections related CVT in high-income countries has declined as antibiotic treatments have improved.[89,119] In low- and middle-income countries, septic or infectious CVT is still a frequent and essential cause.[6,24]

SARS-CoV-2 vaccine and infection

During the covid-19 pandemic, severe CVT in combination with thrombocytopenia was reported as a complication within 4-28 days after vaccination with two adenoviral vector SARS-CoV-2 vaccines, ChAd0x1 nCov-19 (Oxford-AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson).[120-122] The condition was named CVT with vaccine-induced immune thrombotic thrombocytopenia (CVT-VITT).[120] Clinically, CVT-VITT resembles spontaneous heparin-induced thrombocytopenia and affected patients have significantly higher in-hospital mortality, more frequently thrombocytopenia and presence of anti-platelet factor 4 antibodies, in comparison with CVT patients from the pre-pandemic era.[64,120,123-126] The incidence of CVT-VITT after receiving a first dose of ChAd0x1 nCov-19 has been estimated to be 12.3 per million doses.[126] Case-fatality in CVT-VITT has declined over time from 47% to 22%, probably as a result of earlier diagnosis and improved coherence to the specific treatment recommendations which differ from CVT in general (i.e. use of immunomodulation with intravenous

immunoglobulin or plasmapheresis, non-heparin based anticoagulants, and reluctance of platelet infusions).[120,127]

In covid-19 patient cohorts, CVT was reported in less than 1% of the patients.[128,129] A meta-analysis covering 57 patients with CVT in relation to SARS-CoV-2 infection suggested a frequency of 0.08% among hospitalized covid-19 patients. However, the occurrence was thereby higher than the expected 5-20 per million per year in the general population.[129-131]

Medication

In addition to oral contraceptives and post-menopausal HRT, numerous drugs have been associated to CVT. Medications for cancer such as L-asparaginase[132], tamoxifen[133,134], thalidomide[135] and cyclosporine[136] have been associated to CVT in case reports or small case series. Corticosteroid treatment may also be associated with CVT and has most frequently been reported in high-dose intravenous administration.[82] The increased risks of thrombosis by the abovementioned treatments, however, are confounded by the underlying diseases themselves, and causal relationships have not been established.

Obesity

In a case-control study by Zuurbier et al, obesity (defined as body mass index 30 or higher) in women was associated with increased risk of CVT as compared to controls (OR 2.63, 95% CI 1.53-4.54). The reported risk was multiplicatively increased among obese women who also used oral contraceptives (aOR 29.26, 95% CI 13.47-63.60). Among women who used oral contraceptives, overweight and obesity increased risk for CVT in a dose-response manner.[60]

Mechanical precipitants

Mechanical precipitants causing damage to the dural sinuses or cerebral veins impose a risk for thrombus formation.[3] When exposed during neurosurgical procedures and interventions, dural sinuses and cerebral veins are vulnerable and at risk for iatrogenic damage.[66] Head trauma, often with fractures of the cranium, including rifts in the dural sinuses, may also cause CVT.[137] Reports suggesting lumbar puncture as a risk factor, often consider either intracranial hypotension or increased tension in the meninges as the cause.[71,138] The risk for CVT secondary to mechanical precipitants is probably increased in patients with underlying chronic risk factors.[72]

Traditional arterial risk factors

Traditional arterial risk factors have repeatedly also been evaluated in CVT. In a recent comprehensive meta-analysis, smoking, diabetes and hypertension

were associated with venous thromboembolism in general, but not with CVT.[72] An association, however, cannot be ruled out due to small number of included patients. Interestingly, alcohol consumption (OR 2.67, 95% CI 1.83-3.88) and hypercholesterolemia, defined as fasting plasma total cholesterol levels ≥ 5.2 mmol/l (OR 2.4, 95% CI 1.31-4.39), were both associated with CVT in pooled analyses. These results need to be confirmed in future controlled studies with adequate size and setting.

2.5 CLINICAL PRESENTATION AND DIAGNOSIS

2.5.1 SYMPTOMS AND SIGNS

Patients with CVT present with a wide panorama of symptoms, ranging from mild, isolated chronic headache to a more severe debut, which can include acute focal neurologic deficits, seizures, coma and death.[3,4] The diagnosis is challenging due to the substantial diversity of presenting symptoms. The prevalence of the most frequently reported symptoms and signs are depicted in Table 2.

The symptoms are mostly subacute and progress over days, but onset may also be acute or chronic. In the ISCVT cohort, time from onset to hospital admission was <48 hours in 37% of the patients, ≥48 hours to 30 days in 56% and ≥30 days in 7% of the patients.[4] Median delay from onset of symptoms to hospital admission was four days and onset to diagnosis seven days.[4]

The characteristic of symptoms depends on the location and extent of the thrombus, collateral blood flow, presence of parenchymal lesions, the underlying etiology, patient's age and time to diagnosis. Symptoms linked to CVT can be categorized into syndromes as either of; i) isolated intracranial hypertension – headache, often accompanied by nausea or vomiting, but without focal neurologic deficit apart from diplopia caused by sixth nerve palsy secondary to mechanical compression. The increased intracranial pressure can also cause bilateral papilledema which, if untreated, may be hazardous to the optical nerve and cause permanent vision impairments; ii) focal syndrome – focal neurologic deficits, typically as a result of parenchymal hemorrhagic or non-hemorrhagic lesions. This syndrome also includes focal or generalized seizures; iii) encephalopathy – bilateral or multifocal signs including mental status disturbances, delirium or dysexecutive disturbances, impaired consciousness and coma; or iv) cavernous sinus syndrome – the most infrequent syndrome, including chemosis, proptosis and orbital pain. Further,

thrombosis in the deep cerebral venous system could present with deterred mental status, delirium, and bilateral thalamic lesions. If untreated, the increased pressure could extent to compression of the brainstem and cause loss of consciousness, coma or death. Coma could also be caused by bilateral thalamic lesions, generalized seizures or CNS infections.

Table 2. *Clinical presentation of cerebral venous thrombosis, most frequent symptoms and signs*

Symptom or sign	**Frequency**[‡]
Headache	63-93%
Focal motor deficit	12-52%
Seizures	34-51% [‡‡]
Coma	1-20%
Papilledema	30-60%
Parenchymal lesions	40-63%
Non-hemorrhagic	13-66%
Hemorrhagic	14-46%

[‡] *Preter 1996, Ferro 2002, Ferro 2004, Gosk Bierska 2006, Wasay 2007, Khealani 2008, Martinelli 2010, Dentali 2012, Narayan 2012, Nasr 2013, Pai 2013, Geisbüsch 2014, Duman 2017, Alet 2020, Bagan 2021.*
[‡‡] *Ferro 2003, Ferro 2004, Masuhr 2006, Davoudi 2012, Kalita 2012, Mahale 2016, Duman 2017.*

Headache

Headache is the most common, but also least specific, symptom and is present in more than 90% of adult patients with CVT.[3,4,8,139] Being frequent, headache is often presented together with other symptoms and may be accompanied by nausea and vomiting. The localization of headache is often, but not exclusively related to the localization of the thrombosed sinus.[140] Onset spans from chronic and progressing over months to subacute over days or acute mimicking thunderclap headache often seen in patients with subarachnoid hemorrhage.[141] In a prospective cohort of conscious patients with CVT diagnosis, headache characteristic was described as throbbing in 45% and aching in 26%.[140] One-third of the patients described unilateral headache, and one-fifth a focal headache. Absence of headache is more common among relatively elderly

patients, patients with malignancy, isolated cortical vein thrombosis, and among men.[99] In the same study, patients with headache had more favorable outcome, but the results were not consistent in multivariable analysis and may be confounded by inability to report headache for patients who are comatose or have neurologic impairments.[99]

Seizures

Seizures frequently occur in the acute phase, either as a presenting symptom or as a complication after CVT diagnosis. Seizures are reported in 34-51% of patients in the acute phase,[4,5,142-146] which is notably more frequent than in ischemic arterial stroke (2-9%)[147,148] or spontaneous intracerebral hemorrhage (ICH, 8-14%).[149-151] Seizures are discussed in chapter 2.7 in this thesis.

2.5.2 IMAGING

Diagnosis of CVT depends on direct or indirect visualization of the cerebral venous system and verification of the thrombus. Essentially three imaging techniques are available: MRI with MR-venography, CT with CT-venography, and digital subtraction angiography.[14] The latter was previously considered as the gold standard, but as quality and availability of non-invasive techniques have improved, cerebral angiography is seldom required. However, catheter angiography is dynamic and constitutes an accurate and important alternative when CT-venography and MR-venography are inconclusive. Cerebral angiography is a prerequisite for cerebral endovascular procedures and play an important role for diagnosis of related conditions such as dAVF.[71,98,152]

Computed tomography and computed tomography venography

Unenhanced CT alone is insufficient to rule out the diagnosis of CVT as the survey is normal in 10-30% of patients diagnosed with CVT.[153] However, features of increased attenuation at location of the sinuses may indicate the presence of a CVT. Those signs represent hyperattenuation by the clots and are termed the “dense triangle sign” when located in the superior sagittal sinus, or the “cord sign” when located in either the cortical or the deep cerebral venous system.[154] Additionally, parenchymal lesions, edema and in particular hemorrhages can be visible on CT. Indirect signs of CVT are ICH of uncertain origin, typically lobar or small juxtacortical bleedings, and localized cerebral edema.[155] Venous hemorrhagic infarctions are not necessarily restricted to arterial regions and may also be bilateral for example caused by a thrombus in the deep venous system or large thromboses in the superior sagittal sinus. Individual anatomic variations of the dural sinuses further complicate the diagnosis, resulting in insufficient sensitivity for CT in the absence of contrast. For visualization of the cerebral venous system, CT-venography has

comparable sensitivity to digital subtraction angiography.[156] CT-venography presents a viable option for diagnosis of CVT and is comparable to MR-venography.[157] A thrombus can be confirmed by insufficient contrast distribution in a sinus, termed the empty delta sign.[158] The main disadvantages are the need of contrast, the ionizing radiation and risk of bone artifacts from the cortical bone which may interfere with visualization of the sinus.[14] However, CT-venography is faster, more widely available in the acute phase and less expensive than MR-venography. However, as a result of the complicated presentation, patients often present in a subacute or chronic manner, making CT-venography an important diagnostic tool. Overall accuracy of combined CT and CT-venography is 90-100%, and considered equal to MR-venography in diagnostic power of CVT.[14,71,98,159]

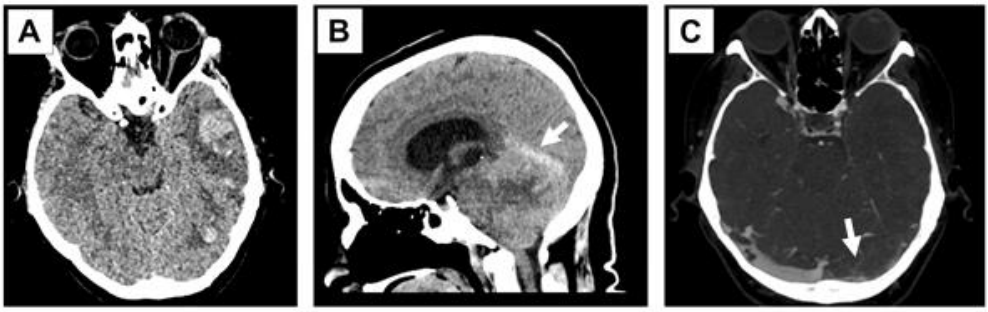

Figure 2. *Computed tomography imaging findings in patients with cerebral venous thrombosis. A: Axial view, non-contrast. Left temporal lobe venous infarction (right side of the picture). White areas indicate hemorrhages and darker surrounding areas edema and infarct. B: Sagittal view, non-contrast. Hyperattenuated straight sinus indicative of a cerebral venous thrombosis (white arrow). C: Axial view, contrast-enhanced computed tomography venography. The patient's left transverse sinus (right side of the picture, white arrow) is hypoattenuated, representing absence of contrast secondary to a cerebral venous thrombosis.*

Magnetic resonance imaging and magnetic resonance venography

For diagnosis of CVT, the accuracy and sensitivity of MRI in combination with MR-venography is almost 100%.[14] Time-of-flight sequences depict venous flow, which additionally can be illustrated on gadolinium contrast-enhanced MR-venography. Absence of flow void (no-flow phenomenon) in combination with an isointense signal on the T1-weighted and a hypointense signal within the sinus or vessel on T2-weighted sequences, are the major early signs for CVT. The imaging signal may differ depending on the age of the thrombus and hemoglobin degradation products. MRI with susceptibility-weighted sequences is the most sensitive technique to visualize cortical vein thrombosis.[160] In these sequences, CVT can be recognized as hypointense areas representing increased levels of deoxyhemoglobin.[161] For visualization of the brain parenchyma and for distinguishing cytotoxic and vasogenic edema, MRI

is considerably superior to CT.[14] Disadvantages are lack of availability in the acute setting, risk of overestimation of the degree of thrombosis by increased flow void in time-of-flight weighted imaging in case of partial occlusion, arachnoid granulations and the long investigation time.[14,162]

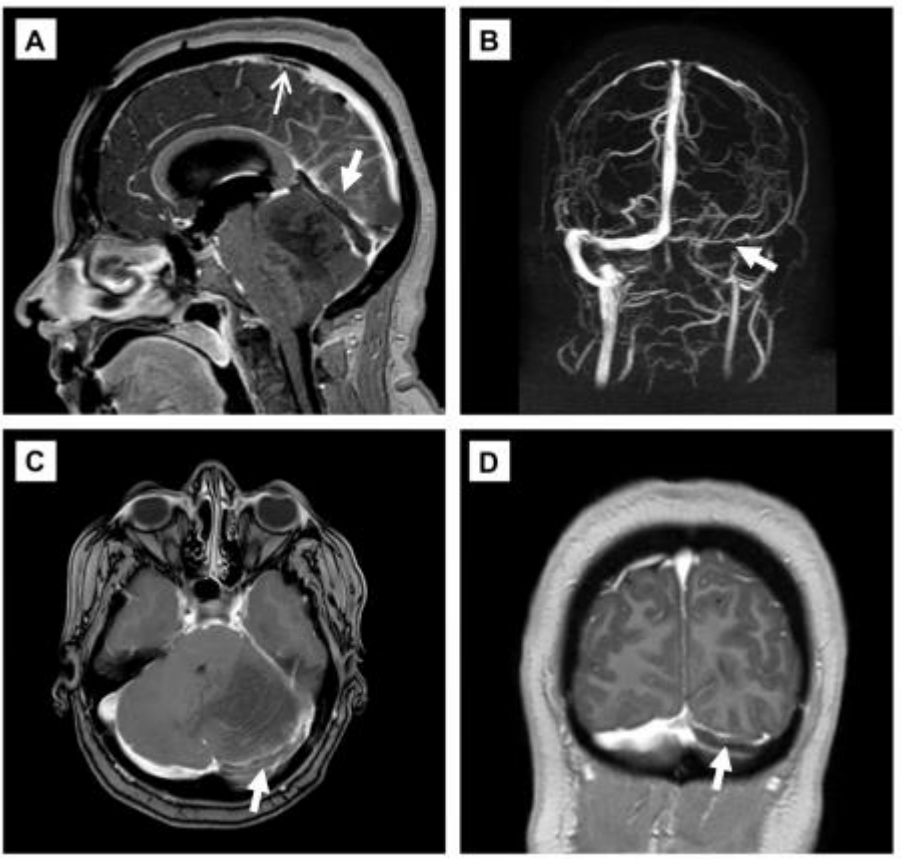

Figure 3. *Contrast-enhanced magnetic resonance imaging venography of a patient with cerebral venous thrombosis. A: Sagittal view. The cerebellar hypointense signal representing a cerebellar non-hemorrhagic lesion. Filling defects in the straight sinus (large arrow) caused by a thrombus and physiological filling defect in the superior sagittal sinus (small arrow) caused by arachnoid granulations. B: Coronal maximum intensity three-dimensional reconstruction time-of-flight angiography. The large arrow indicate the absence of flow in the thrombosed left transverse and sigmoid sinuses. The left jugular vein is also partially occluded. C: Axial view. Contrast filling defect in the left transverse sinus caused by a thrombus (large arrow). D: Coronal view. Absence of hyperintense contrast signal in the left transverse sinus, caused by a thrombus (large arrow).*

The most frequently occluded sinuses in the ISCVT cohort were the superior sagittal sinus (62%), either of the lateral sinuses (around 40%), and straight

sinus (18%).[4] Thromboses of the deep venous system occurred in 11% of the patients, and increased the probability of being comatose. Cavernous sinus thrombosis is rare, amounting to merely 1% of the total cases of CVT.[4]

Parenchymal lesions are present in around 40-60% of patients with CVT at presentation.[3,4] Venous infarcts could be distinguished from arterial infarcts as they are not limited by arterial territories, often lobar or adjacent to the cerebral cortex and may be bilateral.[71,163] Lesions can be either hemorrhagic or non-hemorrhagic, but they are often a combination of the two. It has been suggested that patients without parenchymal lesions have better outcome than patients with lesions. Among patients with parenchymal lesions, patients with non-hemorrhagic lesions have better outcome than patients with hemorrhagic lesions.[164] Hemorrhagic lesions vary in size and location from scattered, multifocal small petechial hemorrhages to deep large and space occupying lesions. Small juxtacortical hemorrhages have been linked to thrombosis of the superior sagittal sinus,[155] whereas bilateral thalamic lesions are strongly associated with deep venous system thrombosis.[14] Non-hemorrhagic lesions are most accurately diagnosed and evaluated at MRI.[164] Vasogenic edema can be distinguished from cytotoxic edema by diffusion-weighted imaging. In cytotoxic edema, the transportation of water from the extracellular space to the intracellular space is typically recognized by decrease in diffusion, identified as a high signal on diffusion-weighted imaging and a low signal on apparent diffusion coefficient maps. [14,20,163,165,166] Around 30% of CVT patients with non-hemorrhagic lesions harbor bilateral lesions.[164]

Abnormal hypointensity of the medullary and subependymal veins depicted at paramagnetic-sensitive MR sequences has been termed the brush sign, and was confirmed in 14% of acute CVT patients in a recent study investigating acute CVT patients with MRI. The brush sign has been suggested to be a marker of hypoperfusion and increased collateral circulation. In the study by Aguiar et al, the brush sign was associated with higher thrombus load and ipsilateral parenchymal lesion, and a more severe clinical manifestation, but was not associated with worse functional outcome as measured by the modified Rankin Scale (mRS).[167]

2.5.3 LABORATORY FINDINGS

Routine laboratory testing and hereditary thrombophilia

American Heart Association/American Stroke Association CVT guidelines recommend routine laboratory testing for patients with suspected CVT including complete blood count, chemistry panel, urinalysis, prothrombin time and activated partial thromboplastin time.[71] Tests for genetic thrombophilia are

not routinely recommended to reduce risk of death, prevent recurrent venous thrombosis or improve functional outcome,[71,98] but should be considered for patients with high pre-test probability of carrying severe thrombophilia. As around 40% of patients with CVT carry multiple risk factors,[3,4] tests for severe hereditary thrombophilia should not be limited to patients without confirmed risk factors.[71,98]

D-Dimer

The importance of laboratory testing for diagnostic purposes for patients with suspected CVT is limited. Fibrin D-dimer is a fibrin degradation product which is produced when fibrin is degraded by plasmin, and is widely used in diagnosis of PE and DVT.[168] Elevated D-dimer has been associated with CVT in patients with acute onset of symptoms and with extensive thrombus, but has lower specificity and sensitivity in patients presenting with isolated headache.[169] However, elevated D-dimer is not pathognomonic for CVT, and patients with focal symptoms or severe acute headache nevertheless necessitate investigation with neuroimaging nevertheless, in order to rule out other acute cerebral diseases. Among patients with chronic headache or isolated headache, data from a meta-analysis report a sensitivity for detecting CVT of around 80%, and this group of patients is at particularly high risk for false-negative results.[169] Low levels of D-dimer cannot rule out the diagnosis of CVT, and for patients with chronic headache or isolated headache, where a robust diagnostic test could guide in selecting patients for imaging, the sensitivity for detecting CVT is too low. Hence, the use of D-dimer in diagnosis of CVT has until recently been considered limited.[169,170] However, in a recent study from Heldner et al,[171] 359 patients with suspected CVT (of whom 94 patients subsequently were diagnosed with CVT) were evaluated clinically in combination with measurement of D-dimer. The authors developed a 6 item clinical score based on seizures at presentation (4 points), known thrombophilia (4 points), oral contraception (2 points), duration of symptoms >6 days (2 points), worst headache ever (1 point) and focal neurologic deficit on admission (1 point). A total score of 0-2 was considered as low probability of CVT (negative predictive value 94%). No patient diagnosed with CVT but categorized as low probability of CVT, had d-dimer levels <500 µg/L.[171] The score is yet to be validated internally and externally.

For patients with onset of symptoms of CVT within 28 days after covid-19 vaccination, CVT-VITT should be suspected. In these patients, blood platelet levels and occurrence of platelet factor-4 antibodies should be tested as soon as possible.[120,123]

2.6 TREATMENT

Treatment of CVT constitutes of prevention of thrombus propagation, facilitation of recanalization, as well as identification and management of treatable underlying diseases and complications. International guidelines for diagnosis and treatment are available from the American Heart Association/American Stroke Association[71] and the European Stroke Organisation endorsed by the European Academy of Neurology.[98] Notably, most recommendations on treatment and management of CVT have been established based on data from observational studies.

General management

In the acute phase, patients with CVT should be admitted and closely monitored, preferably in a stroke unit.[172] Organized stroke care has shown beneficial effects in patients with acute stroke, independent of stroke subtype, age or sex.[71,173,174] Available data suggest that for patients with acute stroke, specialized stroke unit care is associated with a reduced risk of death within one year (OR 0.86, 95% CI 0.76-0.98), reduced risk for death or institutionalization (OR 0.82, 95% CI 0.73-0.92) and reduced risk for death or dependency (OR 0.82, 95% CI 0.73-0.92).[173,174] On the basis of available evidence from stroke unit care in general, initial management of CVT in a stroke unit is recommended to optimize care and to minimize complications.[71]

In presence of large venous infarcts or severe intracranial hypertension, patients with CVT are at risk of prompt deterioration. For these patients, close monitoring at an intensive care unit with neurosurgical readiness may be vital.

General management further include monitoring and treatment of underlying associated conditions such as chemotherapy for specific cancers, antibiotics in case of intra- and extracranial infections, withdrawal of estrogen oral contraceptives and HRT as well as general stroke rehabilitation. Treatment of seizures is discussed in chapter 2.7.

2.6.1 ANTICOAGULATION

The aim with anticoagulant treatment is to avert thrombus propagation, to facilitate recanalization, and to prevent complications with extracranial VTE (PE and DVT).[3] Treatment with anticoagulation has been a matter of controversy and hesitancy as a large proportion of patients with CVT present with ICH.[4] Nevertheless, without adequate anticoagulant treatment, thrombus expansion may lead to worsening of existing or new venous infarcts and hemorrhages.[172]

The safety and efficacy of heparin treatment has been evaluated in two small, randomized clinical trials, one with 20 patients randomized for treatment with dose-adjusted unfractionated heparin (UFH) or placebo, and one with 59 patients randomized for treatment with low-molecular weight heparin (LMWH, nadroparin, 90 IU per kg twice daily) or placebo.[175,176] In a meta-analysis, the pooled effect of anticoagulation treatment as compared to placebo, showed decreased relative risk of death (OR 0.33, 95% CI 0.08-1.21) and for death and dependency (OR 0.46, 95% CI 0.16-1.31). The absolute risk reduction for mortality was -13% (95% CI -27% to 1%).[177] Thus, the available data suggest a statistically non-significant, but clinically important improvement in clinical outcome. Notably, no new ICH occurred in patients treated with heparin, but two patients in the placebo group developed a new ICH and two had probable PE, one of which being fatal.[177] Based on these results, in combination with confirmatory data from observational studies, immediate heparin treatment is recommended by international guidelines, regardless of presence of ICH.[71,98]

In patients with VTE (PE and DVT), data from clinical trials show risk reductions with regard to major hemorrhages, thrombotic complications and death, in favor of LMWH as compared to UFH.[178] In an observational study from the ISCVT patient cohort, patients with LMWH were more often independent at 6 months in comparison with patients treated with UFH (aOR 0.42, 95% CI 0.18-1.0) and had fewer new ICHs (aOR 0.29, 95% CI 0.07-1.3).[179] Two randomized trials have compared LMFH to UFH in patients with CVT.[180,181] In the first study (n=65),[180] LMWH was associated with decreased in-hospital mortality rate, and more often complete recovery after 3 months (relative risk 1.37, 95% CI 1.02-1.83). In the second study (n=52),[181] mortality, functional recovery and bleeding complications were equal in the two treatment groups.

In the most recent European guidelines, LMWH is recommended over UFH as treatment of acute CVT.[98] The therapeutic advantages of LMWH are the stable anticoagulant concentration in plasma, and that treatment does not require dose-adjustment based on activated partial thromboplastin time measurements. However, in patients where LMWH is contraindicated (renal insufficiency) or in patients at risk for neurosurgical intervention where rapid reversal of anticoagulation may be necessary, acute anticoagulation treatment with UFH is preferable.[98]

In clinically stable patients, acute heparin treatment is followed by treatment with oral anticoagulants.[71,98] The optimal anticoagulant treatment is not known as randomized trials, prospective controlled studies and case-control studies

investigating the influence of treatment duration in relation to functional outcome or recurrence of CVT or VTE are lacking.[64,71,98] In the ISCVT, 2.2% (1.5 per 100 person-years) of the patients had a recurrent CVT during the follow-up time, and 4.3% (4.1 per 100 person-years) had a recurrent VTE including extracranial locations despite a majority of patients being treated with anticoagulation at the time of recurrence.[4,182] Most commonly, patients are treated for 3-12 months, but chronic risk factors might warrant lifelong treatments.[71,98,183] American guidelines recommend: i) for patients with CVT associated with a transient risk factor (provoked CVT) - anticoagulation treatment continuation for 3 to 6 months; ii) for patients with unprovoked CVT - anticoagulation treatment for 6 to 12 months and; iii) for patients with chronic severe thrombophilia (i.e homozygous prothrombin mutation, homozygous factor V Leiden mutation, deficiencies of protein C or protein S and antithrombin, combined thrombophilia or antiphospholipid syndrome) – indefinite anticoagulation.[71] European guidelines recommend oral anticoagulants for a variable period between 3 and 12 months after CVT to prevent recurrent CVT and other VTE, for patients in whom medical conditions associated with high recurrence risk are not identified.[98] Patients with recurrent VTE or with an associated prothrombotic condition with high thrombotic risk may be in need of permanent anticoagulation.[98] The optimal treatment duration is currently being investigated in a cluster-randomized study comparing 3 to 6 months vs 12 months of vitamin K antagonists (VKA) in CVT (Extending oral anticoagulation treatment after acute Cerebral Vein Thrombosis, EXCOA-CVT).[184]

Dose-adjusted VKA has been the treatment of choice after the acute phase of CVT.[3] In a recent randomized trial, RE-SPECT CVT,[185] efficacy and safety of dabigatran 150 mg twice daily was compared to dose-adjusted warfarin. After 6 months, none of the 120 randomized patients had experienced any new VTE including CVT. One patient randomized to dabigatran treatment had a major intestinal bleeding event, and two patients allocated to the warfarin group had major intracranial bleeding events. Recanalization rates were 60% in the dabigatran group and 67% in the warfarin group. This study was not powered to prove superiority or inferiority of either treatment and the authors suggest that both dabigatran and warfarin are adequate options to prevent recurrent VTEs in patients with CVT.[185] Consistently in patients with VTE (PE and DVT), randomized trials have reported non-inferiority in efficacy of preventing recurrent VTE for direct oral anticoagulants (DOACs) as compared to VKA. The safety profile of DOAC has been shown to be more favorable than VKA, with a relative decrease in risk of major and clinically relevant non-major bleeding events.[186] Data from a systematic review[187] and a recent retrospective observational study,[188] provide support that a similar correlation

may be present in patients with CVT. In the 845 included patients, treatment with DOAC was associated with similar rates of recurrent VTE as compared to VKA (5.26 vs 5.87 per 100 patient-years) and a lower risk of major hemorrhage (2.44 vs 4.7 per 100 patient-years).[188] Two ongoing prospective studies on DOAC in CVT, DOAC-CVT (Direct Oral Anticoagulants in the Treatment of Cerebral Venous Thrombosis NCT04660747) and SECRET (Study of Rivaroxaban in Cerebral Venous Thrombosis, NCT03178864) will expectantly provide further evidence on the matter.

2.6.2 TREATMENT OF INCREASED INTRACRANIAL PRESSURE

Increased intracranial pressure in CVT is caused by obstruction of venous and cerebrospinal fluid outflow, in combination with the eventual presence of space occupying parenchymal lesions. Increased intracranial pressure commonly occurs in the acute phase of CVT, either isolated or in combination with other symptoms.[4] Typical clinical symptoms and signs are progressive headache, papilledema and sixth nerve palsy.[3] Although not specifically investigated in a randomized trial, general recommendations for management of patients with elevated intracranial hypertension are likely applicable on CVT patients and should therefore be considered. Apart from early anticoagulation treatment, and in severe cases recanalization by endovascular treatment as discussed above, general recommendations include elevating the head of the bed, analgesics, hyperventilation, osmotic diuretics and acetazolamide. In severe cases with altered consciousness, close monitoring at an intensive care unit should be prioritized. Acetazolamide is a carbonic anhydrase inhibitor (dosed 500 to 1000 mg daily) and may reduce intracranial pressure by lowering production of cerebrospinal fluid and its slight diuretic effects. Data from the ISCVT showed no effect on clinical outcome for patients treated with acetazolamide.[98] Despite not being investigated in a controlled setting for patients with CVT specifically, data may be extrapolated from patients with idiopathic intracranial hypertension, and acetazolamide may preclude progressing vision impairment caused by papilledema. The use of acetazolamide in the acute management of intracranial hypertension, however, may be limited.[71,189,190] Close monitoring of the presence and progression of papilledema is warranted in patients with increased intracranial pressure.[71] Optic nerve fenestration is seldom used, but may still be a surgical treatment option to hinder visual loss when medical treatment has been unsuccessful.[191] In patients with isolated intracranial hypertension, instantaneous reduction of intracranial pressure may be achieved by acute lumbar puncture with drainage of cerebrospinal fluid until normalized pressure. However, the procedure requires temporary cessation of anticoagulant treatment and is limited to

patients without signs of pending herniation. Further, the effect duration is short and therefore, therapeutic lumbar puncture is infrequently used in clinical practice.[4,71,192] The effect of acute shunting (external ventricular drain, ventriculojugular and ventriculoperitoneal shunt) to lower intracranial pressure was evaluated in a systematic review, in a total of 15 patients.[193] The mortality was around 25% despite treatment, and another 13% were left with severe functional impairment. European guidelines do not recommended shunting as treatment to prevent brain herniation and death.[98]

Corticosteroid treatment has been suggested in acute CVT to reduce vasogenic cerebral edema and thereby decrease the local and global intracranial pressure, and risk of permanent parenchymal damage. In a post-hoc analysis of the prospective ISCVT cohort, treatment with steroids was not associated with an improved outcome.[194] Additionally, in patients without parenchymal lesions, steroids were deemed detrimental as patients treated with steroids had worse outcome than those treated without steroids, but results may be confounded by indication.[194] Potential hazardous side effects include associated hyperglycemia and elevation of lactate. Steroids are not recommended as a treatment for CVT to decrease intracranial pressure.[71,98] However, steroids may still be used for patients with acute CVT and concomitant inflammatory conditions such as Behçet's disease, vasculitis, inflammatory bowel diseases or systemic lupus erythematosus.[57,58,98,195]

2.6.3 DECOMPRESSIVE SURGERY

The main cause of death in the acute phase of CVT is transtentorial or subfalcine herniation.[27] For patients with clinical and radiological signs of impending herniation, decompressive surgery (i.e. decompressive craniectomy and/or hematoma evacuation) can be lifesaving, but available evidence is limited to observational case series and no randomized trials are available. Data from the ISCVT and a systematic review including 69 patients, suggested that decompressive surgery could avert lethal outcome and that a good functional outcome can be achieved.[196] The overall rates of death or dependence at 12 months was 40%, and the mortality rate was 16%.[196] In a prospective case series of 10 patients with impending transtentorial herniation who underwent decompressive craniectomy, 60% had achieved good functional recovery after 1 year and 20% died despite the intervention.[197] It is unlikely that a randomized trial will be performed comparing treatment with decompressive surgery to conservative treatment, given the ethical concerns in withholding patients a potential lifesaving treatment, and the rarity of the situation. The DECOMPRESS-2 prospective multicenter registry with already more than 100 patients included is ongoing and final results are expected

shortly. European and American guidelines recommend use of decompressive surgery to prevent deaths in patients with parenchymal lesions and clinical and radiological signs of impending herniation.[71,98]

2.6.4 ENDOVASCULAR TREATMENT

In the subgroup of patients with severe CVT, at high risk of death and clinical neurologic worsening despite treatment with anticoagulants, endovascular treatment may present an option to facilitate prompt recanalization. As compared to arterial thrombectomy and thrombolysis, a thrombus of the cerebral venous system carries additional challenges. Due to the often subacute onset and local formation, a cerebral venous thrombus, or part of the thrombus, is more solid and firmly attached to the sinus wall. Further, the bioavailability into the cerebral venous system from systemic thrombolysis is probably lower and therefore, local thrombolysis is most commonly preferred.[198]

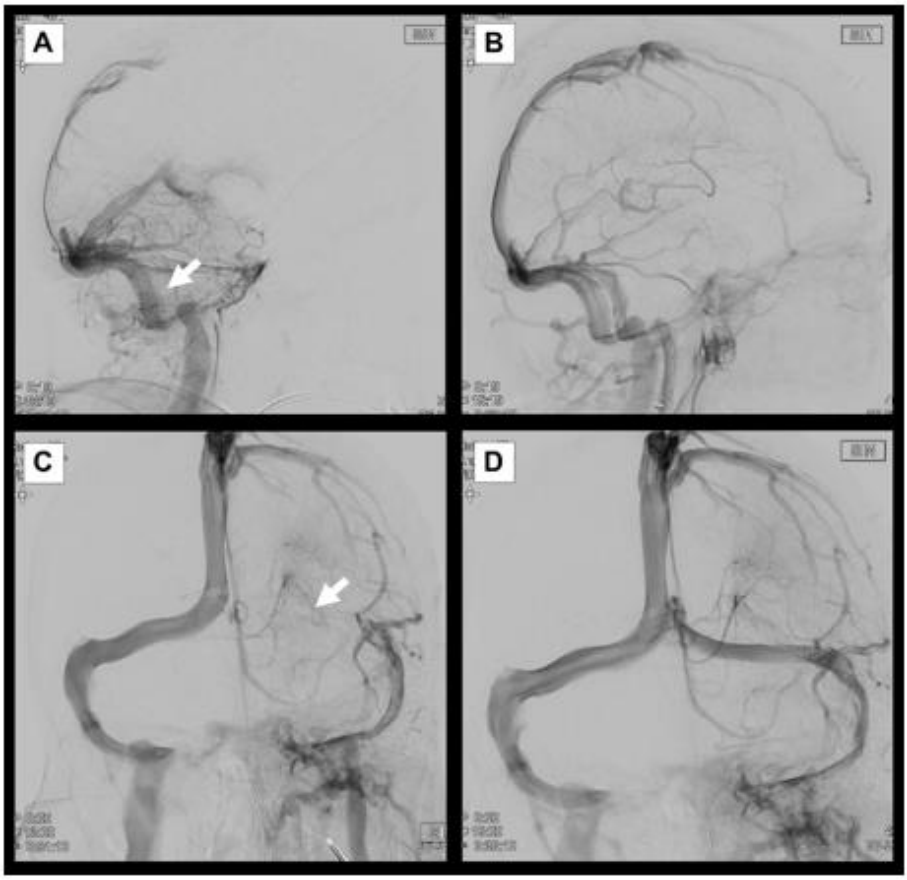

Figure 4. *Digital subtraction angiography before and after mechanical thrombectomy of a left transverse sinus thrombosis, all in late venous phase. A: Before thrombectomy. Lateral projection of cerebral angiography from the right vertebral. Absence of contrast in the left transverse sinus (arrow). B: After thrombectomy. Lateral projection of cerebral angiography from the left carotid. Adequate contrast-filling depicting both the right and left transverse sinuses. C: Frontal projection, angiography through left carotid. Before thrombectomy, Absence of contrast in the left transverse sinus (arrow) and partial contrast filling in the left sigmoid sinus. D: Frontal projection. After thrombectomy, the contrast filling of the left transverse sinus is restored.*

The cerebral venous system is accessed by catheterization of either the femoral or the jugular veins. To date, two modalities of endovascular treatment are available, or a combination of the two. The first is mechanical thrombectomy with either direct aspiration technique, a stent retriever, rheolytic device or balloon angioplasty. The second is local chemical thrombolysis with fibrinolytic medications (Urokinase or recombinant tissue plasminogen activator). The earliest reports on endovascular treatment dates back to the 1980s.[199] In case series, endovascular treatment of CVT has reportedly been

associated with more favorable outcomes, in particular for mechanical thrombectomy.[200,201] In a systematic review from 2017, pooled results from 235 patients with severe CVT (40% coma or encephalopathy) showed a mortality rate of 14% among patients who received endovascular treatment.[201] Rate of complete recanalization was 69%. Clinical worsening or new ICH occurred in 9% while 35% of treated patients achieved complete recovery. However, lack of control groups, high heterogeneity, different treatment approaches and techniques limit the conclusions that can be drawn, and the generalizability from these studies.

The TO-ACT (Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis) trial[202] examined neurointervention (thrombectomy with or without chemical thrombolysis) versus conservative management (anticoagulation) in patients with severe CVT (i.e. presence of deep cerebral venous involvement, ICH, mental status disturbances or coma). The trial was halted prematurely due to futility after randomization of 67 of the 164 targeted participants. The primary endpoint (mRS 0-1 at 12 months) rate did not differ between endovascular (65%) and standard treatment (66%). In 3 of 33 patients in the endovascular treatment group, periprocedural sinus perforation occurred.

Further research, including improvement of selection of patients with high risk of poor outcome as well as safety and efficacy of endovascular interventions in CVT, is needed. The European Stroke Organisation guidelines advice against using endovascular treatment in acute CVT with a pretreatment low risk of poor outcome.[98] American and European guidelines recommend restricting endovascular treatment only to individuals with high risk of death and who continuously are deteriorating clinically despite first-line anticoagulation.[71]

2.7 COMPLICATIONS AND OUTCOMES

The clinical course of CVT is highly varying and the acute phase may be complicated by several conditions including seizures, intracranial hypertension, extracranial VTE, hydrocephalus and infections. With the exception of seizures, the treatments of these conditions are discussed in chapter 2.6.

2.7.1 MORTALITY

Mortality in CVT has declined over the last decades[40] and in most reports from cohort studies, in-hospital mortality ranges between 5 and 10%.[4-8,24,35,38,48,53,203-

[205] Some studies report even lower in-hospital mortality rates, for example Nasr et al (2%),[47] ISCVT[4] (4%) and Dentali et al (0.4%).[8] Reasonable explanations for the declining mortality are the improvement and better availability of non-invasive imaging techniques, and a shift in the etiology from infectious to hormonally caused CVT, which together with increased clinical awareness allows for earlier diagnosis of CVT.[32,39,40] Moreover, general stroke care and intensive care have improved which allow for better prevention and management of complications. The main cause of acute mortality is transtentorial or subfalcine herniation due to unilateral hemorrhagic lesions or diffuse edema and bilateral lesions.[27] Other causes of early death include status epilepticus and medical complications such as PE or sepsis.[27,46,206] In multivariate analyses, numerous independent predictors of death within 30 days have been suggested: male sex, acute seizures, mental status disturbances, coma at admission, thrombus in the deep cerebral venous system, right-sided hemorrhage, posterior fossa lesions, sepsis, malignancy, and infection of the CNS.[6,27,42,47] Further, admission hyperglycemia[207] and admission anemia[208] have been associated with higher risk of both dependency and mortality. On the other hand, patients presenting with isolated intracranial hypertension syndrome are expected to have excellent functional outcomes.[192] One study reported higher probability of favorable outcome for females, attributable to the female sex-specific risk factors (oral contraceptive use, pregnancy or postpartum, HRT).[42] While in-hospital mortality for all CVT patients is relatively low, mortality among patients admitted to intensive care units has been reported up to 30%.[209,210] However, despite severe presentations such as coma and encephalopathy, there may be a potential of full recovery. In a study of 114 comatose CVT patients, one third recovered fully (mRS 0-1), 10% were severely disabled and 30% died.[211] Further, certain etiological subtypes have been associated with higher in-hospital mortality. For patients with CVT-VITT, reports of in-hospital mortality rates ranges from 47-61%.[124,126]

Long-term total mortality rates after CVT vary between 3 and 19%, mostly depending on follow-up time (Table 4). A meta-analysis reported a cumulative mortality rate at the end of follow-up of 9.4% (122 deaths in 1303 included patients, follow-up ≥12 months for 1101 patients).[212] While acute death is typically associated with direct consequences from CVT, long-term mortality are generally caused by underlying conditions, in particular malignancies.[8,27,50,213]

2.7.2 FUNCTIONAL OUTCOME

Functional outcome after CVT is frequently assessed by the ordinal mRS. The scale has been developed for measuring functional outcome after stroke, and

ranges from 0 to 6: score 0 represents no symptoms at all, score 1 is no significant disability, score 2 is slight disability but unable to carry out all previous activities, score 3 is moderate disability, requiring some help, score 4 is moderately severe disability and inability to attend to own bodily needs without assistance and unable to walk unassisted, score 5 is severe disability, bedridden, incontinent with need of constant nursing care and attention, and score 6 represents death. A score above 2 indicates dependency in activities of daily living.[214]

Overall, vital and functional prognosis in CVT is far better than arterial stroke. Data from studies reporting short-term functional outcome by measurement of mRS are depicted in Table 3. In total, short-term functional outcome is considered good with approximately 85% achieving independency (mRS 0-2). Around 9% become dependent (mRS 3-5) and 6% die (mRS 6).[4,5,48,53,119,213,215,216]

Table 3. *Short-term functional outcome after cerebral venous thrombosis*

Study	Year	Patients	Follow-up time, days	Loss to follow-up	Short term functional outcome 1-3 months, n (%)					
					mRS 0-1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
Alet	2020	162	90	19 (12)	128 (93)		9 (6)			9 (6)
Duman	2017	1144	90	285 (25)	764 (89)	54 (6)	41 (5)			
Narayan	2012	428	90	12 (3)	226 (54)	47 (10)	110 (26)			66 (15)
Ruiz-Sandoval	2012	59	30	0 (0)	43 (73)		12 (24)			2 (3)
Stolz*	2005	79	6 months	5 (6)	54 (68)	4 (5)		4 (5)		12 (15)
ISCVT*	2004	624	6 months	8 (1)	481 (77)	49 (8)	44 (7)			42 (7)
De Bruijn	2001	59	84	0 (0)	49 (83)		4 (7)			6 (10)
Bienfait	1995	62	90	0 (0)	41 (66)		10 (16)			11 (18)
Total		2617		329	1936 (85)		197 (9)			148 (6)

Abbreviations: mRS – modified Rankin Scale; ISCVT – International Study on Cerebral Venous Thrombosis

* 6 months follow-up

Large cohorts reporting long-term functional outcome after CVT with follow-up at least 12 months after diagnosis of CVT are scarce. Available data are summarized in Table 4. In total, approximately 88% achieve independency (mRS 0-2), 5% are dependent in activities of daily living (mRS 3-5) and 6%

die.[4,5,7,8,25,26,46,52,70,213,217-219] However, comparisons between studies are afflicted by different follow-up durations and, for some studies, a substantial loss to follow-up (Table 4).

Table 4. *Long-term functional outcome after cerebral venous thrombosis*

Study	Year	Patients	Follow-up	Loss to follow-up	Long-term outcome (≥1 year)			
					mRS 0-1	mRS 2	mRS 3-5	mRS 6
Triquienot Bagan	2021	231	12	18 (8)	181 (85)	24 (11)		8 (4)
Duman	2017	1144	12	453 (60)	643 (93)	22 (3)	26 (3)	
Hiltunen	2016	195	39	13	132 (73)	23 (13)	6 (3)	21 (12)
Geisbüsch	2014	143	36	35 (20)	80 (74)		8 (6)	20 (19)
Dentali	2011	706	40	3 (5)	629 (89)	27 (4)	27 (4)	20 (3)
English	2009	61	50	3 (5)	43 (70)	9 (15)	1 (1)	5 (9)
Wasay	2008	182	12	62 (34)	26 (27)	43 (45)	27 (28)	24 (13)
Stolz	2005	79	48	7 (9)	50 (63)	mRS 2-3: 2 (3)	4 (6)	14 (18)
ISCVT	2004	624	16	7 (1)	493 (79)	47 (8)	32 (5)	52 (8)
Breteau	2003	55	36	0 (0)	42 (76)	3 (5)	3 (5)	7 (13)
Ferro	2002	142	12	0 (0)	108 (76)	12 (8)	4 (3)	11 (8)
De Bruijn	2001	59	18	2 (3)	25 (42)	19 (32)	3 (1)	8 (14)
Preter	1996	85	78	0 (0)	66 (77)	Nr	Nr	8 (9)
Total		3706		596	2518 (81)	205 (7)	141 (5)	198 (6)

Abbreviations: mRS – modified Rankin Scale; ISCVT – International Study on Cerebral Venous Thrombosis; Nr – Not reported.

Predictors of functional outcome

Few studies have investigated predictors of poor and good outcome and a low number of outcome events generally restricts adjustments for potential confounders. Factors that have been independently associated with poor outcome or mortality (mRS >2) are age,[4,5,50] parenchymal lesions[5] or ICH[4,7,26,119] at admission, decreased consciousness or coma,[4,7,48,119] deep cerebral venous system thrombosis,[4,48] cancer,[4,26,50,70] mental state disturbance,[4] male sex,[4] focal neurologic deficits,[48,70] fever[48] or CNS infection,[4] seizures,[48] encephalopathy,[46] clinical worsening after acute admission,[46] hyperglycemia,[207] anemia.[208] low educational level[217] and National Institutes of Health Stroke Scale (NIHSS) score >2 at admission.[217] Suggested predictors for good outcome (mRS ≤2) include isolated intracranial headache at presentation[26,70,119] and female sex-specific risk factors.[42,213]

Risk scores for poor outcome

Developing risk scores to predict poor outcome after CVT is challenging, in particular due to low number of patients seen in individual centers and the limited proportion of patients with poor outcome. Four risk scores have been developed based on clinical and radiologic baseline variables.[220-223]

The first score by Barinagarrementeria et al[220] was developed in the 1990s in a patient cohort of 78 patients. Potential predictors were arbitrarily assigned numerical values based on their univariate statistical significance value; stupor or coma (3p), bilateral pyramidal tract signs (3p), generalized seizures (2p), meningeal signs (1p), bilateral lesion by CT scan (1p) and hemorrhagic cerebrospinal fluid (1p). A score of 0-5 points, had 98% sensitivity and 96% specificity for favorable outcome but the model performance has not been validated in an external patient cohort.

Ferro and colleagues developed a score[221] to predict dependency or mortality (mRS 3-6) at 6 months. Predictors were derived from the ISCVT study and weighted depending on the magnitude of hazard ratios; malignancy (2p), coma (2p), thrombosis of the deep cerebral venous system (2p), mental status disturbance (1p), male sex (1p) and ICH (1p). Age <37 y was a candidate predictor, but non-proportionally associated with the outcome and thus excluded from the final model. Using a threshold of 3 points, sensitivity, specificity and c-statistics were 96%, 14% and 0.77, respectively, when validated in two external cohorts and in the development cohort.

Koopman et al[209] developed a score with eight items to predict mRS 3-6 at last follow-up, based on data from the ISCVT study. Items were weighted based on a natural logarithm of the hazard ratio, multiplied by 10 and rounded to nearest integer; male sex (5p), ICH (6p), mental status disorder (7p), age >37 years (7p), Coma (10p), malignancy (11p), deep cerebral venous system thrombosis (11p), and CNS infection (12p). A score of ≥14p yielded a sensitivity, specificity and c-statistic value of 88%, 70% and 0.81, respectively. The positive predictive value for poor outcome was 39%.

Barboza et al[223] developed a score from a retrospective cohort of 467 patients after excluding, among others, patients with CNS infection. The score ranges from 0-13 points; parenchymal lesion >6cm (3p), bilateral Babinski signs (3p), male gender (2p), ICH (2p), level of consciousness – awake and alert (0p), somnolence (1p), stupor (2p), coma (3p). For prediction of 30-day mortality, a cut-off value of 6 points reportedly yielded a sensitivity, specificity and positive predictive value of 71%, 93% and 50% together with a c-statistic of 0.79.

All available risk scores present qualities that confine implementation in clinical practice. One originates from a relatively small sample size,[220] three have not been externally validated,[209,222,223] three include variables that are either complicated or have potentially low inter-observer agreement[221-223] and one reportedly used time from admission to discharge as the time dependent variable in a cox regression analysis rather than time to death or censoring.[223]

2.7.3 SEIZURES

Seizures frequently occur (34-51%) as a complication in the acute phase of CVT. [4,5,142-146] It has been suggested to consider seizures occurring up to 14 days after diagnosis of CVT as early seizures, or acute symptomatic seizures (ASS),[142] however current recommendations on stroke suggest only including seizures up to 7 days after diagnosis.[224,225] ASS can occur either as a presenting symptom, or after diagnosis as a complication of CVT.[5,89] In multivariate analyses, several factors have been suggested to be predisposing for ASS in CVT, including focal neurologic deficits, supratentorial parenchymal lesions, ICH, focal edema/ischemic infarction, superior sagittal sinus thrombosis, cortical vein thrombosis, and pregnancy or puerperium.[142-146,226,227] Data from large international cohorts are scarce and little is known about the risk of developing status epilepticus (SE).[4,98] ASS may increase the risk of early death,[142] but occurrence of ASS has not been associated with worse long-term clinical outcome after CVT.[4,27,98]

To prevent recurrent and remote seizures, anti-epileptic drug (AED) treatment is recommended by the European and American guidelines on CVT in patients with ASS and supratentorial lesion.[71,98] Efficacy of AED treatment has not been investigated with regard to clinical outcome. The use of prophylactic drugs to prevent a first seizure is controversial. In the group of patients without seizures at the time of CVT diagnosis, no specific group has been identified with a high-enough risk of subsequent postdiagnosis ASS to warrant primary prophylactic AED treatment.[71,98,142,143,226]

2.7.4 LATE SEIZURES

Not much is known regarding frequency and risk factors for late seizures after CVT. In the ISCVT, 11% of the investigated patients had at least one seizure occurring after the acute phase, within the follow-up time of 16 months.[89] Small single-center cohorts have reported explorative data suggesting an increased risk for seizures among patients with ASS, ICH at baseline, sigmoid sinus thrombosis, loss of consciousness at presentation and genetic thrombophilia. However, no studies have investigated seizure characteristics, risk of seizure recurrence and treatment of late seizures after CVT.[4,142,145]

2.7.5 RECANALIZATION

Partial or complete recanalization occurred in around 65% of patients treated with anticoagulation, within the first 6 months after CVT in a clinical trial of 120 patients.[185] In the PRIORITy CVT study,[30] 68 patients were investigated with MRI/MR venography at 48h, 8 days and 90 days after the initiation of anticoagulation. At 8 days, 68% had partial recanalization and 6% full recanalization. At 90 days, 41% had partial and 54% had complete recanalization. Early recanalization was associated with radiologic regression of non-hemorrhagic lesions but there was no association between recanalization and new or enlarged hemorrhagic lesions. These results are suggestive of that recanalization in CVT starts early in patients receiving therapeutic anticoagulation and that recanalization progress over time. Younger age was a predictor for early recanalization.

Available evidence is conflicting whether recanalization is associated with functional outcome or not.[30,228,229] In two recent observational studies, no association could be found between recanalization and functional outcome.[30,228] In a pooled analysis of published cohorts investigating recanalization in more than 800 patients treated with anticoagulation, 85% (95% CI 80-89%) of cases showed recanalization in at least one of the thrombosed vessels during follow up. Complete or partial recanalization was associated with increased odds of functional independence (mRS 0-1).[230]

The role and impact of recanalization in functional outcome and recovery remains to be fully determined.

2.7.6 RESIDUAL SYMPTOMS, COGNITIVE AND VOCATIONAL OUTCOME

Despite the seemingly good outcome with approximately 85% of patients achieving functional independence after the acute phase, chronic residual symptoms are frequent after CVT. Observational studies suggest that merely around 30% of patients are asymptomatic. The most frequently reported long-term residual symptoms are described in Table 5.[4,25,46,70,209,217,219,231,232]

Table 5. *Prevalence of residual symptoms at long-term follow-up (>12 months) after cerebral venous thrombosis*

Residual symptoms	**Prevalence** [‡]
Severe headache	14-53%
Focal deficits	6-13%
Remote seizures	11-13%
Visual defects	<1-12%
Cognitive impairment	18-41%
Speech difficulties	21-28%
Depression	19-30%
No symptoms	31-34%

[‡] *Preter (1996), de Bruijn (2001), Breteau (2003), Ferro (2002), Buccino (2003), Ferro (2004), Koopman (2009), Bugnicourt (2013), Hiltunen (2016).*

Cognitive and vocational outcome

Long-term functional outcome after CVT may be considered good when measured with mRS, however, long-term functional outcome regarding working ability, cognitive dysfunction, headache, and depression rate after CVT, remains poorly investigated.

In a retrospective study by Hiltunen et al[217] (n=161, median follow-up time 39 months), 81% of surviving patients scored mRS 0-1 at follow up, implying a favorable outcome among most patients. Nevertheless, merely 57% had returned to work (RTW) at the end of follow-up. In an earlier study by Koopman et al,[209] (n=56 independent patients, follow-up time >12 months) 21% did not RTW, 75% reported concentration problems, 30% had depression and 30% reported fatigue. Patients with CVT had a lower quality of life as compared to healthy controls. Similarly, de Bruijn et al[219] reported that 40% of 47 patients did not RTW within a median follow-up of 18 months. Interestingly, 16/19 (84%) patients with mRS score 2, were not able to fully RTW after CVT. The authors conclude that mRS score 2 is a broad category and that, mRS 2 cannot be regarded as a good outcome in patients with CVT per se.

Headaches

Half of the surviving patients report significant residual headaches, and severe headaches that require resting or hospital admissions are reported in 14% of the patients.[4,46,70,209,217,219] Persistent or recurrent headache may raise the concern of recurrent or worsening of the thrombosis. Evaluation with CT-venography or MR-venography is appropriate although CVT recurrence rates are low.[182,217] In the PRIORITy-CVT, residual headache was not associated with recanalization status.[30] In a recent study from China,[233] patients with CVT were investigated at a median of 13 months. Of the 325 patients, 43 (13%) reported severe headache (a residual headache attack requiring bed rest or hospital visit within 1 month prior to follow up visit). In multivariate analyses, isolated intracranial hypertension (OR 3.3, 95% CI 1.4-7.6), CVT recurrence (OR 4.7, 95% CI 1.6-13.6) and no recanalization (OR 10.1, 95% CI 4.2-24.6) were associated with severe headache.[233]

Vision impairment

Persistent visual impairment after CVT is a rare complication, merely reported in 1% of patients in the ISCVT.[4] In a study of patients with CVT and isolated intracranial hypertension, 5% developed optic atrophy.[192] Long-term intracranial hypertension may, however, cause optic nerve injury that may remain undiagnosed. In a study by Koban et al, significant axonal loss was discovered by optical coherence tomography in patients who had no vision impairment, normal visual field tests and no papilledema on fundoscopy.[234]

2.7.7 RECURRENCE OF CEREBRAL VENOUS THROMBOSIS AND VENOUS THROMBOEMBOLISM

The risk for recurrent cerebral or a new systemic venous thrombotic event after the index CVT is low. Long-term observational studies report recurrence rates up to 2.2 per 100 person-years for CVT and up to 5.0 per 100 person-years for any VTE.[8,49,50,182,217] A sub-study of the ISCVT showed that the majority of CVT (64%) and VTE (63%) recurrence occurred within the first year after the first CVT diagnosis.[182] Interestingly, however, the cumulative probability of venous thrombotic recurrence has seemingly a linear relationship with time (3% at 1 year, 8% at 2 years, 12% at 5 years, 18% at 10 years).[235] Recurrence of VTE and CVT could not be associated with anticoagulation treatment. Male gender,[49,182] polycythemia/thrombocytemia,[182] severe thrombophilia,[49] previous venous thrombotic events,[235] presence of cancer or malignant hemopathies[235] and unknown CVT causes[235] have been associated with VTE recurrences.

The prothrombotic alterations during pregnancy and the postpartum period are associated with an increased risk of venous thrombotic events. Without thromboprophylaxis, VTE recurs during pregnancy in approximately 10% of women with prior VTE.[236] A case-control study of women with prior VTE reported a relative risk reduction for recurrence by 88% for women treated with thromboprophylaxis.[236] The absolute risk for VTE recurrence for patients with prior CVT, appears to be low with around 8 cases of CVT and 22 cases of noncerebral VTE per 1000 pregnancies.[237] The use of prophylactic anticoagulation during future pregnancies is to be considered and data from a systematic review suggest beneficial effects in reduction of subsequent venous thromboembolic events.[71,237]

2.7.8 DURAL ARTERIOVENOUS FISTULAS

The relationship between dAVFs and CVT has been deliberated since the publication of case reports of patients with simultaneous occurrence of the two conditions, dating back to the 1980s.[238,239] Whether CVT causes dAVF or vice versa is controversial, as dAVF has been described prior to, simultaneously and subsequent to the diagnosis of CVT.[152,240-243] In small CVT patient cohorts, frequency of dAVF has been reported in 0.9%-13% within the first 6 months after diagnosis.[25,89,244,245] Data from large CVT patient cohorts are lacking. Conversely, in a cohort of 69 patients with dAVF, CVT was diagnosed in 39% of the cases.[246] Pathophysiologic hypotheses include enlargement of preexisting physiological arteriovenous shunts by stagnation of venous blood flow, secondary to a thrombus.[240,247,248] Further, thrombus formation with increased venous pressure and relative hypoxia has been reported to stimulate recruitment of angiogenic factors, neoangiogenesis and the development of a dAVF.[249,250] Further, the formation of a dAVF may alter venous blood flow, induce turbulence and thereby increase risk of a venous thrombus formation.

Systematic data on the matter are lacking as the diagnoses of both CVT and dAVF are challenging and require a strong clinical suspicion and specific diagnostic work-up for confirmation of the diagnoses.[251] Symptoms of dAVF may mimic symptoms of CVT with diffuse headache, but more specifically linked to dAVF are tinnitus and bruit. As opposed to CVT patients, dAVF most often appears in patients aged 50-60 years and with equal distribution between sexes.[252] While low-grade fistulas may appear asymptomatic and remain undiagnosed for long periods, high-grade fistulas (i.e. with retrograde cortical venous blood flow) entail a 10% annual risk of mortality and a 15% annual risk of ICH or non-hemorrhagic neurologic sequel.[251-254] The time correlation between CVT and dAVF occurrence, prevalence and characteristics of dAVF have not been systematically investigated in large CVT patient cohorts.

Further, the impact of dAVF on clinical outcome has not been investigated among patients diagnosed with CVT.

2.7.9 KNOWLEDGE GAPS

To summarize, considerable knowledge gaps exist for various features of CVT and in particular regarding complications and outcomes. There are very limited published data on these aspects of CVT, and in particular from large international CVT patient cohorts. Only few studies have investigated the importance of long-term vocational outcome, acute and late seizures, and dAVF on clinical outcome. Further, there are no available robust risk scores that efficiently identify patients with high risk of poor outcome after CVT.

3 AIMS OF THE THESIS

The overarching aim of this thesis is to investigate prognostic factors affecting clinical outcome after CVT. Secondary aims include describing the clinical presentation and disease course of patients diagnosed with CVT in a local Swedish and in a large international population. The specific aims for each study are depicted below.

I. To describe the prevalence and associated factors of RTW after CVT, and the influence of RTW on self-reported patient outcomes.

II. To evaluate occurrence and predictors of ASS, postdiagnosis seizures in the absence of prediagnosis seizures, and acute SE in patients with CVT. Secondary aims include to investigate the association between ASS and clinical outcome.

III. To describe the incidence, characteristics, current treatment and predictors of late seizures after CVT.

IV. To explore the prevalence, time correlation and risk factors for dAVF among CVT patients, and its impact on clinical outcome.

V. To develop a prognostic risk score that uses readily available, routine clinical variables to predict individual risks of dependency or death after CVT.

4 PATIENTS AND METHODS

For paper I, patients were included from a local registry of patients with CVT diagnosis in Gothenburg. In study II-V, patients were also included from the International CVT consortium registries (Table 7).

Data collection of the Sahlgrenska CVT Registry (I-V)
Sahlgrenska University Hospital is a regional hospital covering approximately 780 000 inhabitants in the Gothenburg region. The stroke unit also serves as a tertiary referral stroke department for the Västra Götaland Region.

From an administrative hospital-based registry, we searched for adult patients (≥18 years) consecutively diagnosed with CVT between 1996 and 2016, admitted to the Sahlgrenska University Hospital, using the diagnosis codes for CVT in ICD-9: .437G (Nonpyogenic thrombosis of intracranial venous sinus) and ICD-10: I63.6 (Cerebral infarction due to cerebral venous thrombosis, nonpyogenic), I67.6 (Nonpyogenic thrombosis of intracranial venous system), O87.3 (Cerebral venous thrombosis during puerperium) and O.22.5 (Cerebral venous thrombosis during pregnancy). Medical records were reviewed to confirm the diagnosis of CVT, either by CT venography, MRI combined with magnetic resonance venography, conventional angiography or autopsy, in accordance with international diagnostic criteria.[71] From January 2016, patients were identified prospectively during hospital admission. For identification of eligible patients, research nurses screened the stroke unit for patients with a potential diagnosis of CVT, on a daily basis. Furthermore, the administrative hospital-based registry was screened with a timely interval of 6 months to also identify additional patients with CVT treated at the Sahlgrenska University Hospital who had not been admitted to the stroke unit. After informed consent, medical records were reviewed thoroughly in accordance to a preset study-formula, to gather data on demographics, clinical features, laboratory findings, radiological imaging, treatment and outcome. Variables assessed for the Sahlgrenska CVT Registry are listed in Table 6. Allowing for studies on poor outcomes and mortality, we also collected data from medical records of deceased patients.

All survivors were invited to a clinical follow-up visit, at least one year after diagnosis of CVT. The follow-up visit included an interview, clinical neurological examination, assessment of functional outcome according to the mRS and validated instruments measuring emotional, cognitive and patient-reported outcomes (Table 6). Patients not able to attend clinical visits were invited to participate by telephone interviews.

Table 6. *Variables collected for the Sahlgrenska CVT Registry*

Demographics	Age, sex, education level, profession
Risk factors	Concurrent associated conditions (malignancy, polycythemia vera, essential thrombocythemia, vasculitis, inflammatory bowel disease, chronic obstructive pulmonary disease, severe heart condition, diabetes, epilepsy, eclampsia or preeclampsia, other diseases), medication (contraceptive use, HRT, chemotherapy, other medications), pregnancy, postpartum, infection (systemic, local, CNS), head trauma, surgery, severe dehydration, lumbar puncture, family history of VTE, smoking, weight, height.
Clinical characteristics and symptoms	Date of symptom onset, CVT diagnosis, admission and discharge. Presenting symptoms: headache (type of onset, location, severity, duration), ASS (focal, bilateral tonic-clonic, status epilepticus, dates, frequency, acute treatment, prophylactic medication including type dose and duration, admittance to intensive care unit due to seizure), focal neurologic deficits (motor or sensory deficit, aphasia, other), papilledema, mental state disturbance, nausea, vomiting, stiff neck, coma (Glasgow coma scale score <9), decreased alertness (Glasgow coma scale score 9-14), National Institutes of Health Stroke Scale score at admission. Duration of hospital stay, intensive care unit admittance. Late seizures (focal, bilateral tonic-clonic, status epilepticus, dates, frequency, treatment at time of seizure, prophylactic treatment including type, dose and duration).
Laboratory	Lupus anticoagulants, antiphospholipid antibodies, protein C deficiency, protein S deficiency, antithrombin deficiency, Factor 5 Leiden mutation, prothrombin mutation, hyperhomocysteinemia, admission level of hemoglobin, blood glucose and platelet count.
Imaging	Date of radiological confirmation of CVT (CT, CT-venography, MRI, MR-venography), location of CVT (superior sagittal sinus, right/left transverse sinus, right/left sigmoid sinus, straight sinus, confluence of sinuses, deep cerebral venous system, right/left jugular vein, cavernous sinus, cerebellar veins, cortical veins) number of sinuses involved, dAVF, parenchymal lesion (hemorrhagic, non-hemorrhagic), lesion location (supra-/infratentorial, cortical, subcortical, bilateral), lesion size, (sulcal) subarachnoid hemorrhage, subdural hemorrhage, hydrocephalus, midline shift.
Treatment	Intravenous or subcutaneous anticoagulation, oral anticoagulation, endovascular treatment (local thrombolysis, mechanical thrombectomy), decompressive surgery (hemicraniectomy, hematoma evacuation), intensive care unit admittance
Outcome	Date of death, cause of death. Functional outcome: mRS score (discharge, 6 months, 12 months, last available). Long-term follow-up: date, type (clinical/telephone), employment status, length of sick-leave, reason for unemployment, residual symptoms (headache, epilepsy, focal neurologic deficits, fatigue, spasticity, visual impairment, linguistic impairment, pain, concentration difficulties, depression, venous thrombosis recurrence), medication (duration and type of anticoagulants), subsequent pregnancies. Stroke impact scale, EQ-5D, Lisat-11, D-FIS, HAD, Barthel Index.

Abbreviations: ASS – acute symptomatic seizures; CNS – central nervous system; CT – computed tomography; CVT – cerebral venous thrombosis; dAVF – dural arteriovenous fistula; D-FIS – daily fatigue impact scale; EQ-5D – european quality of life five dimension; HAD – hospital anxiety and depression scale; Lisat-11 – life satisfaction questionnaire-11; MRI – magnetic resonance imaging; mRS – modified Rankin Scale; VTE – venous thromboembolism.

The International CVT Consortium (II-V)

For study II-V, we also used data from the International CVT Consortium which is an ongoing collaboration between CVT research groups from 17 academic hospitals in 5 continents. The consortium was founded in 2015 by researchers with detailed hospital-based registries of consecutive adult patients diagnosed with CVT. Centers participating and included number of patients per center are summarized separately for study I-V in Table 7. Time of recruitment varied between centers, and spanned from January 1987 to June 2021. Retrospective and prospective recruitment periods are described in detail per center in the supplements for each study, respectively.

Table 7. *Summary of centers and number of patients for Study I-V.*

Center	**Study I**	**Study II**	**Study III**	**Study IV**	**Study V**
Adelaide, Australia		99	99	99	
Almada, Portugal					49
Amsterdam, the Netherlands		220	220	257	276
Barcelona, Spain					16
Bern, Switzerland		185	185	160	222
Charlottesville, USA				4	
Gothenburg, Sweden	62	129	129	165	174
Hamadan, Iran		110	110	73	69
Helsinki, Finland		191	191	244	186
Istanbul, Turkey		60	60		40
Jerusalem, Israel					135
Lisbon, Portugal		76	76		74
Manchester, United Kingdom		70	70	72	
Mexico-City, Mexico		126	126	148	137
Newcastle, Australia				1	23
Palermo, Italy		16	16		19
San José, Costa Rica		26	26		35
Total	62	1308	1308	1223	1455

4.1 VOCATIONAL OUTCOME IN CEREBRAL VENOUS THROMBOSIS: LONG-TERM FOLLOW-UP STUDY (I)

In the first study, we used data from the Sahlgrenska CVT Registry. Patients aged 18-62 years were identified retrospectively from 1997 to 2016. Baseline data were extracted from medical records. Follow-up data were assessed based on questionnaires, interviews and clinical examinations at follow-up visits at least 12 months after diagnosis of CVT.

Primary outcome measure was RTW within the follow-up period, defined as ≥50% of gainful work or equivalent activity.

Questionnaires covering residual symptoms, living and vocational status were sent to participants prior to the follow-up visit. The association between RTW and patient reported outcomes was investigated by measurement of validated scales covering life satisfaction (Lisat-11), health related quality of life (EuroQol-5 Dimension questionnaire [EQ 5-D]), participation (Stroke Impact Scale), symptoms of depression and anxiety (Hospital Anxiety and Depression Scale), and fatigue (the Daily Fatigue Impact Scale) at the end of follow-up.

4.2 SEIZURES IN CEREBRAL VENOUS THROMBOSIS (II-III)

For the second and third studies, we included consecutive adult patients with CVT from 12 hospitals within the International CVT Consortium (Table 7). Patients with a history of epilepsy, eclampsia or preeclampsia were excluded from study II, and patients with a history of epilepsy or with <8 days of follow-up were excluded from study III.

Seizures were diagnosed and classified by the treating physician as focal or bilateral tonic-clonic. Focal to bilateral tonic-clonic seizures were classified as bilateral tonic-clonic seizures. Status epilepticus was defined as continuous seizure activity for ≥5 minutes or multiple seizures within 30 minutes without normalization of consciousness in between.

ASS was defined as any seizure between CVT symptom onset and seven days after diagnosis of CVT. ASS was further stratified into prediagnosis and solely postdiagnosis ASS, depending on the timing of the first seizure. Characteristics and frequency of SE were analyzed separately. Late seizures were defined as seizures occurring >7 days after diagnosis of CVT.

Patients with ≥3 months of follow-up time were evaluated regarding clinical outcome, measured by the mRS (II). Poor outcome was defined as a score of 2-6, and mortality was analyzed separately.

4.3 DURAL ARTERIOVENOUS FISTULAS IN CEREBRAL VENOUS THROMBOSIS (IV)

In the fourth study, we included adult patients consecutively diagnosed with CVT from August 1987 through October 2018 from eight centers within the International CVT Consortium. Due to the particularly rare combination of CVT and dAVF, five additional patients with suspected CVT and dAVF were included non-consecutively for descriptively exploring the features of dAVF.

All available neuroimaging data from patients with suspected CVT and dAVF were reviewed centrally at the Sahlgrenska University Hospital to verify the diagnosis of dAVF and to categorize fistulas in accordance with Cognard's classification,[253] and a preset study formula. The dAVF group comprised patients in whom both CVT and a dAVF could be confirmed, and for whom imaging from a digital subtraction angiography was available in the central imaging review. In accordance with Cognard's Classification System for dAVF, fistulas graded as score IIb or higher were categorized as high grade fistulas (i.e fistulas with retrograde cortical venous drainage). The index date for CVT and dAVF was defined as the imaging date when the first radiological signs appeared for each condition, respectively. The time correlation between diagnosis of CVT and diagnosis of dAVF was evaluated. The prevalence of dAVF was examined among consecutively recruited CVT patients. Recurrent CVTs confirmed at different imaging studies and dates were considered as separate events. The degree of relationship between the dAVF and CVT was categorized into three groups depending on the location of the CVT versus the location of the fistula: i) "probable" – CVT and dAVF located in the same sinus; ii) "possible" – CVT located directly downstream of the dAVF, but not in the same sinus; and iii) "unlikely" – CVT located on the contralateral side or upstream of the dAVF without radiological evidence of hemodynamic influence at the location of the thrombus.

Risk factors for dAVF and the impact of dAVF on clinical outcome were investigated using logistic regression analysis, adjusted for age and sex. Poor outcome was defined as mRS score 3-6 at last follow-up.

4.4 A SCORING TOOL TO PREDICT MORTALITY AND DEPENDENCY AFTER CEREBRAL VENOUS THROMBOSIS (V)

For the fifth study, we included patients from 14 hospitals within the International CVT Consortium. Patients were recruited from July 1995 to June 2021. Data on baseline characteristics including demographic data, radiological imaging, admission laboratory parameters, clinical symptoms, treatment and comorbidity were assessed in accordance with a study-specific case report form. Patients with history of disability, defined as mRS score >2 prior to the diagnosis of CVT, and patients who had missing primary outcomes of interest were excluded. Functional outcome was assessed at routine follow-up visits at 6 months using the mRS and poor outcome was defined as dependency or death (mRS 3-6). Mortality rates were evaluated at 30-days and at 1 year, and date of death was recorded.

Two prognostic models were developed in accordance with international guidelines for development of prediction models,[255,256] to calculate individual risks of either poor outcome at 6 months, 30-day mortality or 1-year mortality.

4.5 STATISTICAL ANALYSIS

In all studies, data were considered non-normally distributed and nonparametric statistical tests were used. Two-sided p-values of <0.05 were considered statistically significant (I-V). Continuous data were presented as median with interquartile range (IQR, I-V) and n/N represented number of patients and number of observations for each variable individually (I-V). For analysis of discrete variables, we used chi-square (I) and Fisher's exact test (I-V). For analysis of distribution of continuous variables, we used Mann-Whitney U tests (I-V). We used the Wilson procedure to calculate 95% CI for binomial proportions (III).

Kaplan-Meier survival statistics was used to depict cumulative rates of RTW, time to RTW (I), and late seizure-free survival rates (III). Cox regression statistics was used for multivariable analyses for evaluation of predictors for RTW (I) and late seizures (III), presented with hazard ratios (HRs) and 95% CI. Potential predictors for RTW (I) were included based on clinical experience, previous literature, and potential collinearity: female sex, onset age, >1 sinuses thrombosed at baseline, parenchymal lesion during hospital admission, low education level. Potential predictors for late seizures (III) were selected based on clinical plausibility, ease of clinical use and univariate

analysis ($p<0.1$): age, status epilepticus in the acute phase, ASS without status epilepticus, focal neurologic deficits, ICH, focal edema without parenchymal hemorrhage, sulcal subarachnoid hemorrhage, subdural hematoma, superior sagittal sinus thrombosis and decompressive hemicraniectomy.

Logistic regression analysis was used to investigate potential predictors for ASS, solely postdiagnosis seizures, SE and the influence of ASS on clinical outcome (II), presented with ORs and 95% CI. The following potential predictors were selected based on clinical plausibility and univariable analysis ($p<0.1$): age, female sex, ICH, cerebral edema/infarction only, focal neurologic deficit, sulcal subarachnoid hemorrhage, superior sagittal sinus thrombosis, female sex-specific risk factors, and cortical vein thrombosis. For analysis of poor clinical outcome, we adjusted for factors associated with poor outcome in univariate analysis ($p<0.1$) or previous literature; age, female sex, focal neurologic deficits, coma, infection, ICH, subdural hematoma, sulcal subarachnoid hemorrhage, and cancer. Positive predictive and negative predictive values were calculated for postdiagnosis ASS (II) and for dAVF (IV) for variables with $p<0.05$ in univariate analyses.

Development of prediction models (V)
Models were developed using multiple imputation for missing values, and we pooled results from 5 imputed datasets. We investigated dependency or death (mRS 3-6) at 6 months with logistic regression analysis with backward stepwise selection ($p<0.1$), and mortality up to 1 year with cox regression with backward stepwise selection ($p<0.1$) with time of death as event of interest.

Candidate predictors were selected for both models based on clinical plausibility, previous studies and potential collinearity. Coefficients were shrunken to adjust for optimism, and internal validation was performed using bootstrapping with 1000 samples. Performances of the models were evaluated with calibration plots for goodness-of-fit and c-statistics with 95% CI for discrimination.

Statistical calculations were performed using IBM SPSS Statistic version 23 International Business Machines Corp, Armonk, NY (I-V), and R-statistic programming, version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria (V).

4.6 ETHICAL APPROVAL

Ethical approval was granted from the Regional Ethical Review Board in Gothenburg (Dnr: 898-15. Main application January 11, 2016, supplementary

application February 27, 2017). All studies were performed in line with the principles of the Declaration of Helsinki. For studies II-V, each center within the International CVT Consortium received permission from local authorities and ethics committees to collect observational data and obtained written informed consent when required under applicable national laws. Ethical procedures for centers in the International CVT Consortium (I-V) are described in the Appendix.

5 RESULTS

5.1 VOCATIONAL OUTCOME (I)

Of 150 patients identified from the administrative hospital-based registry at the Sahlgrenska University Hospital from 1997 to 2016, 30 patients had died, 11 patients were aged >62 years old at time of diagnosis, and 2 had inaccessible medical records. Twenty-two patients declined participation in the specific study, and 23 patients were not able to be reached. Of the included 62 patients (median age 42 years, 61.3% female), 44 patients (71%) did RTW within the follow-up period (median 135 months). Thirty-eight patients returned to full-time work and six patients to part-time work ≥50%. Median time to RTW was 7 months (IQR 1-13). Female sex (HR 0.5, 95% CI 0.25-0.99) and parenchymal lesion at acute hospital stay (HR 0.45, 95% CI 0.24-0.82) were significantly associated with no RTW. Patients with RTW reported significantly higher scores on life satisfaction (Lisat-11), quality of life (EQ-5D), health and participation (Stroke Impact Scale) and lesser negative impact of fatigue (Daily – Fatigue Impact Scale) and depression and anxiety (Hospital Anxiety and Depression scale) as compared to the no RTW group.

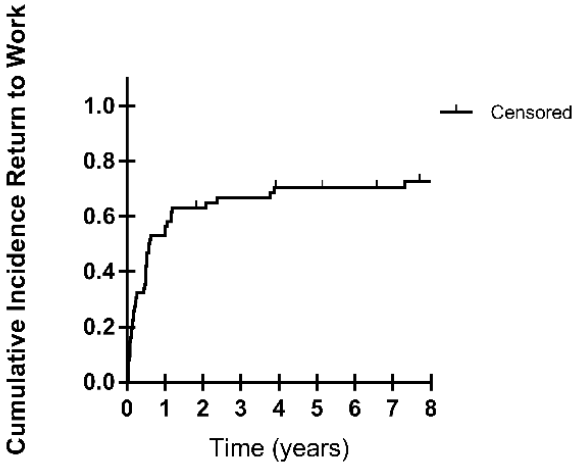

Figure 5. *Cumulative incidence in time to return to work, among 62 patients with cerebral venous thrombosis*

5.1.1 FUNCTIONAL OUTCOME AND RESIDUAL SYMPTOMS

At the end of follow-up, 35 patients (56.5%) achieved favorable functional outcome (mRS 0-1), 19 (30.6%) were independent (mRS 2) and 8 patients (12.9%) had significant disability (mRS 3-5). Six patients (9.7%) had recurrent VTE: 3 DVT (4.8%), 2 had recurrent CVT (3.2%) and 1 PE (1.6%). Residual symptoms were common, as only 12 patients (19.4%) reported no remaining

sequel. Most frequent self-reported symptoms were memory or concentration difficulties (61.3%), headache ≥1 per week (35.5%), fatigue (37.1%) and psychiatric problems (30.6%). Nine patients (14.5%) were diagnosed with epilepsy.

5.2 ACUTE SYMPTOMATIC SEIZURES (II)

From the International CVT Consortium, 1,308 adult patients with CVT were identified. After exclusion of 22 patients with epilepsy and 5 patients with eclampsia prior to diagnosis of CVT, 1,281 patients were considered eligible for the study (median age 41 years, IQR 29-52, 69% female). In total, 441 patients (34%) experienced at least 1 ASS. The first seizure occurred prior to diagnosis in 348 (27%) patients, and 93 (7%) patients had solely postdiagnosis seizures. Focal seizures occurred in 187 (15%) patients, tonic-clonic seizures in 325 (25%) and 80 patients (6%) developed status epilepticus. Among patients with ASS, 161 (37%) received acute treatment with benzodiazepines, and 217 (49%) received intravenous AED. General anesthesia was administered in 61 (14%) patients. Subsequent treatment with an AED was initiated in 410 (94%) patients with ASS. Most common AED types in the acute phase were phenytoin (42%), levetiracetam (35%), or valproic acid (25%).

Neither ASS nor SE was independently associated with clinical outcome at last follow-up, after adjusting for age, female sex, coma, infection, ICH, subdural hematoma, sulcal subarachnoid hemorrhage and cancer.

5.2.1 PREDICTORS OF ACUTE SYMPTOMATIC SEIZURES

Retained baseline predictors for ASS were ICH, (aOR 4.1, 95% CI 3.0-5.5), cerebral edema/infarction without ICH (aOR 2.8, 95% CI 2.0-4.0), cortical vein thrombosis (aOR 2.1, 95% CI 1.5-2.9), superior sagittal sinus thrombosis (aOR 2.0, 95% CI 1.5-2.6), focal neurologic deficits (aOR 1.9, 95% CI 1.4-2.6), sulcal subarachnoid hemorrhage (aOR 1.6, 95% CI 1.1-2.5) and female sex-specific risk factors (aOR 1.5, 95% CI 1.1-2.1).

5.2.2 POSTDIAGNOSIS SEIZURES

Independent predictors for postdiagnosis seizures in absence of prediagnosis seizures were focal neurologic deficits (aOR 4.1, 95% CI 2.2-7.5), ICH (aOR 2.8, 95% CI 1.6-4.8), cortical vein thrombosis (aOR 2.5, 95% CI 1.5-4.2), cerebral edema/infarction only (aOR 2.3, 95% CI 1.3-4.4), and superior sagittal sinus thrombosis (aOR 2.2, 95% CI 1.3-3.7).

Among patients without prediagnosis seizures, subsequent postdiagnosis seizures were best predicted by presence of cortical vein thrombosis (positive predictive value 22% and negative predictive value 92%). In 71% of patients, postdiagnosis ASS occurred within the first two days after diagnosis of CVT (Figure 6).

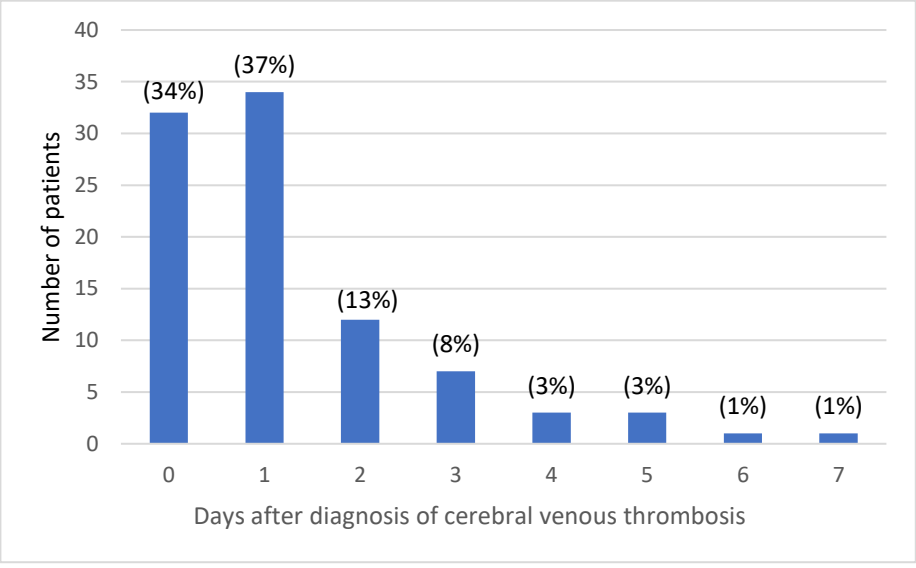

Figure 6. *Number of patients (n=93) experiencing a first postdiagnosis ASS, fractionated per day after diagnosis of CVT*

5.2.3 STATUS EPILEPTICUS

Eighty (6%) patients developed SE and independent predictors in multivariable analysis were ICH (aOR 4.8, 95% CI 2.5-9.4), focal neurologic deficits (aOR 4.7, 95% CI 2.2-10.1) and cerebral edema/infarction only (aOR 3.1, 95% CI 1.5-6.8).

5.3 LATE SEIZURES (III)

From the International CVT Consortium, 1,308 patients with diagnosis of CVT were identified. After exclusion of patients from the Royal Adelaide Hospital (n=99) due to missing follow-up, 29 patients who died within 7 days, 29 patients who had follow-up <8 days, 20 patients with epilepsy and 4 patients with missing information on late seizure occurrence, 1,127 patients were included in the study. During a median follow-up of 2.0 years (IQR 1.0-6.3), 123 patients (11%) experienced ≥1 late seizures. The incidence rate for first

late seizure was 30 per 1,000 person-years (95% CI 25-35). Median time to a first late seizure was 5 months (IQR 1-16). The cumulative late seizure-free survival rates are depicted in Figure 7.

Baseline predictors of late seizures included status epilepticus in the acute phase (HR 7.0, 95% CI 3.9-12.6), decompressive hemicraniectomy (HR 4.2, 95% CI 2.4-7.3), ASS without status epilepticus (HR 4.1, 95% CI 2.5-6.5), ICH (HR 1.9, 95% CI 1.1-3.1), and subdural hematoma (HR 2.3, 95% CI 1.1-4.9). Eighty-five patients (70% of patients with late seizures, 95% CI 61-77) experienced a recurrent seizure during follow-up despite the fact that 94% of the patients received anti-seizure medication after the first late seizure. Median time to seizure recurrence was 1 month (IQR 0-8).

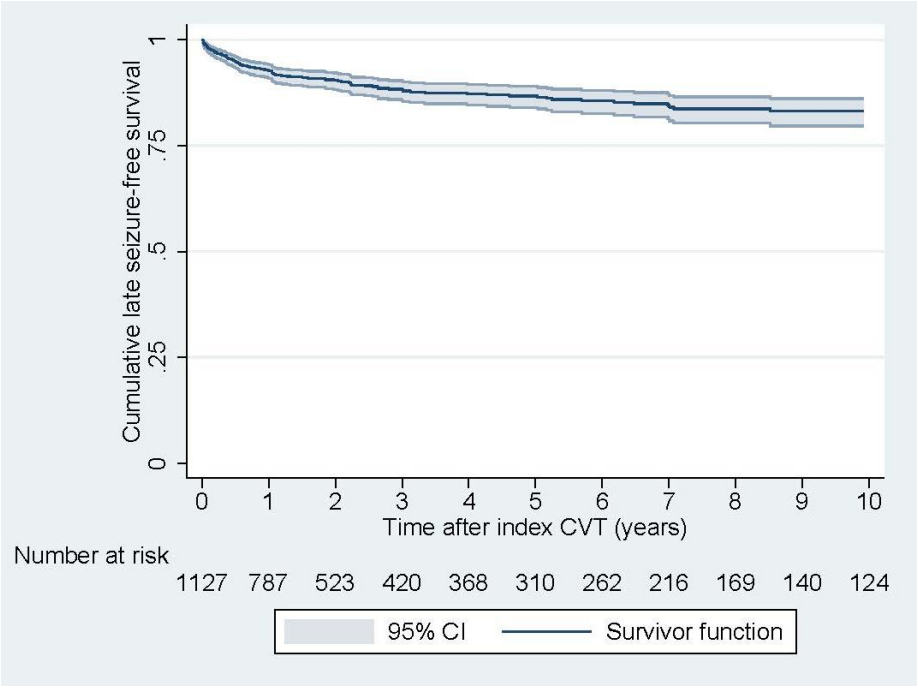

Figure 7. *Cumulative late seizure-free survival after cerebral venous thrombosis. Abbreviations: CVT – cerebral venous thrombosis; CI - confidence interval.*

5.4 DURAL ARTERIOVENOUS FISTULAS (IV)

In study IV, 1,218 patients (median age 41 years, IQR 29-51, 66% female) were included consecutively from 8 hospitals within the International CVT Consortium (Table 7). From the consecutive cohort, neurological imaging of 41 patients were centrally reviewed and presence of CVT and dAVF was

confirmed in 29 patients (2.4%). Median of follow-up was 8 months (IQR 6-12). In univariate analysis, patients with dAVF were older (median 53 years, IQR 44-61 versus 41 years, IQR 29-53, p<0.001), more often male (69% versus 33%, p<0.001), more often had chronic clinical CVT onset (>30 days, 39% versus 7%, p<0.001), sigmoid sinus thrombosis (86% vs. 51%, p<0.001) and less frequently parenchymal lesions (31% vs. 55%, p=0.013) at baseline imaging.

Risk for dAVF as measured by calculation of the positive predictive value was best predicted by chronic CVT onset in combination with either sigmoid sinus thrombosis 10/37 (27%), male sex 9/49 (18%), onset age >41 years 8/52 (15%) or no parenchymal lesion at baseline imaging 7/68 (10%).

Clinical outcome at last follow-up was measured by mRS and did not differ between patients with and without dAVF after adjustment of age and sex.

5.4.1 TIME CORRELATION AND DEGREE OF RELATIONSHIP

By addition of 5 additional patients from non-consecutive CVT cohorts, in total 34 patients were centrally confirmed with CVT and dAVF. As 2 patients had multiple episodes of CVT, each thrombus event was investigated separately in terms of time correlation and degree of relationship. Of the in total 36 CVT events, dAVF was diagnosed prior to CVT in 3/36 cases (8%, median 569 days, IQR 375-574), simultaneously to CVT in 20/36 cases (56%) and subsequently to CVT diagnosis in 13/36 cases (36%, median 115 days, IQR 38-337).

In 32/36 (89%) events with CVT and dAVF, the degree of relationship was categorized as probable (at least one of the thrombi was situated at the same sinus or in direct venous downstream to the fistulas) and 4/36 (11%) CVT events were categorized as possible (thrombus located directly downstream of the dAVF but not in the same sinuses).

5.4.2 DURAL ARTERIOVENOUS FISTULA CHARACTERISTICS

Radiological characteristics of dAVFs are summarized in Table 8. Among all patients with CVT and dAVF, 17/34 (50%) had fistulas at multiple sites, and 23/34 (68%) had at least one high-grade fistula (i.e. with retrograde cortical venous drainage). Fistulas were most commonly located adjacent to the sigmoid-transverse sinus junction.

Clinical symptoms, most frequently reported by the treating physicians as related to the dAVF, included tinnitus, bruit or pulsatile tinnitus in 15/31 (48%) and headache in 14/31 (45%).

Table 8. *Radiological characteristics of dAVFs among patients with CVT*

	CVT and dAVF (n=34)
Radiological characteristics, n/N (%)	
Multiple dAVFs	17/34 (50)
Recanalization of CVT at time of dAVF diagnosis†	
No recanalization	17/31 (55)
Partial recanalization	10/31 (32)
Complete recanalization	4/31 (13)
Location of dAVF, n/N (%)	
Superior sagittal sinus	3/34 (9)
Sigmoid sinus	25/34 (74)
Transverse sinus	24/34 (71)
Involves transverse and ipsilateral sigmoid sinus	19/34 (56)
Cognard's classification of dAVFs: n/N (%)	
I - normal antegrade dural sinus drainage	8/34 (24)
II – drainage into sinuses with insufficient antegrade venous drainage and reflux	
II a – reflux into sinus(es) only	9/34 (26)
II b – reflux into cortical vein(s) only	4/34 (12)
II c – reflux into sinus(es) and cortical veins	16/34 (47)
III - drainage directly into cortical vein without venous ectasia	9/34 (26)
IV - drainage directly into cortical vein, with venous ectasia	3/34 (9)
V – drainage into spinal perimedullary veins	0/34 (0)

Abbreviations: CVT - cerebral venous thrombosis; dAVF - dural arteriovenous fistula.

5.5 RISK SCORE TO PREDICT CLINICAL OUTCOME (V)

In study V, 1,540 patients were recruited from the International CVT Consortium. After exclusion of 85 patients with history of functional dependency (mRS >2), 1,455 patients were considered eligible for the study. For each model, patients with missing data on the outcome of interest were

excluded, leaving 1,454 patients in the mortality model development cohort, and 1,126 patients in the poor outcome model development cohort. For both cohorts, median age was 40 years (IQR 29-52) and proportion of women was 70%.

5.5.1 DEVELOPMENT OF DEPENDENCY OR MORTALITY MODEL

At 6 months (median follow-up time 183 days, IQR 181-184), 137/1,126 (12.2%) patients were dependent or dead (mRS >2). Retained predictors for poor outcome in the logistic regression model with backward stepwise selection were; age, coma, cancer, absence of any female sex-specific risk factor, admission glucose level (mmol/L), lower admission hemoglobin level (g/L), focal neurologic deficits and ICH at baseline. According to the Akaike's information criterion, transformation of age improved the model fit. The risk increase by age is calculated from the two age variables combined (study V, Table 3).

5.5.2 DEVELOPMENT OF A MODEL TO PREDICT MORTALITY

The cumulative mortality rate during the follow-up period (median 365 days, IQR 113-720) was 122/1,454 (8.4%). The cumulative number of deaths at 30-days and 1 year were 44 and 70, respectively. The proportional hazard assumption was met, which indicated that the model can be used both to predict mortality at 30 days and at 1 year.

Retained predictors for mortality in the cox regression analysis with backward stepwise selection were; age, coma, cancer, absence of female sex-specific risk factors, admission glucose level (mmol/L), lower admission hemoglobin level (g/L), neurologic focal deficits and infection in the CNS.

5.5.3 INTERNAL VALIDATION

Assessment of calibration plots indicated adequate goodness of fit between predicted and observed values for both models. C-statistic indicated good discrimination for the poor outcome model, mortality at 30 days and mortality at 1 year (study V, Figure 2).

5.5.4 CALCULATION OF INDIVIDUAL RISKS

To facilitate practical use, we gathered all models into the combined SI_2NCAL_2C score, comprising predictors for all of the investigated outcomes (absence of female Sex-specific risk factor, Intracerebral hemorrhage,

Infection in the CNS, Neurologic focal deficits, Coma, Age, lower Level of hemoglobin at admission, higher Level of blood glucose at admission and Cancer). The formulas, coefficients and baseline risks are depicted in study V, Table 3.

6 DISCUSSION

General discussion

The research field of CVT is underinvestigated, mainly due to the relatively low incidence of the disease and limited number of patients seen in individual centers. Most knowledge originates either from extrapolation of data from other subtypes of stroke or VTE, or from relatively small patient series. In this thesis, we present detailed data from a local single-center cohort, the Sahlgrenska CVT Registry, and from a large multicenter registry – the International CVT Consortium. The continuously growing collaboration has been established over the last years, to date amounting up to more than 1400 well-investigated CVT patients from 17 different research groups. Updated information about the consortium is available online at www.cerebralvenousthrombosis.com. The consortium enabled elaboration on several features of complications and outcomes that previously have not been investigated in large cohorts of CVT patients. Future similar collaborations are a necessity for the continuous work of deciphering the multifaceted aspects of CVT.

This thesis emphasized the fact that CVT is a highly heterogeneous disease. As exemplified in study I, subtle residual symptoms influencing RTW and life satisfaction, are frequent even among seemingly independent survivors in working age, and are not limited to patients with identifiable parenchymal injury. Frequent acute complications such as ASS occur in all age groups, and are not only associated to permanent parenchymal damage, but also to occasionally reversible conditions. Late seizures occur in every tenth patient, often secondary to parenchymal damage, and study III highlights both the high risk for late seizure recurrence and the importance of distinguishing late seizures from ASS.[257] Within the CVT patient group as a whole, dAVFs are a comparatively more frequent complication in relatively older male patients with an insidious onset. Searching for infrequent outcomes and complications in an already uncommon disease is challenging. Predictive models for calculation of individual risks for poor outcome and mortality may help identifying high-risk patients with CVT.

Study I

The main findings of this single-center observational study including 62 working-aged adults with CVT, were as following. Functional long-term outcome among survivors after CVT is relatively good. A majority of the patients (56%) achieved a favorable functional outcome (mRS 0-1), and another 30% were independent (mRS 2) at the end of follow-up. However,

despite the seemingly good outcome, more than one-quarter of the surviving patients (29%) were not able to RTW and all but 19% reported residual symptoms. Almost every third participant reported symptoms of depression. Residual symptoms were more frequent in the no-RTW group. Our results emphasize signals from previous studies, that the potentially more subtle neuropsychiatric and cognitive symptoms are both frequent and of importance after CVT.[8,217] Hence, screening for cognitive symptoms and depression at follow-up visits is to be encouraged to optimize individualized rehabilitation. The pathophysiological mechanism of cognitive impairment, in particular in patients without clinical or radiological evidence of parenchymal damage, is not understood. Post-thrombotic syndrome similar to after leg vein thrombosis,[258] inadequacies in venous or cerebrospinal fluid drainage[228] or impairment in the glymphatic system[259] are potential explanations. We used validated instruments to assess self-reported cognitive outcome, but further studies with neuropsychological examinations are needed to thoroughly map cognitive symptoms and profiles, characteristic for CVT.

Few studies have evaluated long-term vocational outcome after CVT, all measuring RTW cross-sectionally at follow-up.[209,217,232,260] Novel data from our study include the description of the temporal profile of RTW, with most patients RTW within the first year. The rate of no-RTW in study I resembles previously reported unemployment rates from 20 to 40% after CVT.[209,217,219] Female sex and parenchymal lesions during the acute hospital stay were associated with no-RTW, after adjustment for low educational level, multiple sinus involvement and onset age. Parenchymal damage has been linked to worse functional outcome after CVT,[4] whereas female sex conversely has been associated with more favorable outcomes.[42] Social gender aspects with unequal expectations on work return may in part explain these differences as RTW is not explicitly dependent on health. Socioeconomic factors such as retirement and social benefit systems and unemployment benefits may also explain differences in RTW between countries. Additionally, patients in the RTW group reported better life-satisfaction, health-related quality of life, participation and less often symptoms of depression, anxiety and fatigue, as compared to the no-RTW group. These associations underline RTW as an important measure of high functional outcome in young adults, otherwise potentially overlooked when measured with global scales such as the mRS.[119] Our study provides valuable data on the distribution of residual symptoms and importance of RTW after CVT. The findings are of particular importance since most working-aged patients affected by CVT have otherwise long and healthy life expectancies. For these young individuals, sequel and unemployment is of significance, not only for the individual affected but also for their families and socioeconomically for the society at large. However, the results should be

implemented with caution given the retrospective design, risk for recall bias, the modest sample size, and the substantial loss of patients to follow-up.

Study II

In study II, we investigated the incidence, characteristics, treatment and predictors of ASS in a large international cohort of 1,281 patients. We found that around one-third of patients with CVT experience ASS, an occurrence that essentially matches previous reports from CVT patient cohorts.[4,5,143] The frequency of ASS after CVT, is thereby much higher than after both ischemic arterial stroke (2-9%)[147,148] and in patients with spontaneous ICH (8-14%).[149-151,257] We confirmed that focal neurologic deficits, ICH, superior sagittal sinus thrombosis and cortical vein thrombosis are predictors of ASS.[142,143,226] In addition, we identified new independent predictors; cerebral edema/infarction without ICH, sulcal subarachnoid hemorrhage and female sex-specific risk factors. After arterial ischemic stroke, suggested mechanisms for ASS include parenchymal structural damage, accumulation of intracellular calcium, and biochemical neuron damage caused by glutamate release secondary to hypoxia and ischemia.[147] In patients with ICH or subarachnoid hemorrhage, hemoglobin degradation products or blood-borne factors suggestively trigger epileptogenesis.[261] Similar mechanisms of epileptogenesis are expectedly apparent in patients with hypoxia or hemorrhages caused by a CVT.

Not only lesion type, but also lesion location seems important for development of ASS after CVT. Previous studies report supratentorial lesions and lesions anterior to the central sulcus to be predictive of ASS.[226] Due to lack of detailed data, we were not able to comprehensively investigate the importance of lesion locations specifically. Nevertheless, our results indirectly implied that thrombosis or hemorrhage adjacent to the cerebral cortex (superior sagittal sinus thrombosis, cortical vein thrombosis, sulcal subarachnoid hemorrhages) are more susceptible to carry an increased risk of ASS.

To prevent seizure recurrence, current guidelines recommend treatment with AED for a limited time after ASS. In the absence of seizures at time of CVT diagnosis, the American Heart Association/American Stroke Association guidelines recommend against routine use of AEDs, while the European Stroke Organisation/European Academy of Neurology guidelines present no recommendation.[71,98] In our cohort, 93 patients had solely postdiagnosis ASS, which was best predicted by cortical vein thrombosis and focal neurologic deficit, with a positive predictive value of 22% and 17% respectively. We were unable to identify a subgroup of patients without prediagnosis ASS, that harbored ≥25% risk of postdiagnosis seizures. As such, our results provide no further support to prophylactic treatment since we could not identify a specific

subgroup with high enough risk of postdiagnosis seizures where the potential benefit from an AED would outweigh the risk of side effects. Additionally, there are no data supporting that prophylactic AEDs reduce the risk of seizures in CVT. Patients with high risk of seizures may also be more vulnerable to inadvertent treatment side effects. However, pertinent for discussion is that the calculated risk increase in our study per definition corresponds to seizures within the first 7 days after diagnosis. The risk increase was highest within the first 48h after diagnosis. Therefore, prevention strategies potentially demand shorter treatment durations and thereby lower risks of long-term inadvertent effects. Future studies may more accurately identify such a patient group, for example by calculation of individual risks based on risk factors found in our cohort. In patients with solely postdiagnosis ASS, most seizures (including SE) occurred within the first 48 hours after diagnosis. Therefore, for patients in whom AED treatment is considered, it needs to be administered as soon as possible.

Neither ASS nor SE in the acute phase was independently associated with an increased risk of poor clinical outcome in our study, after adjustment for potential confounders. Seizures may be considered as a clinical sign or symptom of an underlying disease. Our results indicated that, for patients with CVT, injuries adjacent to the cerebral cortex were associated to both ASS and SE. Thus, when adjusting for potential confounders for poor clinical outcome, which in part are similar to risk factors for ASS and SE, the remaining influence of the seizure itself on clinical outcome is limited. Nevertheless, untreated ASS, and SE in particular, are hazardous. In our study, prompt AED treatment may have averted induction or worsening of brain injury in most treated patients.

Study III

In study III, we investigated the incidence, treatment and recurrence rate of late seizures (>7 days after diagnosis of CVT) in an international cohort of 1,127 consecutive patients with CVT. The main findings included that around one in ten patients with CVT had ≥1 late seizures during a median follow-up period of 2 years. The prevalence of late seizures in our cohort was similar to that reported in the ISCVT.[4] Further, 70% (95% CI 61-77) who experienced a first late seizure, had a recurrent late seizure within the study period despite the fact that 94% received AED treatment after a first late seizure. The high recurrence risk supports a diagnosis of epilepsy at time of a first late seizure, in accordance with the current International League Against Epilepsy definition.[262] Guidelines recommend treatment with AED after a first late seizure after stroke.[263] Diagnosis of epilepsy corresponds to a chronically increased risk for future seizures, which in postapoplectic epilepsy is caused by a permanent

parenchymal injury. At diagnosis of epilepsy, treatment with AED is typically recommended (i.e. the potential benefits from AED normally outweigh the risk of treatment side effects). In our study, the high recurrence rate despite a large proportion being under AED therapy implies that AED treatment after CVT in general clinical practice either is not optimized or possesses extra challenges with treatment resistance or tolerance to AEDs. We could not compare the treatment effect of different AED types in our cohort.

Independent risk factors for late seizures were SE in the acute phase, ICH, subdural hematoma and decompressive hemicraniectomy. The risk factors for late seizures were similar to those of ASS as the extent of cortical damage and hemorrhage in particular, predicted both diseases. Interestingly, non-hemorrhagic lesions predicted ASS but not late seizures. This discrepancy exemplifies the importance of distinguishing the two conditions, and their respective underlying etiologies.[257] Four in five patients with ASS (78%) did not develop late seizures. Thereby most patients with ASS did not seem to harbor a chronic tendency of increased epileptogeneity. On the other hand, patients experiencing late seizures, often experience seizure recurrence which most likely arises from more permanent changes in neuro-excitability.[147] Decompressive surgery is probably partially a marker for CVT severity. Nevertheless, epileptogenesis caused by intraoperative advertent parenchymal damage cannot be disregarded.

By combining the novel predictors of late seizures suggested in our study, high risk patient groups for epilepsy may be identified to select patients for future clinical trials evaluating the efficacy and safety of long-term AED treatment in prevention of epileptogenesis after CVT.

Study IV

The main findings of study IV comprise the detailed description of dAVFs in a large international cohort of 1,218 CVT patients. The estimated prevalence in our cohort was approximately 2% within a median follow-up of 8 months, which was slightly higher than most previous reports among CVT patients.[4,244] In a substudy from the RE-SPECT CVT trial, 120 patients with CVT were investigated with contrast-enhanced MR angiography at 6 months, and not a single dAVF was detected.[244] However, calculation of a 95% CI of the prevalence of dAVF among these patients would be 0-2.5%.[264] Patients in the International CVT Consortium routinely are admitted to follow-up visits within the first 6 or 12 months after CVT. Typically, patients undergo follow-up imaging with either CT or MR venography, thus increasing the likelihood of incidental suspicion of dAVF. Nevertheless, the suggested prevalence might still be an underestimation given the observational rationale of the study.

Further, detection of dAVF was limited to the follow-up period of the study, and despite occasional high suspicion of dAVF, cases with any uncertainty were excluded from the dAVF group on central imaging review. Detection rates are also dependent on the imaging modality. In a recent exploratory study with 30 CVT patients who were investigated with four-dimensional MR venography, dAVF was detected in 4 patients (13%).[245] Dynamic non-invasive angiographic imaging techniques may play a future role in screening of selected patients with suspected dAVFs after CVT, but require evaluation regarding sensitivity for detection of dAVF in large cohorts prior to implementation in routine care. No guideline regarding dAVF screening after CVT exists. Study IV provides new evidence that despite the low prevalence of dAVF after CVT, detection rates were high in certain subgroups of patients (i.e. chronic CVT onset in combination with sigmoid sinus thrombosis 27%, male sex, 18%, onset age >41 years 15%). In these high-risk patients, clinicians should be alerted that new onset symptoms of tinnitus, pulsating tinnitus and bruit could signify an underlying dAVF.

In a majority of cases, dAVF was diagnosed either simultaneously or subsequently to the CVT. These findings support the concept of a CVT increasing the risk of a subsequent dAVF. Nevertheless, the relationship remains inscrutable and potentially bidirectional as in 8% of patients, dAVF was diagnosed prior to the CVT. Most fistulas were diagnosed in patients with more insidious CVT onset, but as one quarter of patients with dAVF had acute symptom onset, the development of a fistula within just a few days after CVT diagnosis cannot be ruled out. Our results indicate an association between dAVF and CVT. First, although no data were available from healthy unselected individuals, the prevalence of dAVF amounts from 0.15 to 0.29 per 100 000 persons per year in population-based patient cohorts with previous intracranial arteriovenous malformations.[265-267] Second, in 89% of our cases, the fistula was situated either at the same or adjacent sinus.

Neither dAVFs nor high-grade fistulas were associated with poorer clinical outcome as compared to CVT patients without dAVF. However, these results are probably heavily influenced by treatment and that dAVF patients had lower occurrence of parenchymal lesions at baseline.

Study V

In study V, we developed a risk score to predict dependency or mortality (mRS 3-6) at 6 months as well as mortality at 30-days and at 1 year. The main findings included the combined SI_2NCAL_2C score (absence of female **S**ex-specific risk factors, **I**CH, **I**nfection in the CNS, **N**eurologic focal deficits, **C**oma, **A**ge, lower **L**evel of hemoglobin at admission, higher **L**evel of glucose

at admission, **C**ancer). The included models showed promising results in internal validation in its ability to estimate individual risks for dependency and mortality after CVT.

Predictors for mortality at 30-days are likely to differ from predictors for mortality at 1 year after CVT. Mortality in the acute phase typically is caused by consequences and the severity of CVT, while the influence of underlying risk factors for CVT increase relatively over time.[27] However, for all included variables, we found no violation against the proportional hazards assumption, indicating that the influence of the increased risk of death was relatively stable during the study time. Therefore, we were able to utilize the model as a whole for prediction of mortality at 30-days and at 1 year.

The two most recently developed risk scores for estimating risks of dependency or death at 6 months (CVT risk score) and mortality at 30 days (CVT-GS) also include the predictors cancer and coma.[221,223] Novel predictors included in the SI_2NCAL_2C score were absence of female sex-specific risk factors,[42] and the laboratory parameters hemoglobin and glucose, in line with recently published data where anemia[208] and hyperglycemia[207] were predictive of both dependency and death. While our analyses indicated linear relationships, it is also possible that severe hypoglycemia or polycythemia (as indicative of myeloproliferative neoplasms) could be predictive of poor outcome. Such associations could be overlooked due to the limited sample size and relatively few cases of hypoglycemia and polycythemia in our cohort.

Although the retained predictors resemble previously suggested risk factors for dependency and mortality after CVT, the variables predicting each outcome should essentially be interpreted as markers, rather than definite risk factors to poor outcome and mortality. Our study was not designed to provide evidence for causal relationships between the predictors and poor outcome and mortality. Similarly, associations with the outcomes of interest cannot be ruled out for several variables that were not retained in the final models.

The methods were coherent to the international guidelines for development of prognostic models.[255,256] The risk of overestimation of model performances is apparent as the models were developed and then validated in the same cohort. The rationale behind this strategy was to maximize the statistical power and accuracy in the development stage. To compensate for potential overestimation, we applied shrinkage of the model coefficients, and evaluated the performance in bootstrapped samples of the cohort. However, before validation of the score in an external cohort, the generalizability is limited. Major strengths of our study include the relatively large patient cohort, the

clarity of the included variables that also are available in routine CVT care and therefore easy to collect as well as the ability to calculate individual risks for different outcomes using the same calculator.

To help identifying subgroups of CVT with poor outcome, the development and validation of a reliable risk score is of importance. Particularly to identify high-risk patients who could be eligible for novel treatments and thereby avert redundant detrimental effects in low risk patients. The SI_2NCAL_2C score shows promising results in internal validation, but requires validation and further comparison to previous scores in an external patient cohort, prior to implementation in clinical practice. However, in lack of a better score and since large international cohorts are sparse, SI_2NCAL_2C may already be a viable option for use in clinical studies.

General methodological considerations

The strengths of the thesis corresponds to the relatively large, multicenter cohort of consecutive patients diagnosed with CVT. The International CVT Consortium Registry included highly detailed data on patient characteristics and symptoms, risk factors, imaging, laboratory values and functional outcome. The relatively large patient cohort allowed for adjustment for potential confounders for most of the investigated outcomes. As patients were consecutively included, the risk of selection bias was relatively low. However, most included patients originate from northern or central Europe (Sweden, Finland, the Netherlands, Switzerland), whereas other regions are apparent, but underrepresented. The demographics, distribution of risk factors, treatments and outcomes may not be representative for low-income countries.

The main limitations include the partly retrospective design, and that the major aims were not predefined questions when cases were enrolled in the cohort. Further, inherent to the observational design is the risk for local variances and dissimilarities in patient selection, patient characteristics, treatment strategies, data recording, missing data, follow-up times and investigations.

The coverage of adult patients with CVT in the Sahlgrenska CVT Registry is considered adequate. The retrospectively included patients were identified by ICD-codes. Patients with mild symptoms, for example receiving symptomatic treatment for mild chronic headache may have remained undiagnosed. The Sahlgrenska University Hospital serves as a tertiary center, and it is possible that included patients carry a heavier burden and complexity of CVT and associated conditions. For all patients, the diagnosis of CVT was radiologically confirmed, thereby the risk of misclassification with inclusion of non-CVT patients into the registry is considered very low.

7 CONCLUSIONS TO GIVEN AIMS

Although long-term functional outcome after CVT is favorable with a high proportion of patients achieving functional independency, residual symptoms are frequent. About a quarter of survivors are not able to RTW, and those patients report worse across many life quality measures. Parenchymal lesion and female sex seem to be associated with no RTW.

Seizures complicate the acute phase in approximately one-third of all patients with CVT. Predictors include variables related to parenchymal damage adjacent to the cerebral cortex. Postdiagnosis seizures were common, but in absence of ASS at time of diagnosis, no risk factor sufficiently predicted postdiagnosis seizures to justify prophylactic AED treatment. Predictors for SE in the acute phase resembled predictors for ASS. We found no influence of ASS on functional outcome.

Late seizures occur in every tenth patient with CVT. Status epilepticus in the acute phase, ASS without SE, ICH, subdural hematoma and decompressive hemicraniectomy predict late seizures. The high risk of seizure recurrence justifies the diagnosis of epilepsy after a first late seizure.

The frequency of dAVF among CVT patients is low. However, at least 2 per 100 patients have dAVF. The vast majority of CVT-related dAVFs are detected simultaneously or subsequently to diagnosis of CVT. Chronic CVT onset, sigmoid sinus thrombosis, male sex and higher age predict dAVF among patients with CVT. The presence of dAVF was not associated with worse functional outcome.

The combined SI_2NCAL_2C score shows promising performance in prediction of poor outcome at 6 months, mortality at 30 days and at 1 year after CVT. The SI_2NCAL_2C score may be used to calculate individual risks of dependency or death from parameters easily available in routine CVT care, but an external validation of the score is warranted.

8 FUTURE PERSPECTIVES

The field of CVT remains an entity under investigation. Searching for infrequent outcomes and complications in an already uncommon and heterogenic disease is challenging. This thesis illustrates such endeavors and benefits of investigations in the setting of a large multinational cohort. Similar large international collaborations facilitate the opportunity to further investigate risk factors, clinical manifestation, treatment and outcomes in CVT.

Core areas of interest concern treatment and the prevention of permanent parenchymal damage. It is pathophysiologically intriguing to further investigate procedures of prompt recanalization that may preclude development of permanent damage in the acute phase. Although the TO-ACT[202] trial showed no benefit of endovascular treatment as compared to standard medical treatment in patients with severe CVT, there are potentially subgroups of patients that would benefit from such treatment. By distinguishing different subtypes of CVT, comparisons of distribution of risk factors for stroke development may help reveal some of the pathophysiological reasons behind why some patients with non-stroke CVT eventually develop stroke. Again, large cohorts are crucial to enable such comparisons. Continuous development and validation of risk scores or identification of prognostic biomarkers may improve the ability to identify patients at high risk of poor outcome.

Several studies evaluating treatment are currently under investigation in the setting of multicenter collaborations. In a prospective registry, data is collected on patients that have undergone decompressive surgery (DECOMPRESS-2). The EXCOA-CVT is comparing short-term (3-6 months) versus long-term (12 months) anticoagulation treatment for prevention of VTE after CVT. The efficacy and risk of anticoagulation with DOACs is compared to VKA in routine clinical care in the DOAC-CVT study. The safety of rivaroxaban is being investigated in the SECRET study.

Data are lacking on imaging properties, characteristics and risks for hemorrhagic lesions. It is possible that traditional risk factors for parenchymal arterial hemorrhages (hypertension, diabetes, obesity, hypercholesterolemia) also increase risk of developing hemorrhages in CVT. Risk factors for CVT that have not been thoroughly investigated in large cohorts and case-control settings include inflammatory diseases such as inflammatory bowel disease and thyrotoxicosis.

Only a few studies have investigated long-term outcome (>12 months) after CVT. Mapping of the neuropsychological profile of patients with cognitive impairment and detailed description of characteristics of common residual symptoms after CVT could be a first step in understanding pathological mechanisms. The possible importance of the glymphatic system has not been investigated in CVT patients or CVT animal models.

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10 APPENDIX

Supplemental table: Ethical review procedure for each participating center

Hospital and research site	National, regional or local ethical review board permission required	Date of decision of ethical permission	Decision or reference number	Informed written consent	Informed oral consent	Description of ethical review procedure
Royal Adelaide Hospital, Adelaide, Australia	Regional	July 27th, 2010	R20100732	No	No	Royal Adelaide Hospital Ethics committee provided review, agreeing individual consent was not required as medical record review only was required (as per section 2.3.10 of the NHMRC National Statement on Ethical Conduct in Human Research (2007))
Hospital Garcia de Orta. Almada, Portugal	Local	Retrospective data collection - 25/03/2021	38/2021	No	No	Permission granted by the Ethics committee of Hospital Garcia de Orta in accordance with Portuguese health regulations
Amsterdam UMC, Amsterdam, the Netherlands	No	-	-	Yes (opt-out consent procedure for patients included before GDPR enforcement)	Yes (opt-out consent procedure for patients included before GDPR enforcement)	Ethical Review Committee of the Amsterdam UMC decided study is not subject to the Dutch Medical Research Involving Human Subjects Act
Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Yes	Prospective dataset approved on 27/09/2016	COLECCION 03/2016	Yes	Yes	The prospective dataset was reviewed and approved by the Ethics Committee of Hospital de la Santa Creu i Sant Pau
Inselspital, Bern University Hospital, Bern, Switzerland	Yes	July 7th, 2017	Local ethics committee of the canton of Bern 231/2014	Yes	Yes	The study was approved by the local ethics committee of the canton of Bern/Switzerland.

Sahlgrenska University Hospital, Gothenburg, Sweden	Yes	January 8th, 2015 and February 27th, 2017.	898-15	Yes, with exception from deceased participants included retrospectively.	Yes, with exception from deceased participants included retrospectively.	Permission granted via the Swedish Ethical Review Authority in accordance with the Swedish Ethical Review Act (SFS 2003:460).
Sina Hospital, Hamadan, Iran	No	-	-	Yes. All patients received informed consent. In patients with decreased consciousness, consent was obtained from first degree relatives.	Yes. Oral and written consent.	The ethics committee of the university decided to collect information after receiving patient consent.
Helsinki University Hospital, Helsinki, Finland	Local	March 22nd, 2018	HUS/125/2018	No. Informed written consent is not needed for retrospective registry- based research according to Finnish law.	No. Informed written consent is not needed for retrospective registry-based research according to Finnish law.	The study was granted research permission by a local ethical committee (22.3.2018 decision reference number HUS/125/2018).
Istanbul University Hospital, Istanbul, Turkey	No	-	-	Yes, written consent signed by patients for all procedures during hospital stay	Yes, oral consent taken with the written consent.	A local ethics committee application was not made for retrospective collection of observational data (all of the patients were admitted before GDPR enforcement).
Hadassah-Hebrew University Medical Center, Jerusalem, Israel	Yes	Retrospective data	0711-20-HMO	No, classified as a non-interventional study, with data extracted from the dataset and medical files.	No, classified as a non-interventional study, with data extracted from the dataset and medical files.	The study was approved by the local ethics committee of HMO.
Hospital de Santa Maria/CHULN, Lisbon, Portugal	Yes	Prospective – 16th, July 2014 Retrospective - 4th, September 2018	294/18 and 331/14	Retrospective – No Prospective - Yes	No	Permission granted by the Ethical committee of Centro Hospitalar Lisboa Norte (CHLN) and Centro Académico de Medicina de Lisboa (CAML), Lisbon, Portugal

Salford Care Organisation, Greater Manchester, United Kingdom	Yes	Retrospective data collection – March 23rd, 2017 Approval to share data – July 11th, 2018	IRAS reference number for approval from the Health Research Authority: 217688	No	No	A two stage process. Approval for proportional review of retrospective date from the Health Research Authority 2017 (not requiring written or oral consent). Amendment granted in 2018 to share data.
National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico-City, Mexico	Yes	September 14th, 2017	CEI/141/17	No	Yes	Permission granted by the Ethics committee of the National Institute of Neurology in Accordance with Mexican health regulations.
Priority Research Centre for Brain and Mental Health Research, John Hunter Hospital, University of Newcastle, Newcastle, NSW	Yes, Regional	21/6/2021 (permission for prospective and retrospective data analysis)	2021/ETH01005	No	No	The Hunter New England Research Ethics Committee approved a waiver of consent under the section 2.3.10 of the National Statement of Ethic Conduct in Human research, 2007 protocol.
University Hospital Policlinico Paolo Giaccone, Palermo, Italy	No	-	-	Yes (Participant must affirm dissent if he/she wishes to be excluded from the study).	Yes (Participant must affirm dissent if he/she wishes to be excluded from the study).	The Ethical local Committee (Palermo) takes account of this study. According to Italian legislation, non-interventional studies do not require ethical approval.
Hospital Dr. R.A. Calderón Guardia, CCSS, San José, Costa Rica	Yes	Prospective dataset approved on February 7th 2014; subsequent approval on July 10th, 2017, and renewal on 2020 (pending)	12-2014	No, classified as a non-interventional study, with data extracted from the dataset and medical files.	No, classified as a non-interventional study, with data extracted from the dataset and medical files.	Institutional IRB from the Caja Costarricense del Seguro Social, CLOBI-HRACG, in accordance with national research policies and Helsinki Declaration.