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CEREBRAL OEDEMA AFTER REPERFUSION THERAPY IN PATIENTS WITH ISCHAEMIC STROKE: PREDICTORS, OUTCOMES AND TREATMENT

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Cerebral oedema after reperfusion therapy in patients with ischaemic stroke: predictors, outcomes and treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Carina, Anton and Edvin

"Forty-two!" yelled Loonquawl. "Is that all you've got to show for seven and a half million years' work?"
"I checked it very thoroughly," said the computer, "and that quite definitely is the answer. I think the problem, to be quite honest with you, is that you've never actually known what the question is."

Douglas Adams,
The Hitchhiker's Guide to the Galaxy, 1979

Any model that fits the data acceptably well will be only one of many possible data-generating mechanisms that we cannot rule out given our limited data and understanding.

Sander Greenland,
Am J Epidemiol. 2017 Sep 15;186(6):639-45

ABSTRACT

Introduction

Reperfusion therapy by intravenous thrombolysis (IVT) and/or endovascular thrombectomy (EVT) are established treatments in ischaemic stroke. Cerebral oedema (COED), caused by dysfunction the blood brain barrier (BBB), is common early after acute ischaemic stroke (AIS), can aggravate the symptoms and worsen the prognosis. Data on predictors and the effect of recanalization on early COED is limited. A large infarction with COED involving the middle cerebral artery (MCA) can be life-threatening. Decompressive hemicraniectomy (DHC) reduces mortality and may have a positive effect on functional outcome in younger patients. Animal data suggest that imatinib, a tyrosine kinase inhibitor, may restore BBB integrity, thereby reducing haemorrhagic transformation (HT) and COED. The aim of this doctoral thesis was to contribute to the understanding of clinical aspects of COED in patients with AIS of the anterior circulation.

Methods

Paper I, II and IV reported retrospective, observational studies using data from the Safe Implementations of Treatments in Stroke (SITS) International Stroke Registry, a prospective, multinational registry. These studies included patient data recorded using the SITS Registry data collection protocols for IVT and EVT, and to some extent general stroke, in time periods between 2002 and 2019. All patients had presumed ischaemic stroke. **Paper III** reported a phase 2, randomized, open-label, pilot study of imatinib in patients who received IVT after ischaemic stroke at 5 hospitals in Stockholm 2011-2014. **All papers** evaluated COED using the SITS COED scale (no, mild, moderate or severe COED). Outcomes at 3 months were functional outcome using the modified Rankin scale (mRS) score and death of any cause.

Results

In **paper I**, the most important predictors of COED after AIS were assessed. Among 42 187 patients (median age 70 years), 12.5% had mild COED on follow-up imaging (22-36 hours or any extra investigation) and 10.2% had moderate or severe COED. Baseline National Institutes of Health Stroke Scale (NIHSS) score, followed by hyperdense artery sign (HAS), were the strongest predictors for COED. Additionally, higher blood glucose, impaired level of consciousness and imaging signs of early infarction at baseline were predictors for COED. Increasing degree of COED at 22-36 hours was associated with increasing mortality and worse functional outcome at 3 months.

In **paper II**, the effect of recanalization on COED was assessed. Reperfusion therapy was administered to the 22 184 patients (median age 71 years and NIHSS score 16): only IVT (82.6%), IVT and EVT (13.8%) or only EVT (3.6%). Overall, recanalization was associated with a 10.6% ($p<0.001$) absolute risk reduction of moderate to severe COED at 22-36 hours, relative risk (RR) 0.55 (95% CI 0.52-0.58). Two models with high predictive ability provided the following estimates: adjusted OR 0.52 (95% CI, 0.46-0.59) and, with additional

adjustment for parenchymal haemorrhage (PH), OR 0.46 (95% CI, 0.41-0.52). Moreover, recanalization was associated with a 13.6% ($p<0.001$) absolute reduction of mortality at 3 months, RR 0.58 (95% CI 0.55-0.61), adjusted OR 0.48 (95% CI 0.45-0.53).

In **paper III**, 60 patients were randomized (15 patients in low-dose, 14 patients in medium and high-dose and 17 patients in control). Four serious adverse events (2 in control and 2 in low-dose group) resulted in the death of 3 patients. Of the dead patients 2 were allocated to low-dose group but of these, 1 did not receive imatinib and 1 patient had received only 2 doses. In the per protocol analysis, there were 21 haemorrhagic infarctions (6 in control), 3 PH (1 in control) and 4 remote parenchymal haemorrhages (0 in control). There were 33 cases of COED with moderate to severe COED being less frequent with higher doses, and no cases of moderate to severe COED in the high-dose group. After adjustment for EVT, the mean improvement in the NIHSS score compared to controls was 2 points ($p=0.259$) for the low-dose group, 3 points ($p=0.106$) for the medium-dose groups and 5 points ($p=0.012$) for the high-dose group. Functional independence (mRS 0-2) at 3 months was observed in 61% of the control group and 72% of all imatinib-treated patients; OR, adjusted for EVT, was 2.33 (95% CI 0.48-11.44).

Paper IV reported anterior circulation AIS patients that underwent DHC. In 684 patients from 35 countries median age was 56 years and NIHSS score at baseline 18 and 98.1% received reperfusion therapy. Moderate to severe COED was detected in in 76.0% and PH in 25.8% at 22-36 hours follow-up imaging scans. Surgery-related details, for example timing of DHC, were not registered. Mortality at 3 months was 32.7% (159/486). Among baseline variables, only increasing age was independently associated with death (OR 1.06, 95% CI 1.03-1.08). Good outcome (mRS 0-3) at 3 months was observed in 13.9% (66/475) and mRS 0-4 was observed in 39.4% (187/475). Outcomes differed between patients aged ≤60 years ≥61 years (25.2% versus 47.8% for mortality and 16.6% versus 8.4% for good outcome). Right-sided involvement of vascular territory was more common than left-sided.

Conclusions

The most important baseline predictors for early COED are NIHSS score, HAS, higher blood glucose, decreased level of consciousness, and signs of acute infarction at baseline. This finding can be used to improve selection and monitoring of patients for drug or surgical treatment.

In patients with AIS, recanalization was associated with a lower risk for early COED even after adjustment for higher rate of PH in recanalized patients.

Imatinib is safe and tolerable and may reduce neurological disability in patients treated with IVT after AIS. A confirmatory randomized trial is ongoing.

DHC in routine clinical practice may have worse outcomes than randomized trials, although there are caveats due to short follow-up of the patients in this study. Right-sided arterial

occlusions were more common than left-sided, which indicates a tendency to perform DHC in infarctions of the right hemisphere.

In general, this doctoral thesis added new knowledge about several aspects of COED in AIS and a potential new pharmacological therapy for acute ischaemic stroke. Further research is required to confirm these results which are based on 3 retrospective observational studies and one phase 2 pilot study. In fact, an efficacy trial of imatinib is now ongoing.

LIST OF SCIENTIFIC PAPERS

These papers will be referred to by their numbers.

I. **Thorén M**, Azevedo E, Dawson J, Egido JA, Falcou A, Ford GA, Holmin S, Mukulik R, Ollikainen J, Wahlgren N, Ahmed N. Predictors for Cerebral Edema in Acute Ischemic Stroke Treated With Intravenous Thrombolysis.
Stroke. 2017 Sep;48(9):2464-71.

Poster presentation of an earlier version of this data at the 18th European Stroke Conference in Stockholm, 2009. Abstract in Cerebrovascular Diseases 2009;27(suppl 6):175.

II. **Thorén M**, Dixit A, Escudero-Martinez I, Gdovinova Z, Klecka L, Rand VM, Toni D, Vilionskis A, Wahlgren N, Ahmed N. Effect of Recanalization on Cerebral Edema in Ischemic Stroke Treated With Thrombolysis and/or Endovascular Therapy.
Stroke. 2020 Jan;51(1):216-23.

Oral presentation at the 5th European Stroke Organisation Conference (ESOC 2019) in Milan, Italy. Abstract in European Stroke Journal 2019 May;4(1_suppl):83.

III. Wahlgren N, **Thorén M**, Höjeberg B, Käll T-B, Laska A-C, Sjöstrand C, Höijer J, Almqvist H, Holmin S, Lilja A, Fredriksson L, Lawrence D, Eriksson U, Ahmed N. Randomized assessment of imatinib in patients with acute ischemic stroke treated with intravenous thrombolysis.
J Intern Med. 2017 Mar;281(3):273-83.

IV. **Thorén M**, Escudero- Martinez I, Paiva Nunes A, Tassi R, Sadeghi-Hokmabadi E, Ringleb P, Currò Dossi R, Zini A, Wahlgren N, Ahmed N. Decompressive hemicraniectomy in anterior circulation stroke: Results from SITS Registry.
Submitted manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
AIS	Acute ischaemic stroke
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
AUC	Area under the curve
BBB	Blood-brain barrier
CBF	Cerebral blood flow
CI	Confidence interval
COED	Cerebral oedema
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
DHC	Decompressive hemicraniectomy
EVT	Endovascular thrombectomy
HAS	Hyperdense artery sign
HI	Haemorrhagic infarction
ICA	Internal carotid artery
ICH	Intracerebral haemorrhage
IVT	Intravenous thrombolysis
LAO	Large artery occlusion
LHI	Large hemispheric infarction
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
mTICI	modified Treatment in cerebral ischaemia

mRS	Modified Rankin scale
NIHSS	National Institutes of Health stroke scale
OCSP	Oxfordshire Community Stroke Project
OR	Odds ratio
PDGF	Platelet derived growth factor
PH	Parenchymal haemorrhage
PHr	Remote parenchymal haemorrhage
RCT	Randomized controlled trial
RR	Relative risk
SICH	Symptomatic intracerebral haemorrhage.
SITS-ISTR	Safe Implementation of Treatments in Stroke - International Stroke Treatment Registry (the SITS Registry)
TACS	Total anterior circulation syndrome
TOAST	Trial of ORG 10172 in acute stroke treatment
tPA	Tissue plasminogen activator

1 INTRODUCTION

1.1 OVERVIEW OF STROKE

The first definition of stroke may have originated from Hippocrates of Kos (460-370 BC), who used the Greek word for apoplexy, "being struck down", to describe a sudden loss of consciousness due to brain disease [1]. Using the explications of humoral theory, the cause of this brain disease was believed to be an accumulation of black bile in the arteries of the brain. The word "stroke" has been used in medicine since 1689 [2]. In modern medicine, stroke has until recently been a strictly clinical definition based on an acute loss of focal neurological function of vascular cause, in the brain, retina or spinal cord, and lasting more than 24 hours [3, 4].

The two main pathological subtypes of stroke are ischaemic stroke and haemorrhagic stroke, where the latter term usually includes both intracerebral haemorrhage and subarachnoid haemorrhage. The proportions of these vary with age, race and ethnic origin [4]. Of all patients with stroke (excluding subarachnoid haemorrhage) registered in the Swedish Stroke Registry 2018, 86% had ischaemic stroke (mean age 75 years) and 13% had intracerebral haemorrhage (mean age 74 years) [5].

Every year, 13.7 million people are affected by stroke, ischaemic or haemorrhagic. With 5.5 million people dying of stroke annually, this is the second most common cause of death in the world [6, 7]. It is the number one cause of neurological disability in adults, worldwide and in Sweden [8].

Although the traditional definition of stroke was prevailing throughout most of the time period that the studies reported in this doctoral thesis were carried out, there has been a change in recent years. During the last decade or so, the definition of stroke has been gradually updated because of advances in neuroimaging using magnetic resonance imaging (MRI) which allows the detection of ischaemic brain injury with high precision. In 2013 an updated terminology was published, from the American Heart Association, in which both clinical and tissue criteria were incorporated [2]. This tissue-based definition of stroke allows for episodes of neurological dysfunction to be included if neuroimaging or autopsy shows evidence of focal ischaemic or haemorrhagic injury that explains the symptoms, and other aetiologies are excluded. In the absence of pathological or imaging evidence of tissue damage, however, a necessary criterion for the diagnosis of stroke is that the symptoms last 24 hours or more. Similar definitions of stroke are being implemented in the World Health Organization's 11th version of International Classification of Diseases [9, 10]. For example, the description of "cerebral ischaemic stroke" (8B11) states that "evidence of acute infarction may come either from symptom duration lasting more than 24 hours, or neuroimaging or other technique in the clinically relevant area of the brain." This description excludes the retina.

1.2 ISCHAEMIC STROKE

The incidence of ischaemic stroke by country is shown in figure 1. Both globally and in Sweden, the incidence of ischemic stroke is decreasing, probably because of improved primary and secondary prevention [5-7]. The prevalence, however, is increasing slightly, probably because of reduced stroke mortality, better secondary prevention and better detection [6]. Annually, 2.7 million people die of ischaemic stroke [7].

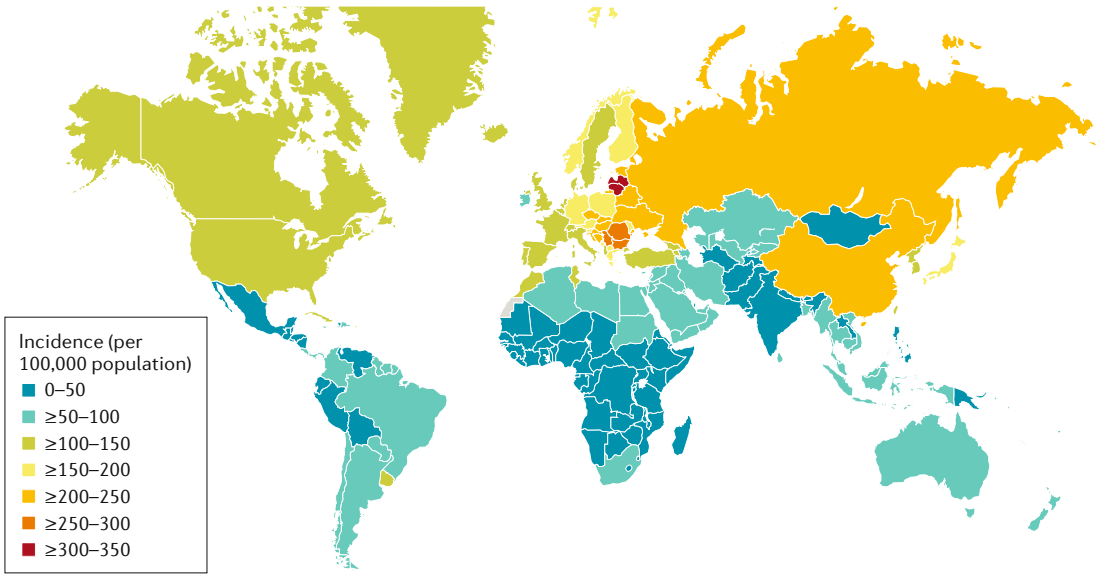

Figure 1. *The global distribution of ischaemic stroke incidence by country. Data from the Global Burden of Disease Study 2017. From Campbell et al. [6]. Reproduced with permission from Springer Nature Customer Service Centre GmbH. Copyright 2019 Springer Nature.*

Figure 2 illustrates the three basic mechanisms for acute ischaemic stroke (AIS): large-artery stenosis (atherothrombotic), cardioembolic and small vessel disease which can cause lacunar infarction but also can manifest as leukoaraiosis or haemorrhagic events.

These basic mechanisms are utilized for aetiological classification in the Trial of ORG 10172 in acute stroke treatment (TOAST) criteria which have been widely used [11, 12]. The TOAST classification scheme for ischaemic stroke contains the following subtypes: large-artery atherosclerosis, cardio-embolism, small vessel occlusion and other determined aetiologies. In addition, the TOAST criteria allow for a patient being classified as having undetermined cause of stroke. The ASCOD classification, proposed in 2009 with an update in 2013, suggested a characterization of every patient according to one of five of the following so-called phenotypes: A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause, D for dissection [13]. Regardless of classification system, the relative proportions of different categories vary depending on age, geographical location, race and ethnic origin. In North American and European studies, approximate proportions are: 25%

large artery stenosis (atherosclerosis), 20% cardiogenic embolism, 25% small vessel disease, 5% unusual causes (for example arterial dissection or arteritis) and 25% of unknown cause (so-called cryptogenic) [14]. Among the group of patients with unknown cause, a proportion of patients have embolic source as a likely mechanism on the basis of clinical evaluation, so-called embolic stroke of undetermined source [14]. The proportion of patients where the cause of stroke is unknown according to traditional criteria, but an embolic source is suspected, varies among studies but may average at approximately 17% of all ischaemic stroke patients [15].

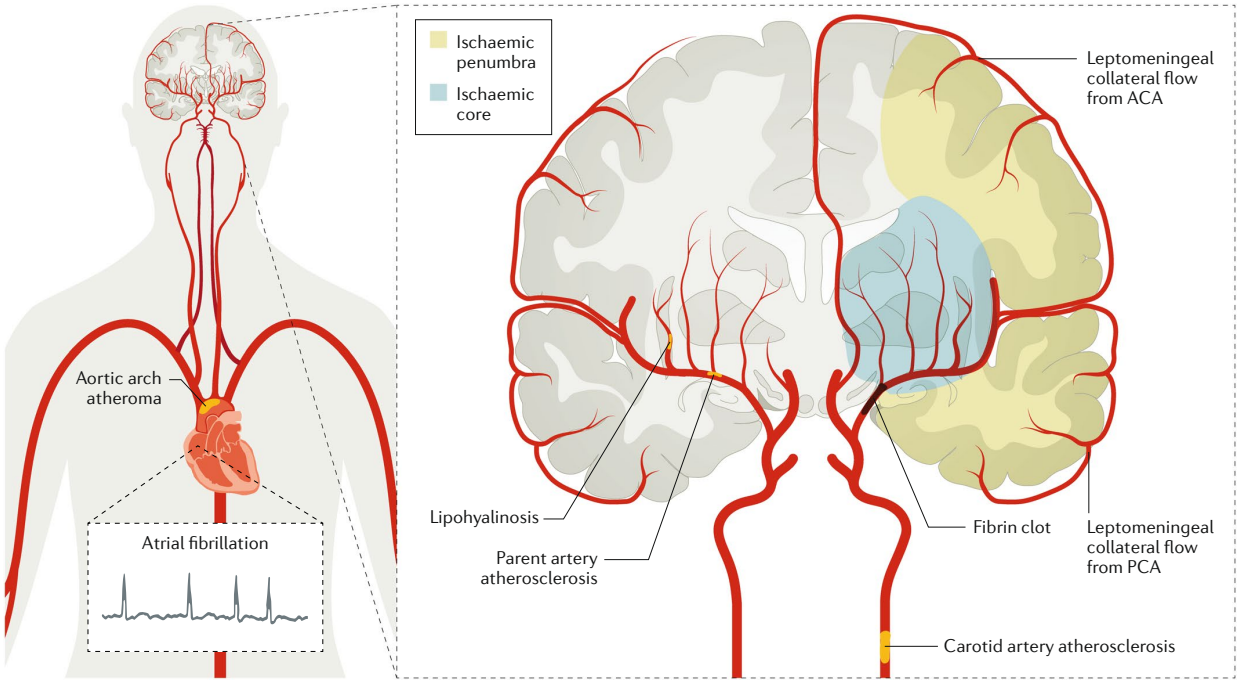

Figure 2. *Ischaemic stroke mechanisms and the concepts of ischaemic penumbra and core. Illustrated stroke mechanisms are cardioembolic in atrial fibrillation, large-artery stenosis with artery-to-artery embolism from an atherosclerotic carotid artery and lacunar infarction in small vessel disease due to lipohyalinosis or parent artery atherosclerosis. Here, a thrombus (clot) is occluding the middle cerebral artery (MCA). As a compensation, the territory of the MCA receives retrograde flow via collateral circulation through leptomeningeal anastomoses with the anterior cerebral artery (ACA) or posterior cerebral artery (PCA). The ischaemic penumbra is the region where blood flow is reduced below the threshold for electrical activity, causing a neurological deficit, but still sufficient for the tissue to survive. The ischaemic core consists of regions without sufficient collateral blood flow that become irreversibly injured (infarcted). The core expands over time at the expense of the penumbra. If reperfusion occurs quickly, the core remains small and the contribution of the penumbra to the neurological deficit may be reversed. From Campbell et al. [6]. Reproduced with permission from Springer Nature Customer Service Centre GmbH. Copyright 2019 Springer Nature.*

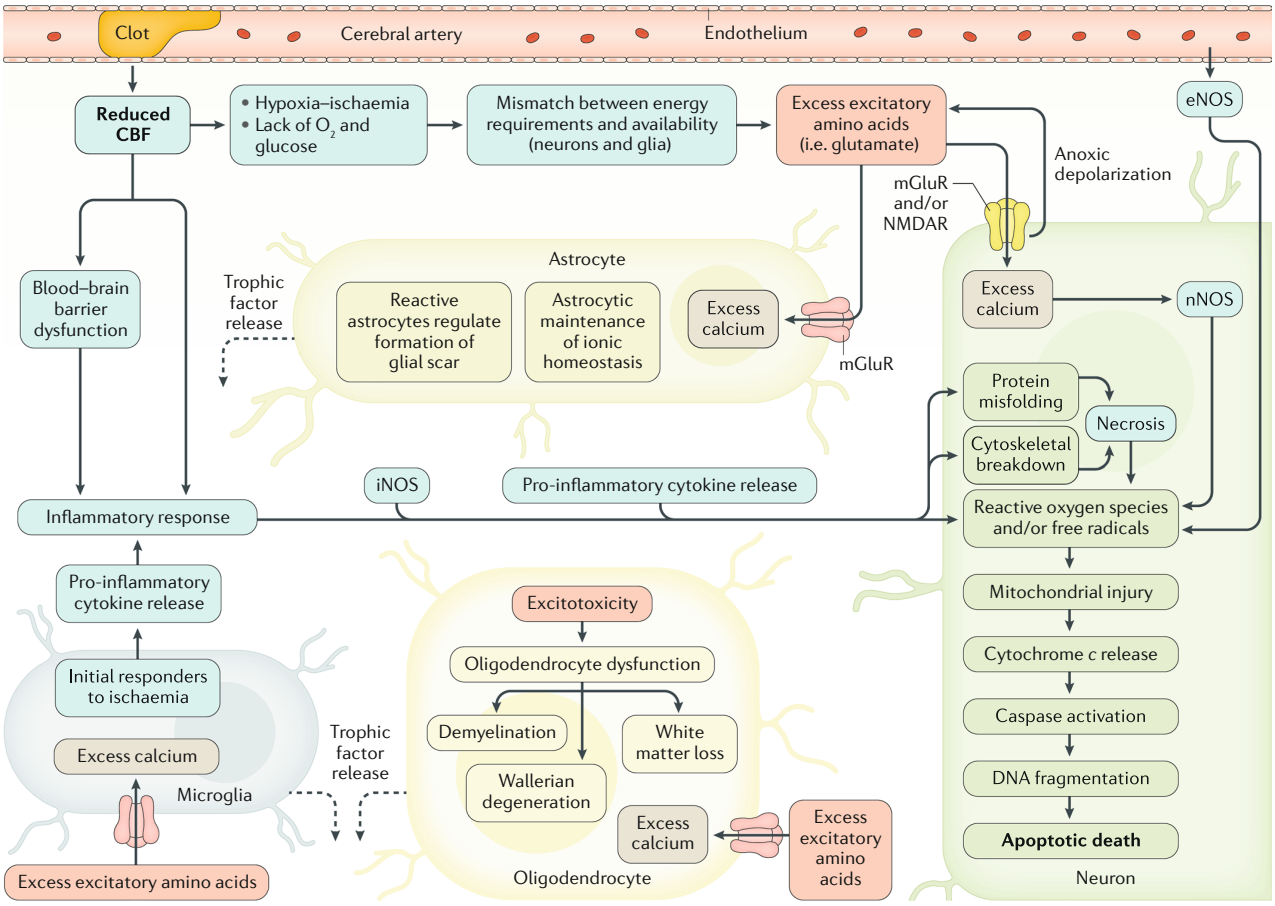

Figure 3. *Cellular mechanisms in cerebral ischaemia. This schematic model illustrates that the sudden occlusion of a cerebral artery initiates many processes that eventually lead to cell death. Reduced blood flow causes lack of oxygen and glucose (energy mismatch) in neurons, glia and endothelial cells while also causing blood-brain barrier (BBB) dysfunction. The electrical activity of neurons is impaired by of lack of ATP, necessary to uphold the transmembrane gradient. Anoxic depolarization of neurons leads to neurotransmitter release while active clearance of excitatory amino acids is decreased due to lack of energy. This results in increased extracellular levels of glutamate and, through ion channels, increased intracellular calcium in neurons and glia. The excess intracellular calcium triggers mechanisms that initiate pathways to cell death. In addition, BBB dysfunction and release of cytokines and other signalling molecules from astrocytes, microglia and oligodendrocytes leads to an inflammatory response that triggers pathways to cell death. From Campbell et al. [6]. Reproduced with permission from Springer Nature Customer Service Centre GmbH. Copyright 2019 Springer Nature.*

The occlusion of an artery in AIS causes an impaired perfusion in the affected brain region. When the blood flow is reduced below a certain threshold, the neurons in that region become electrically inactive, precipitating a clinical deficit. Please see figure 3 for a short description of cellular mechanisms in cerebral ischaemia.

Figure 4 shows some thresholds of the cerebral blood flow (CBF) required to maintain brain tissue structure and function. In animal studies, monkeys gradually developed a neurological deficit as CBF in a region of the brain was lowered, from mild paresis at 22 ml/100 g/min to complete paralysis at 8 ml/ 100 g/min [16]. The lower the remaining flow, the shorter is the time until neurons are irreversibly injured. A sharp decline of CBF, to less than 12 ml/100 g/min or thereabout, will cause cell death and infarction more quickly [16]. If blood flow is reduced to between 16 and 18 ml/100 g/min, the electrical activity of neurons ceases but the tissue may survive for longer [17, 18]. Meanwhile, if the duration of ischaemia is protracted, the tissue may become infarcted.

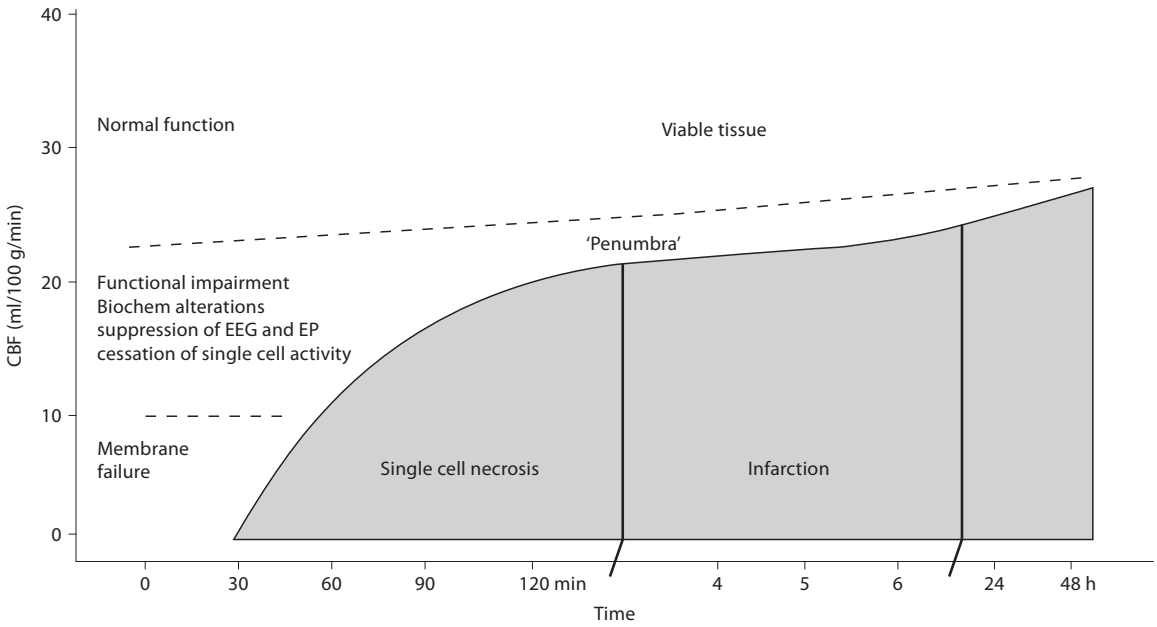

Figure 4. *In an ischaemic region of the brain, the survival of tissue is a function of the degree of impairment of cerebral blood flow (CBF), and the duration of ischaemia. This figure shows some thresholds of CBF required to preserve of brain tissue. Dashed lines indicate the reaction of neurons to decreased blood flow, as seen in animal experiments. The grey area represents structural damage (infarction). With time, the ability to sustain ischaemia decreases so that the infarction grows in size. From: Heiss [16], slightly modified. Reproduced with permission. Copyright 2011 Karger Publishers, Basel, Switzerland.*

The ischaemic penumbra is a region where cerebral perfusion is decreased because of an occluded artery, but not low enough to cause infarction at once. The infarction core, or umbra (Latin for shade), is brain tissue that has already infarcted. If the occlusion remains, the

volume of the core will increase while the penumbra decreases. The speed of this process varies between individuals depending on the capacity of the collateral circulation and other factors. Please see figure 2 for an of illustration of the concepts of ischaemic penumbra and ischaemic core, and their dependence on collateral flow in middle cerebral artery (MCA) occlusion.

The site and size of the occluded artery is a determinant of the extent of ischaemia and is important for the clinical outcome in AIS [17]. In general, larger diameter correlates with larger volume of ischaemia and to cortical symptoms such as aphasia and neglect, thereby with more severe neurological impairment unless revascularization is achieved, either spontaneously or through reperfusion therapy [19, 20]. In small vessel disease, the occluded arteries are typically less than 0.5 mm in diameter. In large artery occlusion (LAO), on the other hand, usually one of the following arteries of diameter 1 between 1 to 4 mm is occluded: intracranial carotid artery (ICA), terminal ICA, the proximal (M1 branch) of the MCA, the secondary (M2) or tertiary (M3) branches of the MCA, the anterior cerebral artery (ACA), the basilar artery, and the posterior cerebral artery (PCA) [17]. In two American studies, LAO was the cause of AIS in 46.0% and 24.1% of patients that presented at medical centres or were being transported by emergency medical services [19, 21].

Ischaemic core volume before reperfusion therapy is known to predict clinical outcome in patients with anterior circulation LAO. In a retrospective analysis of 185 patients presenting with anterior circulation LAO, it was observed that 25% of patients with anterior circulation LAO were so-called fast progressors, defined as an ischaemic core >70 ml within 6 hours of stroke onset while approximately 55% of patients were slow progressors with an ischaemic core ≤30 ml when presenting between 6 and 24 hours [22].

1.2.1 Acute treatment of ischaemic stroke

Stroke unit care and reperfusion therapy by intravenous thrombolysis (IVT) within 4.5 hours of symptom onset, and/or endovascular thrombectomy (EVT), within 24 of symptom onset in anterior circulation AIS are the only evidence-based treatments for AIS and are recommended by national and international practice guidelines [6, 17].

In a stroke unit, multidisciplinary treatment together with monitoring and nursing care measures that prevent complications, improves functional outcomes and reduces stroke mortality [23, 24].

In order to achieve revascularization, which is a restoration of blood that rescues the penumbra, the arterial artery must become open and capillary blood flow restored. Restoration of patency of an occluded artery is recanalization while restoration of downstream capillary flow is reperfusion [25]. In this way, recanalization is necessary, but not sufficient, for reperfusion to occur [26]. In routine practice, measurements of reperfusion are often based on angiographic appearance of the vascular territory, as in the modified Treatment in cerebral ischaemia scale (mTICI) [27]. Other methods, for example computed tomography (CT) with perfusion sequences, have been used [28].

IVT with recombinant tissue plasminogen activator (tPA), alteplase, administrated within 4.5 hours after first stroke symptoms, has been shown to improve the long-term functional outcome after stroke [29, 6]. Randomized trials evaluating tPA in ischaemic stroke were conducted in the 1990s and the drug was approved by the U.S. Food and Drug Administration in 1996. Tenecteplase, which is tPA that has been modified to have a longer half-life, is sometimes used off-license in AIS awaiting ongoing trials. Based on methods for selection of patients in the first trials that evaluated tPA, the diagnostic approach was for many years to use a strictly clinical definition of stroke and rely on neuroimaging to exclude either haemorrhage or a large infarction that would be a contraindication to treatment. With advanced neuroimaging the time window for treatment is now being extended beyond 4.5 hours in selected patients. The WAKE-UP trial and the EXTEND trial used imaging-based criteria for treatment with tPA [30, 31]. They found that tPA treatment can improve functional outcome in patients with uncertain time of onset, such as wake-up stroke, and in patients up to 9 hours after time of last known well.

The outcomes after treatment with both IVT and EVT are time dependent and the earlier the treatment is given the better the outcome. The more proximal the arterial occlusion is, the lower is the recanalization rate in IVT. For example, with transcranial doppler it was found that complete recanalization within 2 hours after tPA administration was achieved in 44% of patients with distal MCA occlusions, in 30 % of proximal MCA occlusions, in 27% of tandem ICA/MCA occlusions and in only 6% of terminal ICA occlusions [32]. EVT, on the other hand, has so far achieved better results in the larger, more proximal arteries.

Since 5 randomized clinical trials, published in 2015, showed that EVT in selected patients with AIS due to LAO, improves functional outcome, EVT has become established therapy. EVT has higher rates of recanalization than IVT. Proportions of successful recanalization varies between studies, but are usually between 60% and 90% [33, 17]. In 2018, the DAWN and DEFUSE trials demonstrated that EVT up to 24 hours has an effect in selected patients which has also been incorporated in latest guidelines [34, 35].

1.3 BLOOD-BRAIN BARRIER DISRUPTION IN ISCHAEMIC STROKE

The blood-brain-barrier (BBB) separates intravascular and interstitial spaces so that the central nervous system (CNS) is separate from the peripheral blood circulation [36-41]. The BBB functions as a selective barrier that restricts and controls exchanges between the blood and brain. It protects the CNS while it maintains homeostasis regarding for example water, ions, and hormones [41]. The BBB is created by endothelial cells, pericytes, and basement membranes. Some of the special features of brain endothelial cells that contribute to the tightness of BBB are the specialized tight junctions between cells, a lack of fenestrations and the continuous basement membranes. The cells that create the BBB are part of the neurovascular unit, please see figure 5. The neurovascular unit consists of several components that interact in order to maintain function and stability of the BBB [41]. Among these components are endothelial cells, pericytes, smooth muscle cells, neurones, and astrocytes [42, 39, 41].

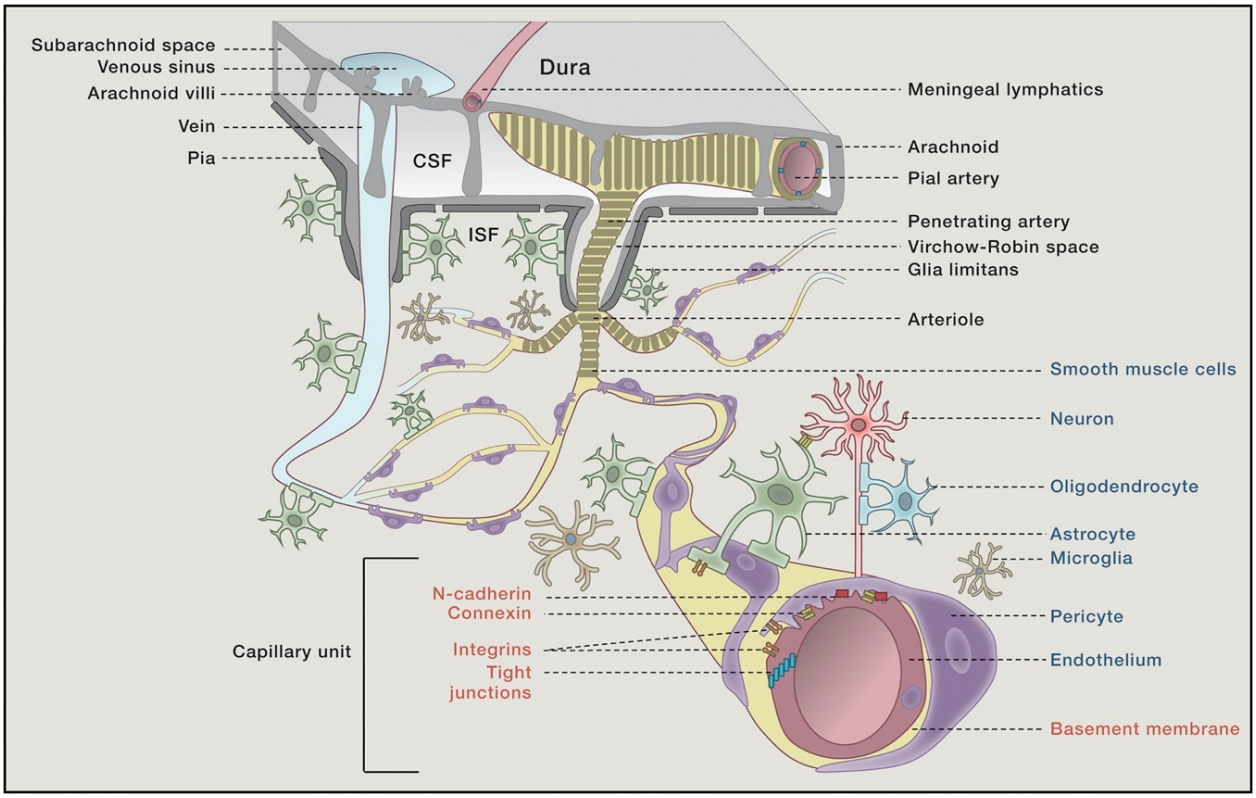

Figure 5. *Cerebral arterioles and capillaries, the neurovascular unit and the blood-brain barrier (BBB). Pial arteries in the subarachnoid space branch into penetrating arteries surrounded by the Virchow-Robin spaces that contain brain interstitial fluid. Arterioles, covered by smooth muscle cells, are branched off from penetrating arteries. Most distal in the arterial tree are the capillaries where endothelial cells, connected by tight junctions and surrounded by pericytes, create the BBB. From Zhao et al. [39]. Reproduced with permission. Copyright 2015 Elsevier Inc.*

The forces driving fluid across the BBB are described by Starling´s equation, in which the movement of fluid is proportional to the sum of two main pressure gradients: the net osmotic pressure and the net hydrostatic pressure [36, 40]. The net osmotic pressure is affected by the number of particles that are dissolved in the blood and in the interstitial fluid. The net hydrostatic pressure is affected by precapillary resistance, capillary resistance, postcapillary resistance, interstitial volume and tissue compliance. The ability of these pressure gradients to cause flux over the BBB depends on the conductivity of the BBB, which can be described as being is divided into two coefficients, one for each pressure gradient: osmotic conductivity and hydraulic (hydrostatic) conductivity.

1.3.1 Cerebral oedema and haemorrhagic transformation

On the molecular level, cerebral ischaemia triggers processes that result in cell swelling and impairment of the BBB. Please see figure 6. Cytotoxic oedema, is caused by an inflow of water into the cells without BBB disruption and occurs within minutes of ischaemic injury. It is caused by failure of cell membrane pumps, which results in intracellular accumulation of

sodium and calcium ions, and water, in brain cells, particularly astrocytes. This process can lead to cell oncotic death but is not in itself associated with increased brain volume or brain swelling [43, 36, 44-47, 40, 48].

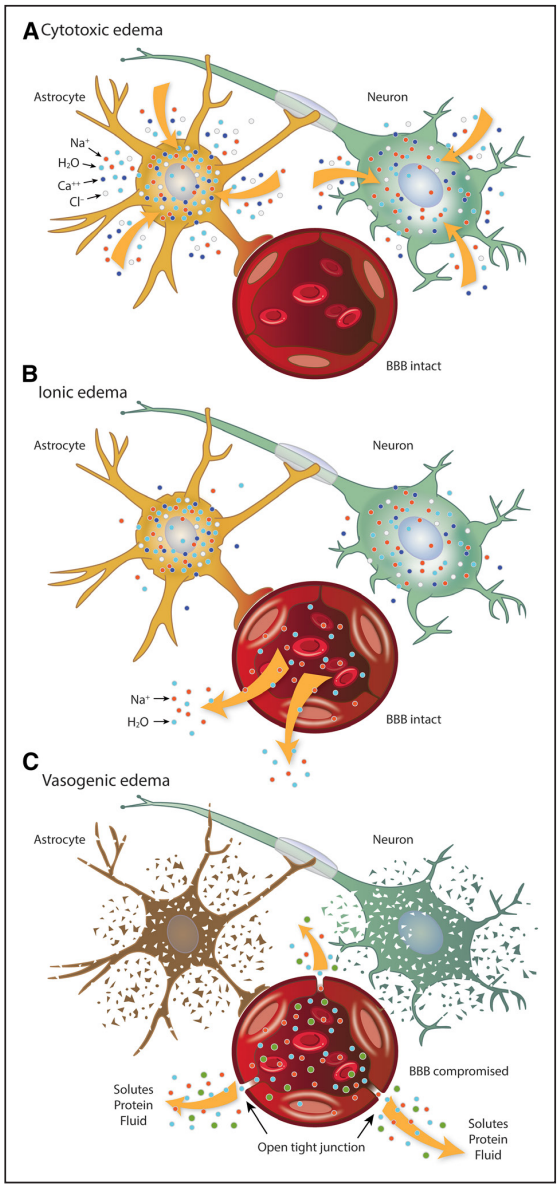

Figure 6. *Development of oedema in cerebral ischaemia. In the normal state, intravascular Na+ concentrations are the same as those in extracellular space in the parenchyma, while intracellular Na+ concentrations in neurons are much lower. A. Cytotoxic oedema. Early during ischaemia, ATP-dependent active transport channels decrease their activity so that ions, mostly Na+, enter the cells followed by water. This causes the cells to swell and may cause so-called oncotic cell death. At this stage, the endothelial cells are not affected. B. Ionic oedema. The osmotic gradient that was created during cytotoxic oedema pulls electrolytes, mostly Na+, from the endothelium. The net effect is that Na+ travels from the intravascular compartment to the extracellular space. The blood-brain barrier (BBB) is still intact. C. Vasogenic oedema. Swollen cells rupture and endothelial tight junctions are split so that proteins, electrolyes and fluid exit from the vessel and accumulate in the parenchyma. The BBB is broken. From Liebeskind et al. [48]. Reproduced with permission. Copyright 2019 Wolters Kluwer Health Inc.*

There is a stepwise progress towards increasingly more severe transvascular oedema where fluid and proteins move across the BBB. This causes brain swelling because of an increased amount of water in the interstitial space [36, 45, 47, 40, 49, 48]. In its earlier stages, the process is driven by sodium and water gradients, a process known as ionic oedema [36, 45]. Later, the BBB is broken down which causes vasogenic oedema which causes the leakage of proteins and electrolytes into the interstitial space [36, 44].

As illustrated in figure 7, a final result in the increasing permeability of the BBB due to ischaemic damage can be haemorrhagic transformation, in which a severe damage to capillaries and arterioles causes extravasation of all blood constituents, including red blood cells, into the parenchyma [36, 50, 46]. Thus haemorrhagic transformation is associated with a more severe disruption of the BBB [40].

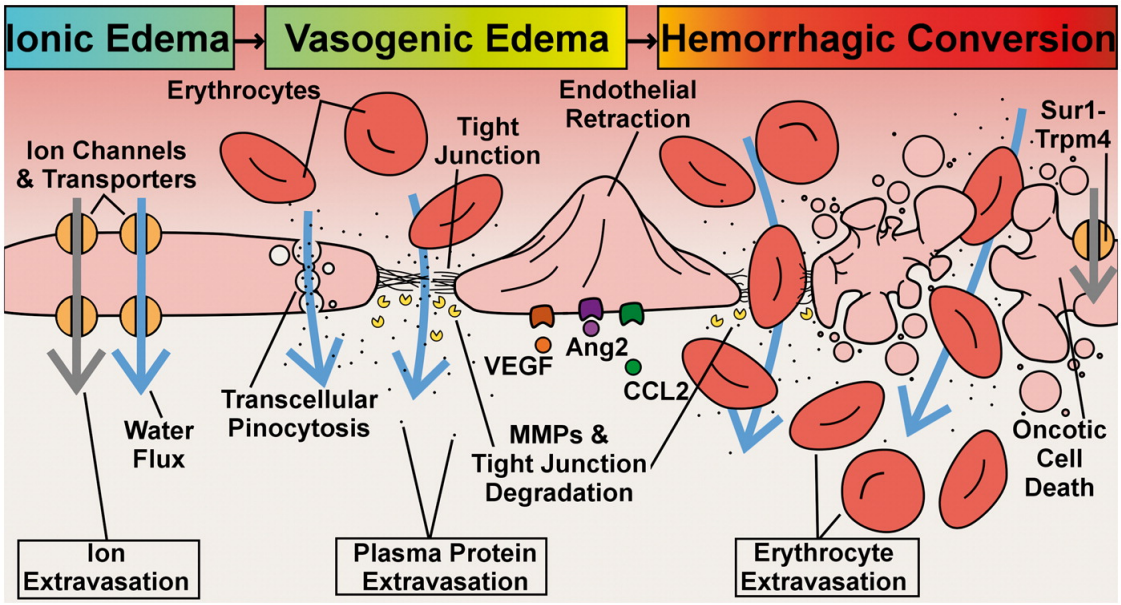

Figure 7. *Transvascular oedema of increasing severity, resulting in haemorrhage. This process is driven by progressive degradation of the endothelial cells until they meet oncotic cell death. Ionic oedema, created by cytotoxic oedema of the endothelial cells and transcapillary flux of Na+, is mediated by channels and transporters. In vasogenic oedema, plasma proteins but not erythrocytes exit from the vessel through transcellular channels, degradation of tight junctions and endothelial retraction. In haemorrhagic transformation, erythrocytes can exit the vessel through a ruptured endothelium and vessel wall structures. From Stokum et al. [40]. Reproduced with permission. Copyright 2016 SAGE Publications.*

1.3.2 tPA

IVT with recombinant tissue plasminogen activator (tPA), alteplase, triggers fibrinolysis by activating plasminogen to plasmin, an enzyme that splits fibrin, which results in in clot disruption [51]. The aim is to dissolve the blood clot and achieve recanalization as soon as possible. The drug is given as an infusion oven 1 hour.

IVT is associated with a risk of intracerebral haemorrhage (ICH). This is an important complication of ischaemic stroke, particularly in patients that receive IVT where the risk of haemorrhage is increased after administration of IVT. However, IVT in itself also increases the risk of haemorrhage. The frequency of symptomatic ICH (SICH) after IVT is between 2-7% depending on the definition of SICH [52]. From published studies in humans, there is no

definite clinical evidence that the risk of COED is increased by IVT. A meta-analysis, compiling six smaller studies, did not find IVT a statistically significant predictor for cerebral oedema [53].

1.3.3 Experimental treatment: imatinib

Animal studies have suggested that IVT using alteplase disrupts the BBB, thus increasing the risk for both COED and haemorrhage [54].

In the late 1990s, researchers at Karolinska institutet isolated new members of the platelet-derived growth factor (PDGF) family, a group of growth factors [55]. One of these factors, PDGF-CC, is produced in several tissues, including the brain. In order to be able to bind to its cellular receptor, the PDGF-receptor-alpha, PDGF-CC must first be activated by tPA [56]. Further experimental studies showed that activation of PDGF-CC with tPA is an important mechanism for regulation of the BBB integrity. In stroke, this mechanism is activated, potentially leading to oedema and haemorrhage in the brain. Imatinib, a tyrosine kinase inhibitor, blocks the signalling of PDGF-receptor-alpha on perivascular astrocytes. In experimental stroke models, imatinib was shown to significantly reduce BBB permeability, oedema and haemorrhagic complications in thrombolytic tPA treatment. PDGF-CC levels were increased in the plasma of ischaemic stroke patients after thrombolytic tPA treatment and higher levels of PDGF-CC were associated with an increased risk of haemorrhagic transformation. Based on these and other results, it was hypothesized that by blocking PDGF-CC mediated signalling in ischaemic stroke with imatinib, a substantial reduction of oedema and haemorrhage, and their resulting brain injury, could be achieved [41].

Imatinib is commercially available as a drug for long-term treatment of haematological cancer. It is available as tablets, 100 mg and 400 mg. The dose range for treatment within oncology is between 400 and 800 mg daily. Doses up to 1000 mg have been examined in pharmacokinetic studies. The average bioavailability is 98% with high variability between patients.

1.4 CEREBRAL OEDEMA IN ANTERIOR CIRCULATION ISCHEMIC STROKE

The presence of COED (as measured by MRI) independently predicts worse outcome in all including smaller ones [57]. However, it is in large infarctions that the effect is most pronounced.

1.4.1 Large hemispheric infarction and malignant MCA infarction

The term large hemispheric infarction (LHI) describes a large cerebral infarction that affects most of, or the whole, MCA territory, with or without additional vascular territories. It occurs in patients with anterior circulation LAO who have an occlusion is situated in the ICA or MCA, with or without involvement of ACA or PCA [58, 48]. Less than 10% of patients with AIS develop LHI [48]. Clinical symptoms and signs include contralateral hemiparesis, contralateral sensory loss, aphasia, inattention and neglect, hemianopia or gaze deviation. Patients usually have a NIHSS score of more than 16-20 in the dominant hemisphere and 15-

18 in the nondominant hemisphere [59, 60]. The risk of life-threatening COED in LHI is reported to be more than 50% [48]. However, various definitions of LHI have not been entirely consistent.

A recent guideline from the German Neurocritical Care Society provided a definition of LHI as "a large ischaemic stroke affecting the total or subtotal territory of the MCA, involving the basal ganglia at least partially, with or without involvement of adjacent ACA or PCA territories" [58]. This definition is similar to "malignant" MCA infarction, a term that was introduced by Hacke et al. in the 1990s [61, 62] and refers to a large and potentially life-threatening infarction in the MCA territory, with or without involvement of additional vascular territories. Although the term "malignant" MCA infarction is widely used, there is no generally accepted definition [44, 60, 63].

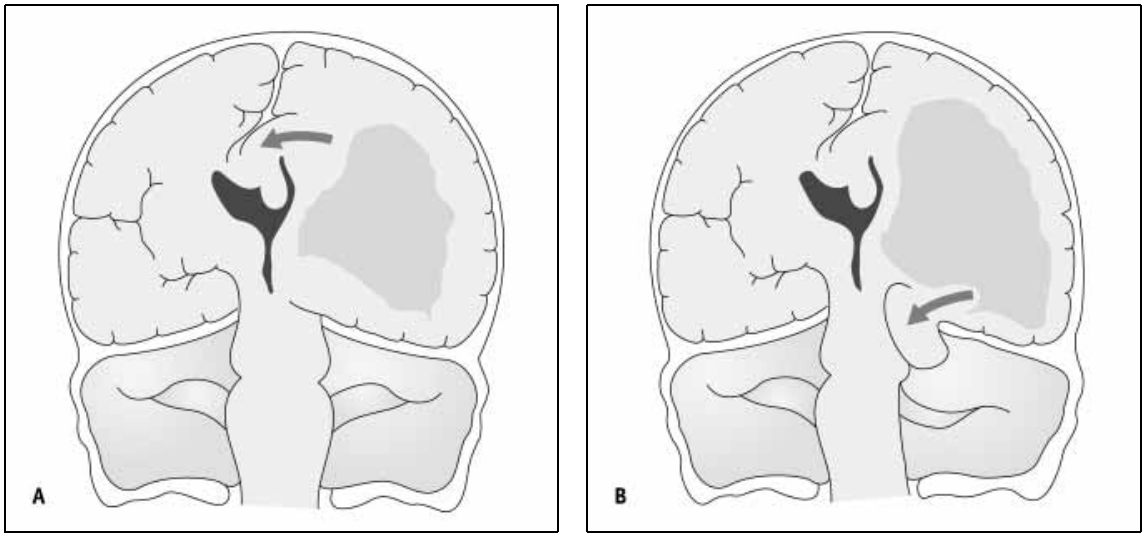

Figure 8. *Tissue shifts created by a space-occupying large hemispheric infarction (LHI), for example a large middle cerebral artery infarction. A. The brain swelling initially causes compression of a ventricle and initial midline shift in the direction of the most easily yielding structures. B. As these become compressed, their ability to yield further decreases, and increasing pressure results in transtentorial herniation. From Steiner et al. [66]. Reproduced with permission from Springer Nature Customer Service Centre GmbH. Copyright 2001 Springer Nature.*

Please see figure 8 for a schematic drawing of a space-occupying LHI leading to tissue shifts. When transvascular oedema develops, the swollen part of the brain pushes on its surroundings, causing tissue shifts. The swelling is initially counteracted by a decrease of intracranial blood volume and cerebrospinal fluid (CSF) but if these adaptive mechanisms are exhausted, the intracranial pressure starts to rise [64]. As a consequence of continued swelling, in the anterior circulation, ischaemia and tissue shifts are worsened leading to transtentorial and uncal herniation and subsequent brainstem damage [65, 44]. During this

process, the patient suffers from progressive symptoms of a space occupying intracranial process (headache, vomiting, reduced level of consciousness) and eventually death.

A time course of maximum cerebral oedema between the third and fifth day after after stroke onset has been confirmed in several studies [67]. In an autopsy study 1959, Shaw et al. [68] observed that the midline shift was largest in patients with MCA infarctions that died approximately 4 days after stroke onset, indicating that the swelling peaked at that time point. Please see figure 9. Previous to that, the clinical appearance of large oedema after cerebral infarction had been described in detail, for example by Scarcella et al. who also described the radiological appearance, with midline shift, using pneumoencephalograms [69]. Later work continued to combine data from necropsy and radiology to describe time course and pathological macroscopic appearance [70-73].The neurological deterioration related to cerebral oedema after a large MCA infarction usually starts within 48 hours after onset of stroke symptoms but with even earlier deterioration, within 24 hours, seen in up to one third of patients [74]. Hacke et al. [61], who measured midline shift on CT, observed that maximal midline shift occurred between day 2 and day 4 in patients that died but between day 3 and day in survivors.

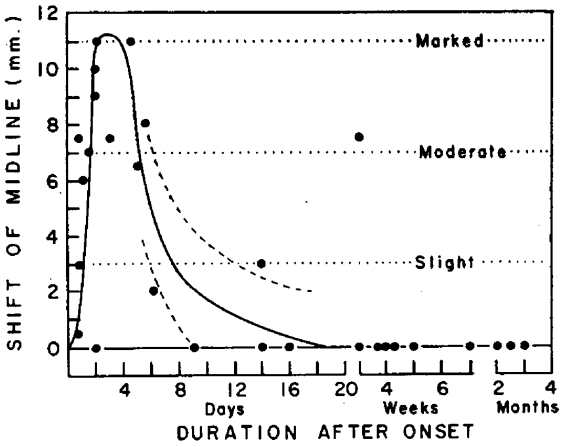

Figure 9. *Autopsy data on the time course of brain swelling in 28 fatal cases of middle cerebral artery (MCA) infarction. Midline shift at post-mortem examination is plotted against the time between stroke onset and death. The figure shows that for most cases that died during the first 20 days, the midline shift at death fits a curve with maximum at 4 days. From Shaw et al. 1959 [68]. Reproduced with permission. Copyright 1959 American Medical Association.*

If treated conservatively, approximately 70% of patients with a large infarction and expanding COED in the territory of the MCA territory will have died within 6 months [75, 76]. COED is a cause of death in 5% of all patients with hemispheric infarction [73, 77]. In a study performed among 1073 consecutive stroke patients before modern reperfusion therapies, Silver at al. [73] described that early mortality after stroke has a bimodal distribution: one peak occurs during the first week, and a second during the second and third

weeks. Of the 125 patients with ischaemic stroke that died, 46 patients died during the first week and majority or 78% (36/46) of those patients died of transtentorial herniation.

1.4.2 Detection of cerebral oedema in ischaemic stroke

The most common method used today is neuroimaging. Since attenuation of X-rays correlate with the tissue´s water content, CT detects ionic oedema with a high specificity but does not detect cytotoxic oedema [78, 79]. Cytotoxic oedema, in which cell swelling decreases diffusion of water molecules in the extracellular space, can be detected with diffusion-weighted MRI. Vasogenic oedema can be detected with CT or MRI [80, 79]. Details on radiological classification of COED can be found in Subjects and Methods. Transcranial sonography, which displays the brain parenchyma and ventricular system through the skull, may be used to detect midline shift secondary to mass effect. However, this is not routinely done [81]. Shift in CSF volume has been proposed as a measurement of oedema severity; a decrease in volume correlated with infarction volume and maximal midline shift [82].

1.4.3 Predictors for cerebral oedema

Hofmeijer et al. [53] summarized research on predictors until 2004. They found 23 cohort or case-control studies published between 1998 and 2004 that fulfilled criteria for inclusion in a meta-analysis of predictors for life-threatening COED. Of 27 factors evaluated for the meta-analysis, 12 proved to statistically significant associations. The strongest predictors for the development of life-threatening COED were mechanical ventilation, a large infarction size and large perfusion deficit. For infarction size, the increase in risk was dependent on different cut-offs used in the individual studies, from 50% to 100% of the MCA territory, larger infarction corresponding to higher risk. Other, weaker but still statistically significant, predictors for life-threatening COED were early mass effect, involvement of more than one vascular territory in addition to MCA, higher body temperature at admission and ICA occlusion. A paradoxical finding was that MCA occlusion was associated with a lower risk of life-threatening COED; however, this finding was explained as a result of over-representation of patients with occlusions of the distal parts of the MCA. In a narrative review, Hofmeijer et al. also summarized 11 studies from 1998 to 2004 for reported factors that could not be included in the meta-analysis. Higher stroke severity scores, measured by NIHSS and the Scandinavian Stroke Scale, were associated with a higher risk for life-threatening COED. Their main conclusion was that the risk for life-threatening COED seems to be strongly associated with increased infarction size. Evidence for this was an association with radiologically detected infarction size and with proxies of infarction size such as the need for mechanical ventilation, large perfusion deficit, involvement of more than one vascular territory and ICA occlusion. However, the authors noted limitations to their conclusions, the most important being a large variety of inclusion criteria and methods among the included studies. Therefore, the predictive values for life-threatening COED were generally moderate and depended on the incidence of oedema which varied between included studies. Furthermore, only studies of severe MCA infarction were included.

A post-mortem study provided more evidence that female sex and younger age, together with abnormalities of the circle of Willis, are predictors for a malignant course in COED [83]. In a Finnish cohort of 943 patients treated with IVT, higher baseline NIHSS score, presence of hyperdense artery sign (HAS) or signs of early infarction on CT, and longer onset-to-treatment time for IVT time were all associated with development of COED [84]

In clinical practice, to monitor patients at risk for life-threatening cerebral oedema, repeated neuroimaging is done to follow the clinical course [59]. Attempts have been made to quantify the value of radiology for prediction of a malignant outcome using CT, CT angiography, CT perfusion or MRI. One strategy has been to use size as a predictor. Using MRI, a DWI volume of more than 82 cm^3 within 6 hours after onset, or 145 cm^3 on within 14 hours, predicts a malignant course [85-87]. MRI has the potential to provide information for prediction of malignant MCA infarction also in older patients [88]. Measurements of BBB permeability have been used for prediction of a malignant course, using CT, MRI and SPECT, although with moderate success [89, 90]. Hyperdense MCA has been shown to predict a malignant MCA infarction [91-93]. The inter-caudate distance on MRI, an indicator of brain atrophy, may be used by itself or in combination with DWI volume to predict a malignant outcome [94, 95]. In one study, the ratio of ischaemic lesion volume to CSF volume seemed to predict the development of malignant MCA infarction [96]. Multimodal monitoring including physiological methods, laboratory tests, cerebral microdialysis methods and EEG have been used in attempts to predict malignant MCA infarction [97-99]. In one study, a marker of BBB disruption (plasma c-Fn) was associated with malignant MCA infarction and in other studies S100 levels have been associated with larger volume of infarction, or space-occupying MCA infarction [100-102]. A method of correlation between systolic blood pressure and intervals between heartbeats was used to measure baroreflex sensitivity, which was decreased in patients with large stroke who are at risk for a malignant outcome [103]. EEG and brain stem auditory evoked potentials were evaluated in a small study and found to be somewhat predictive of malignant MCA infarction [104].

Several studies have presented multivariate models with adjustment for background factors. Among patients with large MCA infarctions, an increased risk of fatal cerebral oedema was associated with history of hypertension or heart failure, increased baseline white blood cell count, major early CT hypodensity involving 50% of the MCA territory, and involvement of additional vascular territories [105]. Among patients with MCA infarctions with baseline NIHSS 20 (left-sided) or 15 (right-sided) within 6 hours of symptom onset, nausea/vomiting or 50% MCA territory hypodensity are risk indicators for developing fatal brain swelling [106]. A clinical score, the DASH score, was developed to assess risk for development of malignant MCA infarction in patients with large vessel occlusion [107]. The DASH score consists of the following parameters: 1 point for large infarction, defined as Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ≤3 on diffusion-weighted MRI, 1 point for infarction in the territory of the anterior cerebral artery, 1 point for occluded MCA and 1 point for hyperglycaemia. More than 90% pf patients with a DASH score of ≥3 developed a malignant MCA infarction. In another study, a combination of MRI with six

hours after symptom onset and NIHSS after 24 hours was used to predict malignant MCA infarction [108].

1.5 TREATMENT OF CEREBRAL OEDEMA IN ISCHAEMIC STROKE

1.5.1 Medical management

The usefulness of medical management for COED is not established [109, 110]. There is no evidence from observational studies or randomized trials that drugs that lower the intracranial pressure with osmotic therapy also improve outcome in patients with COED [59, 44, 109, 46]. As osmotic therapy with mannitol or saline quickly lowers the intracranial pressure, this treatment may be used in an acute setting, in patients that deteriorate [111, 46]. Osmotic therapy does not have sufficient long-term effect in space-occupying infarctions. Similarly, corticosteroids or hypothermia have no proven effect [111].

1.5.2 Decompressive surgery in anterior circulation stroke

Decompressive hemicraniectomy (DHC) with duraplasty is a surgical procedure where a bone flap with a diameter of usually more than 12 cm is removed allowing the brain to swell outwards [59, 112-114].

Randomized trials have shown that early DHC reduces mortality and has a positive effect on functional outcome in patients with malignant MCA infarction [115, 116, 86, 117-122]. Three RCTs published in 2007-2008 showed that early (within 48 hours) surgical treatment significantly reduces mortality without increasing severe disability in patients 60 years or below [115, 116, 86, 117, 123]. When pooled together, data from 93 patients showed that numbers needed to treat (NNT) were 2 for survival with a mRS score ≤4, 4 for survival with a mRS score ≤3, and 2 for survival irrespective of outcome, at one-year follow-up [116]. There was also a positive effect on functional outcome in this age group. Criteria for early DHC are radiological evidence of a large MCA (and any additional vascular territory), NIHSS ≥20 (dominant hemisphere) or ≥15 (non-dominant hemisphere) and impairment of consciousness. Based on one of the randomized trials, involvement of the basal ganglia is regarded as a negative prognostic sign for severe oedema which strengthens the indication for surgery [124, 115, 125]. In a meta-analysis of randomized trials, functional outcome among 122 patients at 6 months were as follows, scored using the modified Rankin scale (mRS): 20% mRS 2-3 (no mRS 0 or 1), 36% mRS 4, 18% mRS 5 and 26% mRS 6 (dead) [76]. Data from a randomized clinical trial (DESTINY II) suggest that hemicraniectomy has a life-saving effect also in patients aged 61 years or more, based on approximately the same criteria as above, although the effect on functional outcome is less certain [121].

DHC is recommended in clinical guidelines. Most patients treated with DHC for space-occupying have a reasonable quality of life at long-term follow-up [126, 127]. Complications after DHC include: sinking skin flap syndrome, fluid collections, hydrocephalus, epidural or subdural hematomas, infections and skin or muscle necrosis [128-130, 125]

2 AIMS

2.1 GENERAL AIM

The aim of this doctoral thesis was to contribute to the understanding of clinical, radiological and treatment aspects of cerebral oedema (COED), in patients with ischaemic stroke.

2.2 SPECIFIC AIMS

Paper I

To establish the most important predictors for the occurrence of early (22-36 h) COED in ischaemic stroke patients receiving intravenous thrombolysis (IVT), using data from the SITS Registry. In particular, to determine baseline clinical and radiological parameters that predict development of early COED, as defined by neuroimaging. A secondary aim was to study the association of early COED with long-term functional outcome and death.

Paper II

Test the hypothesis that, in patients with anterior circulation stroke due to large artery occlusion (LAO), recanalization observed at 22-36 hours decreases the risk for moderate to severe COED observed at the same time point. A secondary aim was to investigate the effect of recanalization on short-term and long-term outcomes (death, functional outcome).

Paper III

Perform a phase 2, pilot, randomized trial of oral imatinib versus control in ischaemic stroke patients after IVT and report the results regarding safety and effect on outcomes.

Paper IV

To evaluate the clinical characteristics, including affected side, and outcomes of decompressive hemicraniectomy (DHC) in patients with anterior circulation stroke in the SITS Registry. In addition, to compare functional outcome and death in this population to published randomized controlled trials of surgical treatment for space-occupying large hemispheric infarction (LHI), both overall and in relation to age.

3 SUBJECTS AND METHODS

3.1 OVERVIEW OF PAPERS

Characteristic	Paper			
	I	II	III	IV
Organizer of data collection	SITS Registry	SITS Registry	iStroke Pilot Study	SITS Registry
Setting	Hospitals in 41 countries	Hospitals in 62 countries	5 hospitals Stockholm Region	Hospitals in 35 countries
Study period	2002-2011	2002-2017	2011-2014	2008-2019
Design	Observational	Observational	Randomized open-label	Observational
Study population	Stroke patients that received IVT	Stroke patients with imaging signs of arterial occlusion, had IVT and/or EVT	Stroke patients that received IVT	Stroke patients that underwent DHC
Number of patients	42 187	22 184	60	684
Main predictor(s)	Baseline variables	Recanalization at 22-36 hours	Oral imatinib for 6 days	Baseline variables including age
Main outcome(s)	COED, ICH, mRS, death	COED, ICH, mRS, death	*Primary*: Adverse events, death *Secondary*: ICH, COED, NIHSS, mRS, death	mRS, death

Table 1. *Overview of papers.*
Abbreviations: cerebral oedema (COED), decompressive hemicraniectomy (DHC), endovascular thrombectomy (EVT), intracerebral haemorrhage (ICH), intravenous thrombolysis (IVT), modified Rankin scale (mRS), National Institutes of Health stroke scale (NIHSS)

3.2 PAPER I, II AND IV

Flow diagrams showing the selection of study populations for paper I, II and IV can be found in figures 10, 11 and 12.

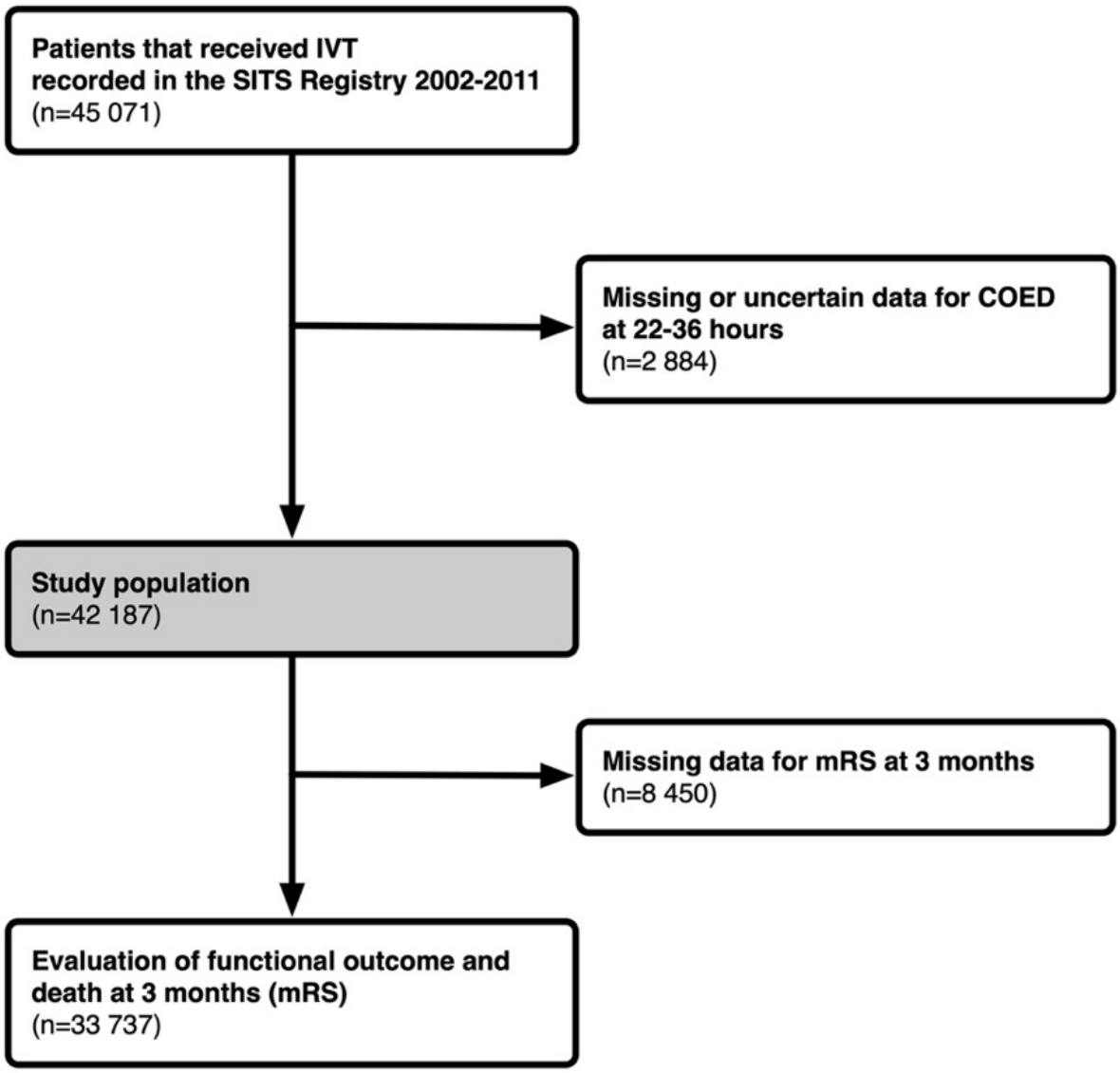

Figure 10. *Flow diagram for paper I.*
Abbreviations: Cerebral oedema (COED), endovascular thrombectomy (EVT), intravenous thrombolysis (IVT), modified Rankin Scale (mRS).

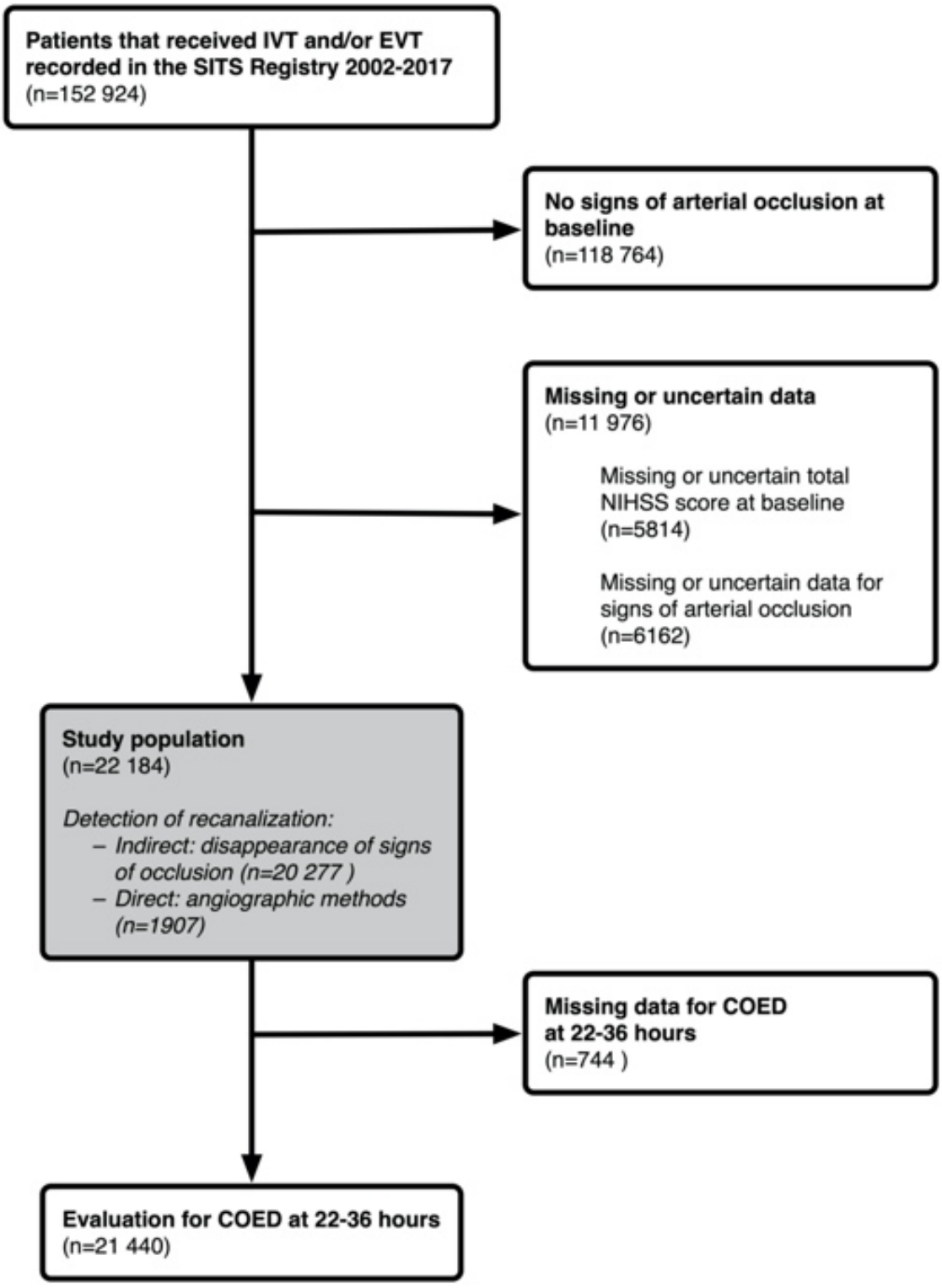

Figure 11. *Flow diagram for paper II. Abbreviations: Cerebral oedema (COED), endovascular thrombectomy (EVT), intravenous thrombolysis (IVT), modified Rankin Scale (mRS).*

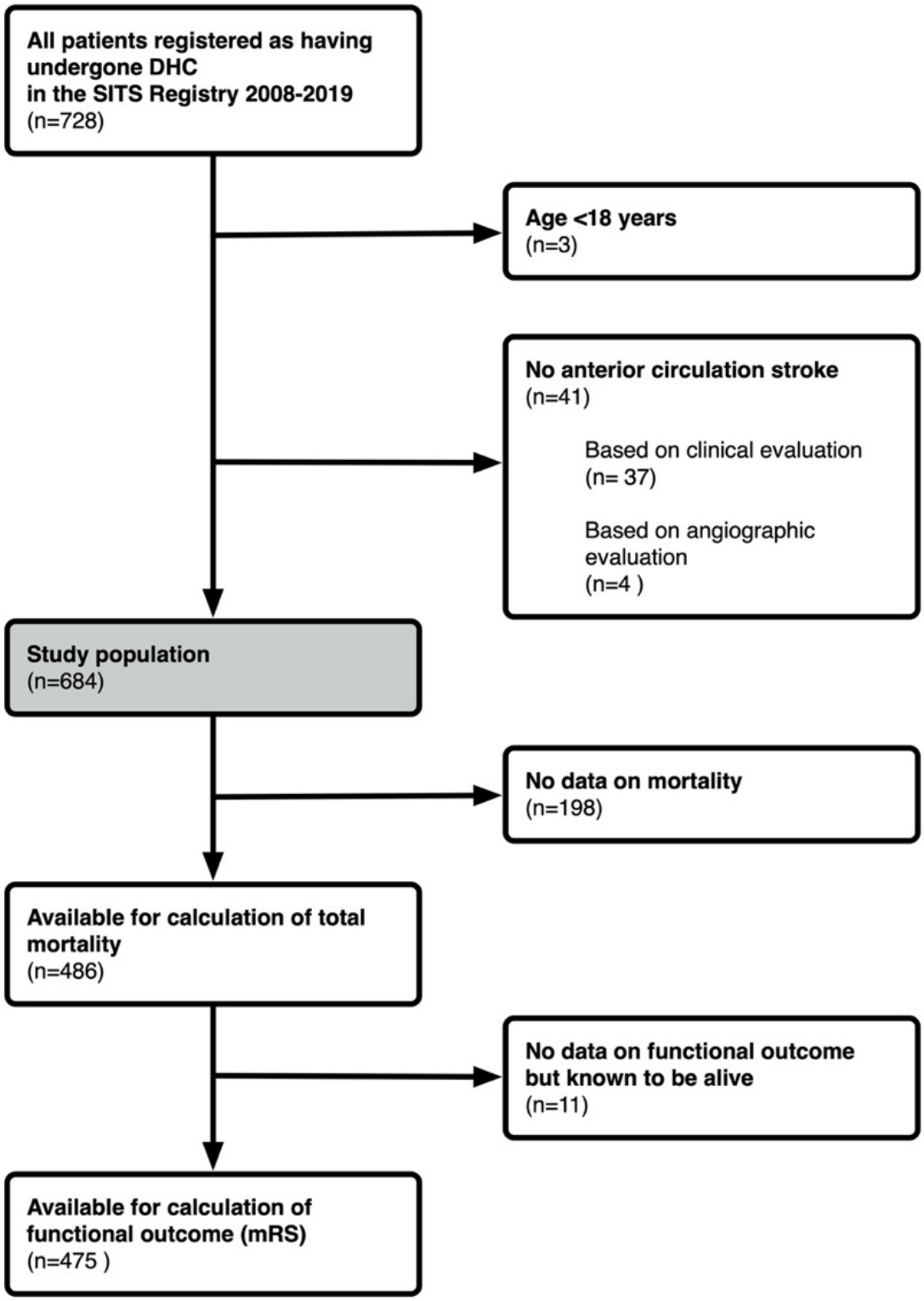

Figure 12. *Flow diagram for paper IV. Abbreviations: Decompressive hemicraniectomy (DHC), modified Rankin scale (mRS)*

3.2.1 The SITS Registry

Paper I, II and IV report observational studies in which patients were collected from the Safe Implementations of Treatments in Stroke-International Stroke Treatment Registry (SITS-ISTR), also called the SITS Registry. This is a prospective, internet-based, academic-driven, multinational stroke register. The SITS Registry is an academic-driven, non-profit, international collaboration. The web site is www.sitsinternational.org.

The SITS Registry collaboration has 2 main levels of organization: individual centres, which usually are equivalent to hospitals, and countries. A centre can participate in the SITS Registry, under the responsibility of the local coordinator, after authorization by the local head of the department. The local coordinator for the SITS Registry is normally the person in charge of acute stroke care at the centre and is responsible for, and verifies, that data is completely and accurately collected according to protocol. The local coordinator is usually a stroke physician. In addition, there is usually at any given centre a local team of investigators that can enter data into the registry. Furthermore, every country has a national coordinator, usually a senior stroke researcher, appointed by SITS International. The national coordinator has access to all data from that country and has a supporting role for the centres of that country. SITS International has a Scientific Committee, consisting international stroke researchers, that oversees all scientific activities and projects based on the SITS Registry database. The SITS Scientific Committee approved the research plans for paper I, II and-III, which are all based on SITS Registry data, before data analysis was started.

The SITS Registry currently has several different data entry protocols with different purposes. There is, however, a core list of data collection that is identical between most of these protocols. Upon participation, a centre agrees to register data according to one or more of these protocols. The following protocols were used in varying degrees for paper I, II and IV: IVT Standard Protocol, IVT Minimal Protocol, Thrombectomy Protocol, All Patients Protocol Standard and All Patients Protocol Minimal. Two other protocols, SITS Quality Registry and SITS Intracerebral Haemorrhage Registry (SITS-ICH), were not used.

By formal agreement between SITS International and both national and local coordinators, a centre is required to accept consecutive registration of all patients according to data entry protocol. For example, if the centre registers only patients treated with intravenous thrombolysis and use the IVT Standard Protocol for data entry, then the centre has to register all patients with stroke symptoms receiving IVT irrespective of whether treatment was on- or off-label. If the centre registers all stroke patients in the registry, using All Patients Protocol, consecutive registration of all patients with stroke diagnosis is obligatory.

Data in the SITS Registry are entered on-line through the SITS website. Every investigator logs in through a 2-way authentication system, a personal access code which must be kept secret and used only by the owner and an e-mail or SMS verification code. All data entry from a centre can be made by each member of the local team, but once the data entry is confirmed (and cannot be changed), the person who made the confirmation will be identified

on the data entry form. The current SITS registry is developed, maintained and upgraded by Zitelab, Copenhagen, Denmark, in collaboration with SITS. For the purpose of scientific publication, a download is made in Excel/CSV format which then is transferred to statistical analysis software, for example Stata.

3.2.2 Subjects

All patients in paper I, II and IV had presumed ischaemic stroke, were admitted to a hospital and given whatever routine treatment that was best practice at that hospital. Patients may also have been referred to secondary or tertiary hospitals for surveillance or treatment.

3.2.3 Data collection

Data was collected and entered into the registry by local investigators at each hospital. The SITS Registry protocols recommend that data is to be registered from certain points in time during hospitalization and follow up. The following list includes data that was used for paper I, II and III, with time points counted from initiation of first treatment (IVT or EVT):

- At baseline: demographic data, pre-stroke mRS, medical history including comorbidities, risk factors and concomitant medication, date and time of stroke onset, date and time of admission, NIHSS score including sub-items, systolic and diastolic blood pressure, laboratory values (for example blood glucose, total level of cholesterol, APTT), imaging scans (CT and/or MRI) with date and time of examination.
- At 2 hours: NIHSS score including sub-items, systolic and diastolic blood pressure
- At 24 hours: NIHSS score including sub-items, systolic and diastolic blood pressure, imaging scans (CT and/or MRI) with date and time of examination (allowed time interval between 22 and 36 hours).
- During the hospital stay: details of concomitant medications, any additional imaging scans, treatments given (EVT, DHC, stroke unit care) and some details of treatments
- At 7 day or at discharge, whichever comes first: date and time of discharge, NIHSS score including sub-items, systolic and diastolic blood pressure, type of stroke, any atrial fibrillation, medications.
- At 3-months follow up, done at 90 days plus or minus 10 days: mRS score, any new events including recurrent stroke (haemorrhagic or ischaemic).
- Whenever appropriate: date and time of death

3.3 PAPER III

Please see flow diagram of the iStroke Pilot study in figure 13.

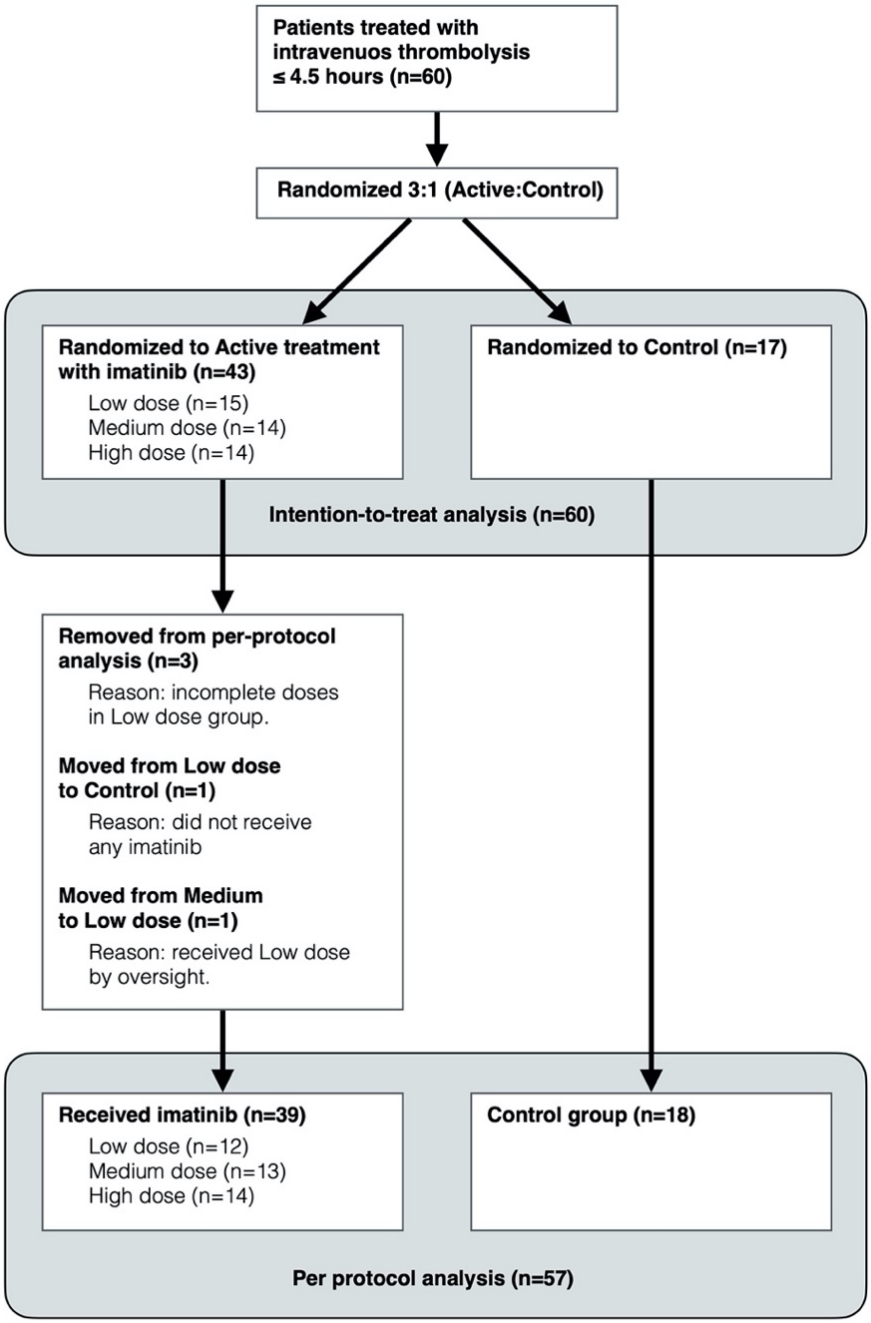

Figure 13. *Flow diagram of the iStroke Pilot Study reported in paper III.*

3.3.1 The iStroke Pilot study

The iStroke Pilot study was a prospective, randomized, open, blinded evaluation, ascending-dose pilot trial of oral imatinib in acute ischaemic stroke. The primary objective was to evaluate the safety and tolerability of imatinib when administered in patients treated with IVT in AIS. The secondary objective was to evaluate the efficacy of imatinib when administered in patients treated with intravenous thrombolysis in acute ischaemic stroke. Since the goal

was to evaluate a drug by giving it to patients that had the health condition of interest, while monitoring safety, it was a phase 2 study [131]. As it was a small-scale evaluation of the feasibility of study methodology, in preparation for a larger study, it was also called a pilot study [131].

The primary endpoints, regarding safety, were the following:

- Serious and non-serious adverse events (in particular those listed as reported adverse events in long-term treatment with imatinib for oncological indications).
- Mortality.
- Laboratory values, in particular blood cell count, bilirubin, aspartate aminotransferase (ASAT), alanine amonotransferase (ALAT), amylase and creatinin.

According to the protocol, secondary endpoints for efficacy were:

- Occurrence and severity of haemorrhagic transformation, or intracerebral haemorrhage on post-treatment CT or MRI.
- Occurrence and severity of COED on post-treatment CT or MRI.
- Neurological outcome at 2 h, 24 h and 7 days.
- Functional outcome at 3 months.

Patients were recruited at 5 hospitals in the Stockholm Region between 2011 and 2014. Patients who met routine criteria for intravenous thrombolysis were screened for the study as soon as possible after initiation of IVT. If inclusion criteria were met, and informed consent was obtained, the patient was randomized to either imatinib or no imatinib treatment. The randomization was done not later than 1 h after completion of IVT, or, if applicable, within 1 h after completion of EVT. Administration of oral imatinib was done as soon as possible after randomization. Tablets were preferably taken with a glass of water. In case of difficulties to swallow, tablets could be dissolved in in a fluid and, if needed, administered through nasogastric feeding tube. The acute treatment period was 6 days.

In the first part of the study, a dose of 400 mg imatinib was given, followed by a second step with 600 mg and a third step with 800 mg. Before any increase of dose was initiated, an independent safety committee had to decide that no safety issues, that would motivate a termination of recruitment, had occurred. Each of the 3 parts of the study included 15 patients that were treated with imatinib and 5 patients that received no treatment. Randomisation was done through an interactive web system (Viedoc).

Table 2 gives a summary of the major investigational events according to the study protocol. Patients were followed at the hospital ward during the study period. CT scans were performed before initiation of IVT and 22-36 hours after IVT, according to the standard

clinical protocol. MRI examinations were performed, as a part of the study procedures, within the same interval as the follow-up CT (22-36 h post IVT initiation) and at day 7. CT and MRI examinations were evaluated blindly by two experienced neuroradiologists to reach a consensus.

	Day								
Event	0	1	2	3	4	5	6	7	90‡
Brain CT	Before start of IVT	22-36 h after IVT						X†	
Brain MRI		22-36 h after IVT						X	
Informed consent and randomization	Within 1 h after end of IVT or EVT								
Administration of treatment drug (oral imatinib)	Immediately after randomization	X	X	X	X	X			
Blood sample for imatinib concentration	3 h after first dose of imatinib	X	X						
Blood sample for other lab tests	X	X						X	X
Blood pressure	X*	X	X	X	X	X	X	X	X
Registration of adverse events	X	X	X	X	X	X	X	X	X§
NIHSS scoring	X*	X	X	X	X	X	X	X	X§
mRS scoring	X							X	X§

Table 2. *Major investigational events of the iStroke Pilot Study (paper III), from day 0 (the day of inclusion) to final follow-up at 90 days (3 months).*
** Done both before and 2 h after start of IVT*
† CT on day 7 was optional
‡ Final follow-up between day 85 and day 100 (3 months).
§ At final follow-up, the investigator was blinded to treatment status.

Patients were followed for 3 months after stroke onset. The final follow-up and evaluation was done between day 85 and day 100 with evaluations of the NIHSS and mRS scores by an investigator at a different hospital from the one responsible for the acute treatment. The investigator was blinded to treatment group.

The study was conducted according to the Good Clinical Practice standard for clinical trials. Patient data was documented in a paper case record form and later transferred to electronic records for analysis. Adverse events, defined as any untoward medical occurrence in a study participant, were registered daily until day 7 and then at 3 months. Adverse events were classified by the investigator as related or not related to imatinib and furthermore classified as serious or non-serious.

3.3.2 Subjects

The most important inclusion criteria were:

- Clinical diagnosis of acute ischaemic stroke causing a measurable neurological deficit. Ischaemic stroke was was defined clinically, as an event characterized by sudden onset of acute focal neurological deficit presumed to be caused by cerebral ischaemia, after CT scan had excluded haemorrhage
- Neurological deficit with NIHSS score ≥7 at the time of randomization
- Age between 18 and 85 years
- IVT was indicated on clinical grounds and was initiated within 4.5 h of stroke onset
- Patients were be competent to make a decision and has provided informed consent with regard to participation in the study, retrieval and storage of data and follow-up procedures

The most important exclusion criteria were:

- Severe stroke as assessed clinically (for example, NIHSS > 25) and/or developing extending into more than one third of the MCA territory or half of other vascular territories
- Acute pancreatitis, severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Ongoing treatment with chemotherapy
- Drugs that may increase och decrease the plasma concentration of imatinib
- Contraindications against MRI

3.4 CLINICAL ASSESSMENTS

3.4.1 NIHSS

The NIHSS is a 15-item scale that measures neurological impairment using components of a standard neurological examination [132, 133]. A person with no measured deficit scores 0. In theory the maximum score is 42, which in practice however is never reached. While originally designed to assess differences in treatments in clinical trials, it is today being used to clinically assess and follow patients in routine stroke care all over the world. NIHSS has overall high inter-rater reliability. Moreover, it has a high degree of validity in that the score correlates with volume [133]. However, because several of the items measure language-related deficits, NIHSS measures the severity and size of strokes in the right hemisphere a

little differently than strokes in the left hemisphere. In a study that used CT to measure volume, median volume of a right hemisphere stroke was roughly equal to the median volume of a left hemisphere stroke in the next highest 5-point category of the NIHSS [134]. Thus, at a given NIHSS score, the median volume of right hemisphere strokes is larger than the median volume of left hemisphere strokes.

3.4.2 Treatments

In paper I, II and IV, treatments registered in the SITS Registry were used to different degrees. Treatments at baseline, that is to say treatments that were registered as being present at the time of stroke onset, were antiplatelet, statin, anticoagulant and antihypertensive treatment. Treatments given during the care of the patient were IVT, EVT, DHC and stroke unit care. Data on other treatments given during the care of the patients were not used when data was analysed.

In paper III, treatments were registered according to the iStroke Pilot study protocol. Medications that could be registered as being present at the time of stroke onset were aspirin, warfarin, oral diabetic agents, insulin and statins. While all patients received IVT, any EVT or intra-arterial thrombolysis were registered.

3.4.3 Functional outcome

The modified Rankin scale (mRS), originally presented in 1957 and modified in 1988, is a commonly used scale used to assess disability in stroke patients [133, 135, 136]. The scale spans from 0 (no symptoms) to 6 (death) and contains the following grades [105]:

- 0. No symptoms
- 1. No significant disability, despite symptoms. Able to perform all usual duties and activities
- 2. Slight disability. Unable to perform all previous activities but able to look after own affairs without assistance.
- 3. Moderate disability. Requires some help, but able to walk without assistance.
- 4. Moderately severe disability. Unable to walk without assistance and unable to attend to own bodily needs without assistance.
- 5. Severe disability. Bedridden, incontinent, and requires constant nursing care and attention.
- 6. Dead

The scale is short which makes it relatively easy to use but also affects it reliability. To improve inter-rater variability, an approach based on rules or structural interviews is recommended [105].

3.4.4 Death

In paper I, II and IV, death of patients was registered through the variable for mRS in the SITS Registry, which was assessed at 3 months. Local investigators had an option to register a patient as alive, but with unknown mRS score, at 3 months.

In paper III, which was a clinical study performed in accordance with Good Clinical Practice guidelines, death was registered by study investigators.

3.4.5 Variables derived from NIHSS

In paper I, II and IV, NIHSS item was 1a used to measure impairment of level of consciousness, which was defined as NIHSS item 1a scoring 1 or more, indicating a patient with decreased consciousness (not alert but arousable with different degrees of stimulation) or in coma.

In paper II, 1 of the 4 subtypes of stroke defined by the Oxfordshire Community Stroke Project (OCSP) classification was derived from items of the NIHSS [67, 137]. The subtype Total Anterior Circulation Syndrome (TACS), which has a high compatibility with infarctions of the MCA territory, was used as a proxy for LAO involving the MCA territory [138, 139]. In the case of cerebral ischaemia, the OCSP classification correctly predicts the site of infarction in 75% of all patients, and slightly better in TACS where four of five patients (79%) are correctly classified [139]. TACS corresponds to large cortical MCA infarcts, involving the whole of the cortex supplied by the MCA plus white matter and at least part of basal ganglia, or infarcts of more than half of the MCA territory plus anterior cerebral artery ACA or PCA territory [139, 140]. The TACS subgroup consisted of patients with clinical characteristics of TACS according to the NIHSS, inferred when all the following 3 criteria were met: first, aphasia (NIHSS item 9) or inattention (NIHSS item 11), second, a right or a left sensorimotor deficit (NIHSS items 4, 5, and 6) and, third, any visual defect (NIHSS item 3).

In paper II, early neurological deterioration was defined as an increase in total NIHSS score of 4 points or more from baseline to 24 hours.

In paper IV, baseline NIHSS items 5a and 6a (motor function of right arm and leg), 5b and 6b (motor function of left arm and leg) were used to infer right- or left sided hemiparesis while NIHSS item 9 for aphasia and item 11 for extinction/inattention were used to suggest localization of a lesion to the left or right hemisphere.

3.4.6 Time intervals in the SITS Registry

In the final follow up at 3 months, if mRS was missing then information on death was completed from several time points, such as date/time of death, outcome at 24 hours and at 7 days. In paper II, onset-to-treatment time for IVT was derived from time of stroke onset and time of IVT administration. In paper IV, time from onset to neuroimaging was derived.

3.5 THE SITS COED SCALE

In all papers of this doctoral thesis, the same 4-level ordinal scale is used to grade cerebral oedema. Since this scale was first being used in the SITS Registry, it is referred to as the SITS COED scale [141].

The SITS COED scale expresses brain swelling, as detected on CT or MRI, in thirds of the hemisphere, ignoring vascular territories. The scale has 4 levels, defined as follows:

- No COED.
- Mild COED. Focal brain swelling up to one third of the hemisphere.
- Moderate COED. Focal brain swelling greater than one third of the hemisphere.
- Severe COED. Brain swelling with midline shift.

Please see figure 14 for examples. The term "focal brain swelling" remains undefined in the SITS protocol. In practice, however, signs of focal oedema are usually defined as narrowing of the CSF space, for example effacement (reduction) of cortical sulci or ventricular compression [142-144, 79].

In general, radiological grading scales and guidelines for reporting cerebral oedema in acute ischaemic stroke usually consist of some of the following elements: extent of hypoattenuation and swelling, effacement of sulci and/or lateral ventricles, midline shift, effacement of basal cisterns and/or third ventricle and uncal herniation. This is based on research into the natural clinical and radiological course of cerebral infarcts that cause oedema [65, 142, 61, 144, 78]. According to von Kummer et al. in 1995 [143], the clearest way to express extent of parenchymal hypodensity may be as a proportion of the whole hemisphere. This was based on experience as no empirical evidence was presented. Elements of the scale were used in the ECASS 2 and the ECASS 3 trials, although not explicitly mentioned in the final publications [145, 146]. According to the study protocol of ECASS 3, investigators rated focal brain swelling ≤33% or >33% of the hemisphere, and furthermore graded focal brain swelling as "effacement of CSF space" or "midline shift". When the SITS-MOST Registry was started, the SITS COED scale was included in the study protocol in 2002 at the suggestion of the SITS-MOST study´s Brain Imaging Committee using that experience. The scale has been used by the SITS Registry ever since. Prior to this doctoral thesis, the SITS COED scale had been used in an analysis of local data from Helsinki [84].

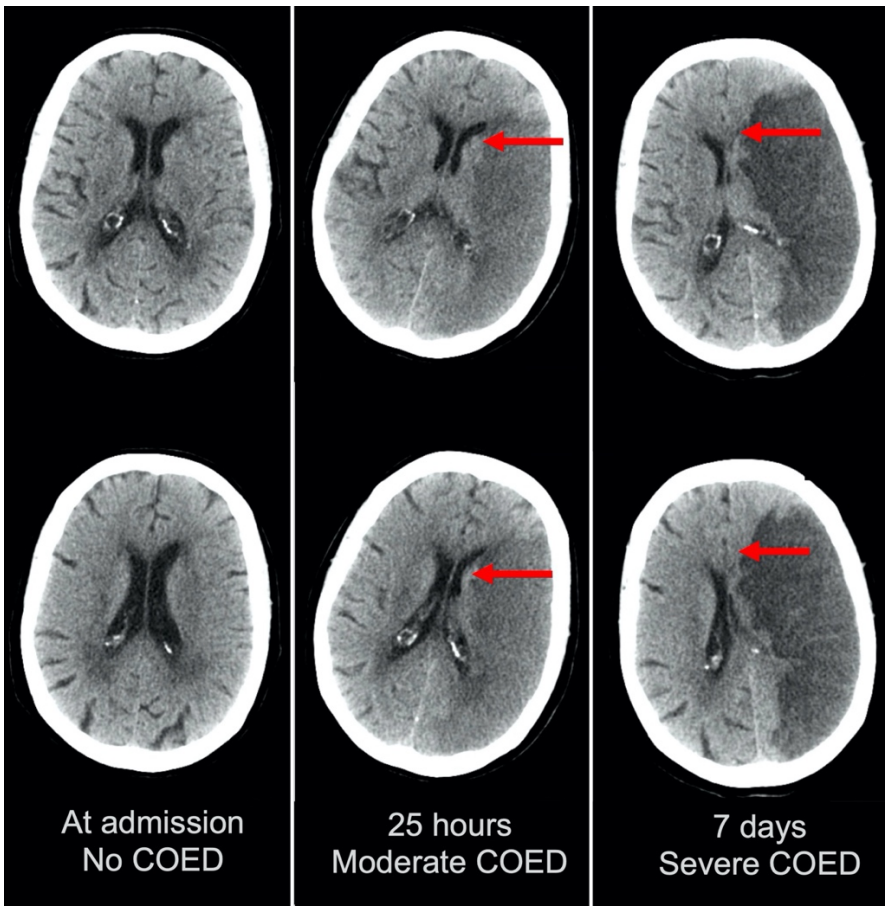

Figure 14. *Computed tomography (CT) images from the iStroke Pilot Study showing the development of a large infarction in the territory of left middle cerebral artery and development of cerebral oedema (COED), at different time points. At 25 hours, there is focal oedema and a slight ventricular compression (arrow). At 7 days a midline shift is visible (arrow).*

The reliability of the SITS COED scale has not been formally tested. However, in 1994 Wardlaw et al. [142] published results regarding a 7-level cerebral oedema scale that provides indirect evidence. This scale was part of a score that classified radiological findings according to 3 variables: infarction size and location, swelling (oedema) and haemorrhage. The inter-observer agreement for the cerebral oedema scale was excellent between experienced radiologists. The scale was subsequently used, for example in studies on reliability of early ischaemic signs and in the Third International Stroke Study [140, 147, 148]. When this 7-level grading scale was abbreviated to only 3 levels, with some similarity to the SITS COED scale, the inter-observer agreement between experienced and more junior doctors was very good. Variants of similar scales to grade cerebral oedema, with 3 or 4 levels, have been used in several publications [105, 149, 101, 57, 150].

3.6 HAEMORRHAGIC TRANSFORMATION

All papers use the same definitions of haemorrhagic transformation [145, 151, 141]. Haemorrhages were detected on CT or MRI. Every examination could be assigned one rating

for local haemorrhage and one rating for remote haemorrhage. If there was no haemorrhage, this too was registered.

Local haemorrhage

- Haemorrhagic infarction (HI) type 1. Small petechiae along the margins of the infarction.
- HI type 2. A more confluent petechiae within the infarction area but without space-occupying effect.
- Parenchymal haemorrhage (PH) type 1. Blood clot(s) not exceeding 30% of the infarction area with some mild space-occupying effect.
- PH type 2. Blood clots exceeding 30% of the infarction area with significant space occupying effect

Remote haemorrhage

- Remote parenchymal haemorrhage (PHr) type 1. Small or medium sized blood clots located remote from the actual infarction; a mild space occupying effect could be present.
- PHr type 2. Large confluent dense blood clots in an area remote from the actual infarction; significant space occupying effect may be present.

In addition, paper I used 3 definitions of SICH [141]. SICH per SITS-MOST was defined as PH type 2 or PHr type 2 on the 22 to 36 hours post-treatment imaging, combined with a neurological deterioration of ≥4 NIHSS points on from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death. SICH per ECASS 2 was defined as any haemorrhage plus a neurological deterioration of ≥4 NIHSS points from baseline, or from the lowest NIHSS value within 7 days. SICH per NINDS was defined as a haemorrhage that leads to any neurological deterioration (NIHSS score ≥1) or death within 7 days.

3.7 OTHER RADIOLOGICAL ASSESSMENTS

In paper I, II and IV, infarction signs on CT or MRI were registered. The terminology used in the SITS Registry protocol is "current infarction", allowing the rating of yes, no or unknown.

In paper I, II and IV, a thrombus was visualized as a HAS on CT images [152, 153], a visible occlusion on MRI images or an occlusion that was detected using CT angiography (CTA) or MRI angiography. Please see figure 15. In paper II, recanalization at 22-36 hours was inferred from disappearance of radiological signs of occlusion on computed tomography, MRI, or angiographic examinations. If records of more than one modality was available, angiographic data took precedence.

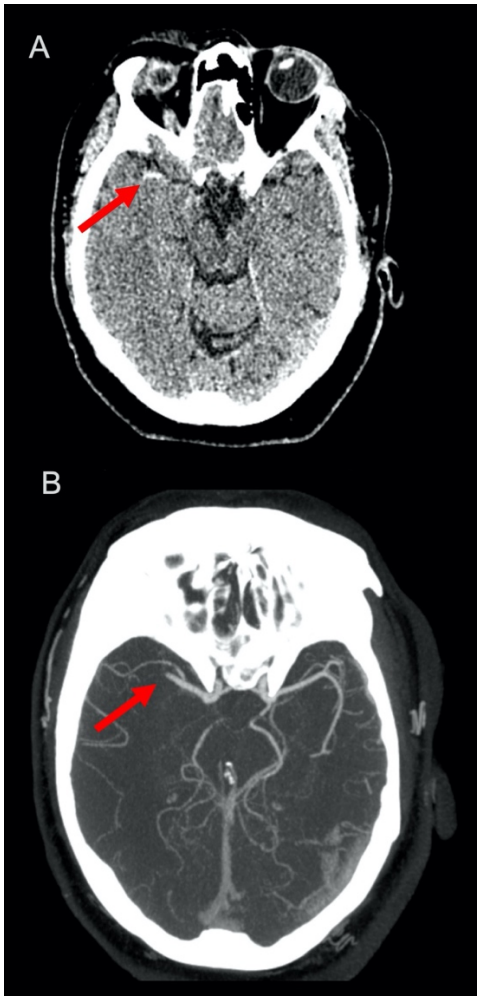

Figure 15. *Computed tomography (CT) images from the iStroke Pilot Study. A. Hyperdense artery sign at the location of the right middle cerebral artery. B. CT angiography showing occlusion of the right MCA in the same patient.*

In paper IV, CT or MRI data was used to localize arterial occlusions within the cerebral vascular tree. Patients were classified according to side of occlusion (left, right or bilateral), whether the occlusion was in the anterior or posterior circulation and level of occlusion (for example, carotid T or MCA). The purpose of this was to identify patients with anterior circulation LAO.

3.8 STATISTICAL CONSIDERATIONS

3.8.1 Paper I

The aim was to find the most important, or strongest, predictors. This involved calculating the odds ratio (OR) of outcomes that had to do with COED (for example severe COED), comparing patients with different values of predictors (for example HAS versus no HAS). The analysis was done using different definitions of the outcome.

Using logistic regression, univariable relationships between baseline variables and each of these outcomes were investigated. To study the relationship over a range of values, continuous variables were categorized into quartiles. Logistic regression was used to address two questions: first, whether odds ratios differed across categories (test of homogeneity) and,

second, whether there was a linear trend in the OR of the outcome with increasing values (test for trend).

The procedure of selection of variables to keep in the models was done using a process of backward elimination starting with all statistically significant variables from the univariable analysis [154, 155]. After the procedure was done and models had been finalized, the predictive ability of final models was evaluated in two ways. First, performance regarding misclassification was calculated by the C-statistic, equivalent to the Area under the curve (AUC) for the Receiver operating characteristic curve [156, 154, 157]. Second, a Hosmer-Lemeshow test, in which a non-significant result can rule out gross lack of fit of the model in question, was done [154].

3.8.2 Paper II

In an initial univariate analysis, baseline characteristics and outcomes between recanalized and non-recanalized patients were compared. In addition, baseline characteristics between patients with no or mild versus moderate to severe COED were compared. Analyses were done with mRS either dichotomized or in 7 steps with ordered logistic regression using the proportional odds model. Logistic regression methods compared crude and adjusted odds.

As the goal was to use different methods to adjust for potential confounders, covariates were chosen using three strategies. The first strategy was to select all baseline variables associated ($p<0.05$) with moderate to severe COED. The second strategy was to perform stepwise backward elimination among baseline variables associated with either recanalization or moderate to severe COED. The third strategy was to select variables that potentially confound the association between recanalization and COED using a model of potential causal relationships that was created beforehand. This model was expressed as a directed acyclic graph [158-161]. Using the assumptions of this model, adjustment variables were first selected so that total the effect of recanalization on COED could be estimated. Since PH was hypothesized to act as an intermediate variable, the direct effect of recanalization on COED was estimated through adjustment for PH [162]. The predictive ability of all three models was evaluated by calculating AUC. The robustness of the results was evaluated with a sensitivity analysis using calculated E-values for the effect of recanalization on CED. E-values can be interpreted as the minimum strength of association (on the risk ratio scale) that an unmeasured confounder needs to have with both recanalization and CED, given covariates, to fully explain away the estimated effects [163, 164]. Finally, the effect of CED on the secondary outcomes was investigated, both crude associations and controlled for the baseline factors associated with moderate to severe CED.

3.8.3 Paper III

Treatment groups were compared with descriptive statistics for baseline, demographic and imaging data. Fishers exact test, two-sample t-test and median regression were used. he dose of imatinib was treated both as a categorical and a continuous variable. To analyse whether imatinib had any effect on the NIHSS score, different regression models were used, with and

without adjustment for EVT. Regression methods were used to look at separate time-points, to evaluate the mean effect over the entire time course and to compare the mean percentage NIHSS change from baseline. Logistic regression was used to analyse the association between treatment groups and functional independence.

3.8.4 Paper IV

Univariate and bivariate statistical analysis was performed using t-test without equal variances assumption, Pearson´s chi-square test and Kruskal-Wallis test. A significance level of $p<0.05$ was used throughout. To study influence of age on outcomes, we categorized age into decades, with lowest interval ≤30 years and highest interval ≥71 years, and into quartiles. To facilitate comparison with results from randomized trials, age was also dichotomized into ≤60 years and ≥61 years. Estimation of proportions was based on reported cases, excluding unknown or uncertain values from the denominator. When modelling the association between baseline variables and outcomes using logistic regression, the baseline variables that were significantly associated in univariate analysis were included, adding sex and treatments (IVT, EVT, stroke unit care). Finally, the sensitivity of the results to missing data was evaluated.

4 RESULTS

4.1 PAPER I

After exclusion of patients with missing or uncertain data regarding COED, the study population consisted of 42 187 patients recorded at 752 centres in 41 countries. Median age was 70.

4.1.1 Proportions of COED and haemorrhage at 22-36 hours

The proportion of mild COED on follow-up imaging (22-36 hours or any extra investigation), was 12.5%. The incidence of moderate and/or severe COED was 10.2%, divided approximately 1:1 into moderate COED (4.9%) and severe COED (5.3%). Of all cases of mild, moderate or severe COED, >99% was detected on the 22-36 hours examination and not on any extra examination while only 3.5% had their COED status changed between the 22-36 hours examination and any extra examination.

Regarding haemorrhagic transformation, any local haemorrhage at 22-36 hours was seen in 15.1% of all patients, please see table 3 (data not in paper I). In patients with moderate COED, any PH was observed in 17.5% (PH type 1 in 8.1%, PH type 2 in 9.4%). In patients with severe COED the proportions of PH were higher; any PH was observed in 33.0% (PH type 1 in 10.5% and PH type 2 in 22.5%). The proportion of all types of SICH increased by severity of COED. The most severe type of SICH, SICH per SITS-MOST, was detected in 5.5% of patients with moderate COED and 15.9% of patients with severe COED, compared to 0.5% of patients with no COED.

4.1.2 Predictors for COED

Almost all baseline variables showed statistically significant differences between patients with no COED and patients with any COED. As the proportion of oral anticoagulant use was very low at 2.5%, this variable was omitted from analyses.

Five baseline variables remained in all final multivariate models for all COED outcomes: baseline NIHSS score, HAS, higher blood glucose, impaired level of consciousness and signs of infarction at baseline. Please see table 4. The point estimates are of odds ratios from models of various COED outcomes that have to do with moderate or severe COED. The outcome in model A and B was that a patient had a certain level of COED instead of no COED while the outcome in model C and D was calculated using the whole study population. Results were similar across all models although the estimated odds ratios were higher in models A and B compared to models B and C. NIHSS score was the strongest predictor. Comparing patients with NIHSS score ≥17 versus 0-6 in model A, the OR for moderate COED was 15.4 (95% CI 11.5-20.6) while the OR for severe COED in model B was 16.5 (12.3-22.1). Patients with HAS at had an OR of 2.1 (1.9-2.4) for moderate COED in model A and 2.5 (2.2-2.8) for severe COED in model B. Blood glucose, impaired level of consciousness and signs of early infarction at baseline showed odds ratios between 1.2 and

1.9. Variables positively associated with only one or two outcomes were: diabetes mellitus, hypertension, atrial fibrillation, congestive heart failure and mean arterial pressure. Age and previous stroke were negatively associated with moderate COED. In addition to the five predictors already mentioned, the models for mild COED contained sex, onset-to-treatment time, hyperlipidaemia and atrial fibrillation.

Calculation of receiver operating characteristics resulted in AUC 0.72-0.82, levels that are usually taken to be indicators a good discriminatory ability. The Hosmer-Lemeshow test indicated that gross lack of fit could probably be ruled out for all models except model B.

			COED			
Intracerebral haemorrhage	N	All	No	Mild	Moderate	Severe
Local haemorrhage	42 178					
No local haemorrhage, %		84.9	91.8	66.6	62.9	48.7
PH type 1, %		3.0	1.4	8.1	8.1	10.5
PH type 2, %		3.1	1.2	4.4	9.4	22.5
HI type 1, %		5.3	3.7	12.2	9.6	8.1
HI type 2, %		3.6	1.9	8.7	10.1	10.2
Remote haemorrhage	42 177					
No remote haemorrhage, %		96.9	98.1	94.3	92.2	89.4
PHr type 1, %		2.0	1.4	4.3	3.9	3.9
PHr type 2, %		1.1	0.5	1.4	3.9	6.8

Table 3. *Haemorrhagic transformation among patients in paper I, by cerebral oedema (COED) status, on follow-up neuroimaging at 22-36 hours or extra examinations. Abbreviations: parenchymal haemorrhage (PH), haemorrhagic infarction (HI), remote parenchymal haemorrhage (PHr).*

Outcome	OR of the outcome					Additional predictor(s)
	Highest quartile of NIHSS score (≥17)	HAS	Highest quartile of blood glucose (≥7.9 mmol/l)	Impaired LOC	Infarct signs	
A. Moderate COED (relative to no COED)	15.4	2.1	1.2	1.4	1.3	Age* Previous stroke* Diabetes mellitus† Hypertension† Atrial fibrillation† Congestive heart failure†
B. Severe COED (relative to no COED)	16.5	2.5	1.9	1.6	1.5	–
C. Moderate or severe COED (relative to no or mild COED)	12.7	2.0	1.5	1.4	1.4	Atrial fibrillation†
D. Severe COED (relative to no, mild or moderate COED)	12.3	2.0	1.8	1.5	1.4	Mean arterial pressure†

Table 4. *Predictors that remained in the final multivariable models for moderate and/or severe cerebral oedema (COED) of paper I. Five predictors remained in all models: National Institutes of Health Stroke Scale (NIHSS) score, presence of hyperdense artery sign (HAS), blood glucose, impaired level of consciousness and infarction signs on CT. The various definitions of outcomes all had to do with COED. The table shows examples of odds ratio (OR) of the outcome. Abbreviations: hyperdense artery sign (HAS), level of consciousness (LOC)*

** Negative association (OR < 1.0)*

† Positive association (OR > 1.0)

4.1.3 Death and functional outcome at 3 months

Follow-up with mRS at 3 months was completed for 33 737 patients (80% of study population). Increasing COED at 22-36 hours negatively affected outcomes at 3 months, please see figure 16.

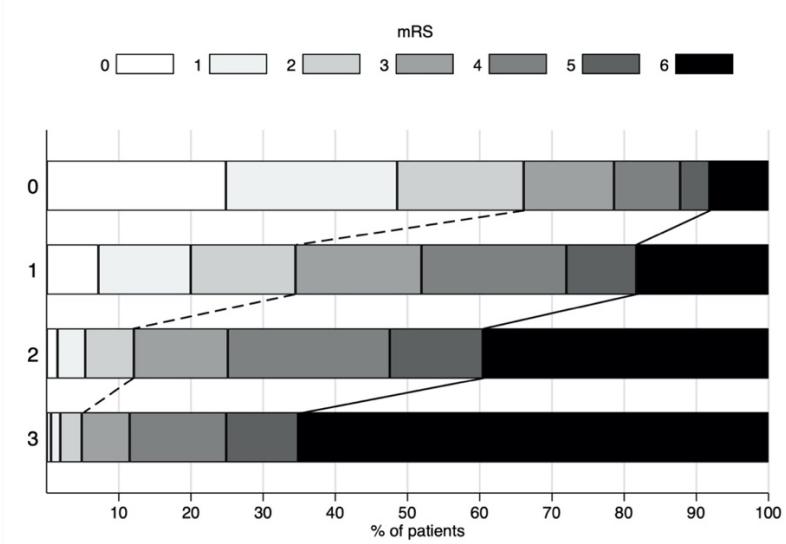

Figure 16. *Distribution of modified Rankin scale (mRS) scores at 3 months among patients in paper I, by degree of COED at 22-36 hours: no (0) mild (1), moderate (2) and severe (3). Dashed line indicates mRS 0-2 and solid line indicates mRS 6 (death). The proportion of patients with good outcome (mRS 0-2) was 66% in those with no COED, 34% with mild COED, 12% with moderate COED and 5% with severe COED. The proportion of patients dead within 3 months was was 8% in those with no COED, 18% with mild COED, 39% with moderate COED and 65% with severe COED.*

4.2 PAPER II

The study population consisted of 22 184 patients recorded at centres in 62 countries. Median age was 71 years and median NIHSS score at baseline was 16. Reperfusion therapy administered was IVT only (82.6%), IVT and EVT (13.8%) or EVT only (3.6%). Recanalization status was determined directly, using angiography, for 8.6% and indirectly, inferred from disappearance of hyperdense artery sign or disappearance of visible thrombus, for 91.4% of patients. Using this definition of recanalization, 64.1% of patients had recanalized at 22-36 hours.

4.2.1 The effect of recanalization on early COED

Overall, recanalization was associated with a 10.6% absolute risk reduction of moderate to severe COED at 22-36 hours (13.0% versus 23.6%, $p<0.001$), RR 0.55 (95% CI 0.52-0.58), crude OR 0.48 (95% CI 0.45-0.52). Please see figure 17. Ordered logistic regression showed a significant shift toward lower level of COED in recanalized patients; however, the proportionality assumption did not hold. Meanwhile, recanalization was associated with a

2.4% absolute increase of PH at the same examination (8.9% versus 6.5%, p<0.001), RR 1.37 (95% CI 1.24-1.51), crude OR 1.40 (95% CI 1.26-1.56).

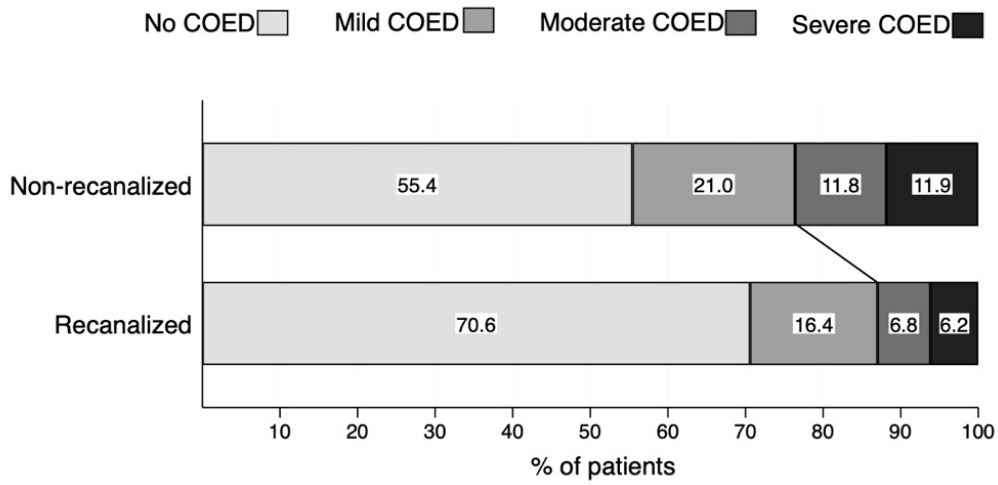

Figure 17*. Distribution of COED at 22-36 hours in patients without, and with, arterial recanalization at 22-36 hours (paper II). The line indicates that the absolute difference in proportion of moderate to severe COED was 10.6%.*

Table 5 shows a summary of models that estimated the adjusted effect of recanalization on moderate to severe COED. For selection of covariates for models, three different procedures, based on statistical testing or prior hypothesis, were used. In addition, all models were estimated with and without PH as a covariate. Adjusted OR for the effect of recanalization were similar to the crude OR, between 0.42 and 0.52. Adjustment for PH resulted in slightly lower point estimates for COED; however, the relative difference was at most 12%. Values for AUC ranged between 0.69 and 0.79; highest AUC values were seen in models adjusted for PH. E-values were similar (2.1-2.4) across all models. Two models with high predictive ability showed the following estimates: OR 0.52 (95% CI, 0.46-0.59), AUC 0.74, not adjusted for PH, and OR 0.46 (95% CI, 0.41-0.52), AUC 0.79, adjusted for PH. Restriction to the TACS subgroup (not shown in table) resulted in slightly lower point estimates.

Regarding clinical outcomes recorded at 24 hours, recanalization was associated with a lower NIHSS (median 8 versus 16, p<0.001) and lower incidence of END (8.3% versus 14.5%, p<0.001). While the full NIHSS score was not used in a multivariate model, the lower risk of END after recanalization remained after controlling for baseline variables, adjusted OR 0.50 (95% CI 0.45-0.55).

Procedure for selection of covariates	Adjusted for covariates		Adjusted for covariates and PH	
	OR (95% CI)	AUC	OR (95% CI)	AUC
1. Associated with moderate to severe COED*	0.47 (0.43-0.51)	0.69	0.42 (0.38-0.45)	0.74
2. Stepwise backward elimination†	0.52 (0.46-0.59)	0.74	0.46 (0.41-0.52)	0.79
3. A priori hypothesis‡	0.52 (0.48-0.56)	0.71	0.46 (0.42-0.50)	0.76

Table 5. *Regression models for the effect of recanalization on moderate to severe cerebral oedema (COED), in paper II.*

** All baseline variables associated (p<0.05) with moderate to severe COED in the study population: onset-to-treatment time, signs of acute infarction on imaging, blood glucose, mean arterial pressure, diabetes mellitus, hypertension, congestive heart failure, aspirin treatment, oral antihypertensive treatment, current smoker, atrial fibrillation, decreased consciousness, endovascular thrombectomy (EVT) and decompressive hemicraniectomy (DHC)*

† Stepwise backward elimination (p<0.05 to eliminate) among baseline variables associated (p<0.20) with either recanalization or moderate to severe COED. Number of remaining covariates: 10-13, varying between models.

‡ Variables that potentially confound the association between recanalization and COED: age, onset-to-treatment time, National Institutes of Health Stroke Scale (NIHSS) score, stroke unit care.

4.2.2 The effect of recanalization on death and functional outcome at 3 months

Follow-up of death and functional outcome at 3 months was recorded for approximately 80% of the study population. Recanalization was associated with a 13.6% absolute reduction of mortality (18.3% versus 31.9%, p<0.001), RR 0.58 (95% CI 0.55-0.61), crude OR 0.48 (95% CI 0.45-0.51). This effect remained unchanged after controlling for baseline variables, adjusted OR 0.48 (95% CI 0.45-0.53). Recanalization was associated with a 26.1% absolute increase of the proportion of patients scoring mRS 0 to 2 at 3 months (48.7% versus 22.6%, P<0.001), RR 2.16 (95% CI 2.06-2.26), crude OR 3.25 (95% CI 3.04-3.49). Please see figure 18. This effect too remained largely unchanged after controlling for baseline variables, adjusted OR 3.20 (95% CI 2.96-3.46). Ordered logistic regression showed a significant shift in mRS toward better functional outcome in recanalized patients; however, the proportionality assumption did not hold.

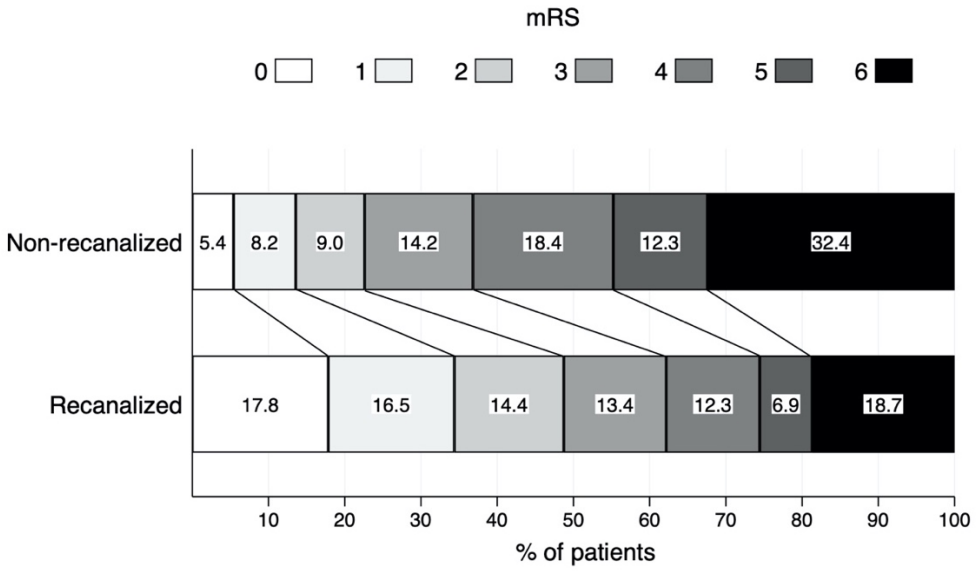

***Figure 18**. Distribution of modified Rankin scale (mRS) scores at 3 months in patients without, and with, arterial recanalization at 22-36 hours (paper II).*

4.3 PAPER III

Sixty patients were recruited. NIHSS score and age were well balanced between treatment groups. Median time from stroke onset to IVT was 86 (range 35-269) minutes. For patients receiving EVT, median time from onset to end of intervention was 290 (range 145-465) minutes with exact time missing for three patients. Patients receiving imatinib were given their first dose within 240 minutes (range 75-714) minutes.

4.3.1 Intention-to-treat analysis (safety outcomes)

After randomization, there were 15 patients in low-dose, 14 patients in medium and high-dose and 17 patients in the control group. Four serious adverse events (2 in control and 2 in low-dose group) resulted in the death of 3 patients. Of the dead patients 2 were allocated to low-dose group but of these, 1 did not receive imatinib and 1 patient had received only 2 doses. There was no likely connection between study treatment and serious adverse events, according to investigators and safety committee. There were 118 non-serious adverse events in 41 patients including 11 cerebral haemorrhagic events, in 9 patients, in the medium-dose group. There were 6 patients with itching and skin reaction and 4 patients with nausea and vomiting in the high dose group.

4.3.2 Per protocol analysis

There were 21 HI (6 in control) and 3 PH (1 in control), divided quite evenly among treatment groups. In addition, there were 4 PHr (0 in control). There was a total of 33 cases of COED, please see table 6, with moderate to severe COED being less frequent with higher doses. In fact, there were no cases of moderate to severe COED in the high-dose group.

Group	N	COED, n			
		No	Mild	Moderate	Severe
Control	18	9	7	0	2
Low dose (400 mg)	12	6	4	2	0
Medium dose (600 mg)	13	5	7	1	0
High dose (800 mg)	14	4	10	0	0

Table 6. *Cerebral oedema (COED) at day 1 or day 7 per treatment group of paper III. There were no cases of moderate or severe COED in the high-dose (800 mg) group.*

For the time points specified in advance by the protocol, the mean NIHSS score, adjusted for EVT, was significantly improved in the high-dose group compared to the control group: -5.28 (95% CI -9.60 to -0.96) on day 1, -5.68 (95% CI -10.38 to -0.98) on day 7 and -4.81 (95% CI -10.39 to -0.98) at 3 months.

Please see figure 19 for a graph of the mean NIHSS score per treatment group and time point between baseline and 90 days. On visual inspection, there seemed to be a tendency for higher dose groups to have lower NIHSS scores. Moreover, the mean unadjusted improvement in the NIHSS score compared to controls over all timepoints after baseline was 2 points for the low-dose group (p=0.283), 3 points for the medium-dose group (p=0.084) and 4 points for the high-dose group (p=0.037). After adjustment for EVT, the corresponding mean improvement compared to controls was 2 points (p=0.259), 3 points (p=0.106) and 5 points (p=0.012).

Using linear regression, it was found that mean NIHSS score decreased by 0.50 points per 100 mg imatinib (95% CI -0.98 to -0.02), and after adjustment for EVT 0.59 points (95% CI -1.08 to -0.09).

Serum creatinine was modestly increased in the high-dose group versus the control group from baseline to day 7 (17% increases versus 0.5% increase, p-value for difference 0.010). Changes in other laboratory values, complete blood count, ALAT and ASAT, did not differ significantly between treatment and control groups.

Functional independence (mRS 0-2) at 3 months was observed in 61% of the control group and 72% of all imatinib-treated patients. For the high-dose group there was a 18% absolute increase in the proportion of functional independence over the control group with OR, adjusted for EVT, 2.33 (95% CI 0.48-11.44), please see figure 20.

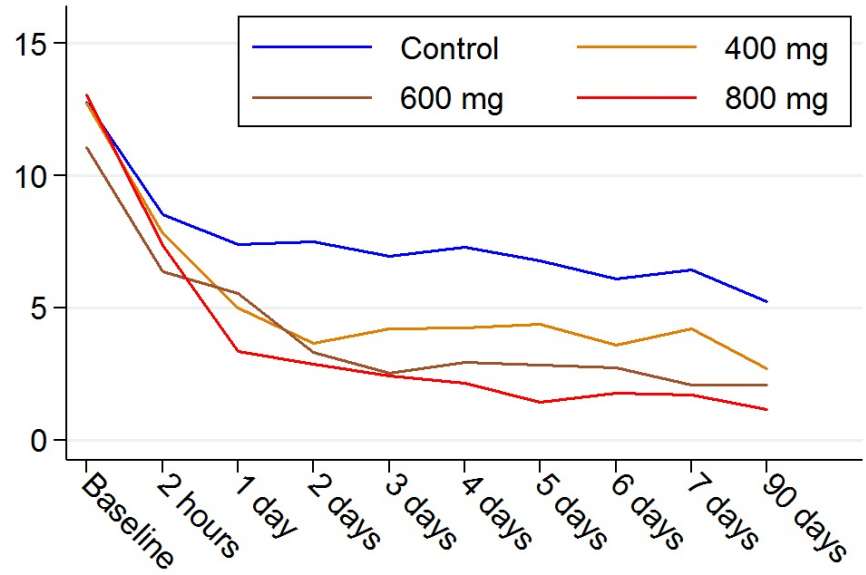

Figure 19. *Mean NIHSS score per treatment group and time point in paper III. On visual inspection there seemed to be a tendency for higher dose groups to have lower NIHSS scores. The mean improvement in NIHSS score compared to control over all these time points also increased with higher dose. Statistical significance, however, was achieved only for the high-dose (800 mg) group, in which an improvement of 5 points (p=0.012) was observed after adjustment for EVT status.*

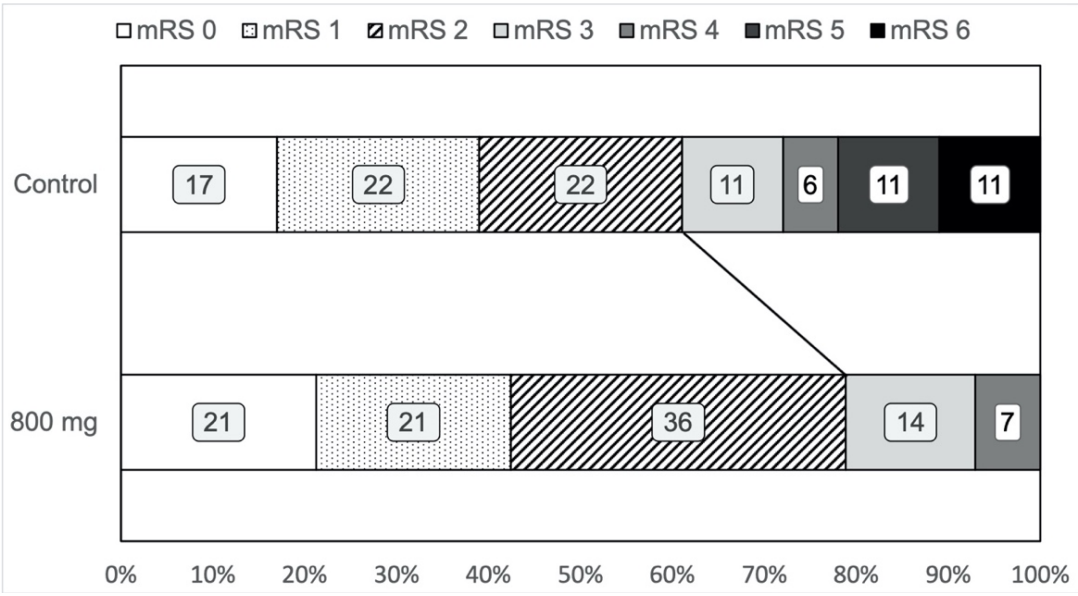

Figure 20. *Distribution of modified Rankin scale (mRS) scores at 3 months in patients of the control and high-dose (800 mg) groups of paper III. Line indicates functional independence (mRS 0-2). For the high-dose group there was an 18% absolute increase in the proportion of functional independence over the control group, adjusted OR 2.33 (95% CI 0.48-11.44). The numbers in this figure are slightly different due to rounding.*

In post-hoc subgroup analyses, among patients receiving high-dose imatinib, there were no local or remote haemorrhages in 2 different groups found by stratification: first, patients that received imatinib within 5 hours of stroke onset and, second, patients where reperfusion therapy (IVT alone or in combination with EVT) had ended within 4.5 hours of stroke onset.

4.4 PAPER IV

The study population consisted of 684 patients recorded at centres in 35 countries. Median age was 56 (range 20-86). Males were in majority (64.2%). Median NIHSS score at baseline was 18 (interquartile range 15-21). Any reperfusion therapy had been given to 98.1% of all patients; 52.5% received only IVT, 10.2% only EVT and 35.4% both IVT and EVT. Stroke unit care had been given to 73.5%

Median and mean times between stroke onset and follow-up imaging were similar; median 24.8 (interquartile range 18.8-27.3) and mean 23.3 hours. The prevalence of moderate to severe COED on follow-up imaging was 76.0%. However, no or mild COED was reported in some cases (15.9% and 8.1% respectively). Furthermore, 25.8% had PH.

4.4.1 Death and functional outcome at 3 months

486 patients (71% of the study population) had complete data on being alive or dead at 3 months. The age distribution of this subgroup was similar to that of whole study population. A total of 159 patients (32.7%) died. Mortality increased with age as shown in figure 21. Among baseline variables, only increasing age was independently associated with death (OR 1.06, 95% CI 1.03-1.08) in multivariate regression analysis.

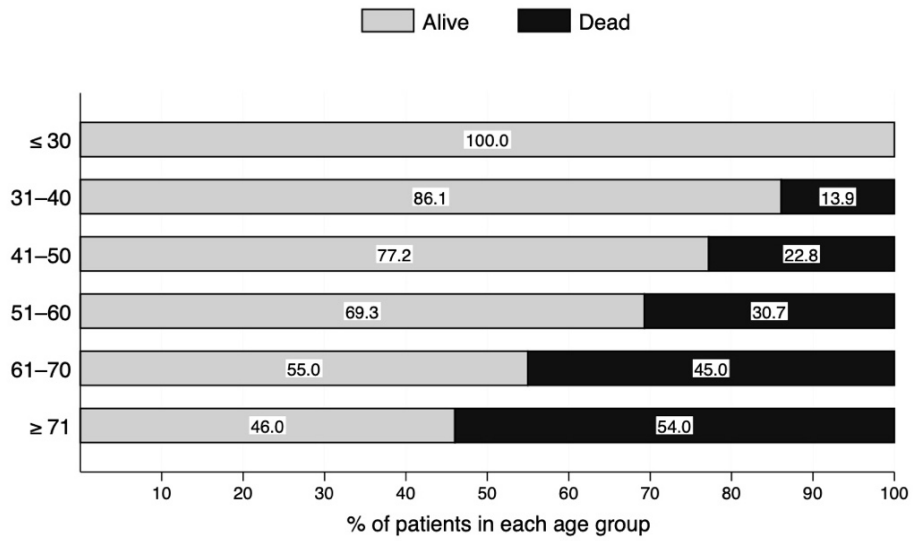

***Figure 21**. Mortality at 3 months increased with age in patients who underwent decompressive hemicraniectomy (DHC), as seen with age stratified by decades (n=486) from paper IV.*

475 patients (69% of the study population) had complete data on functional outcome (mRS) at 3 months. Among these patients, good outcome (mRS 0-3) was observed in 66 (13.9%) and mRS 0-4 was observed in 187 (39.4%). Both outcomes decreased with increasing age as seen after stratification into quartiles and decades of age. Among baseline variables, 3 variables were independently associated with good functional outcome in multivariate regression analysis, although with odds ratios close to 1: lower age (OR 0.95, 95% CI 0.92-0.98) shorter onset-to-imaging time at baseline (OR 0.99, 95% CI 0.99-1.0) and lower mean arterial pressure (OR 0.97, 95% CI 0.94-0.99).

4.4.2 Dichotomization of age at 60 years

After dichotomization of age, the younger (≤60 year) subgroup had median age 51 and mean age 49.5 years while the older (≥61 year) subgroup had median age 67 and mean age 68.0 years. Figure 22 shows functional outcome (mRS) at 3 months. There was a substantial difference in mortality between patients aged ≤60 years ≥61 years (25.2% versus 47.8%), absolute difference 22.6%. There was an 8.2% absolute difference in proportions of good outcome between patients aged ≤60 years ≥61 years (16.6% versus 8.4%).

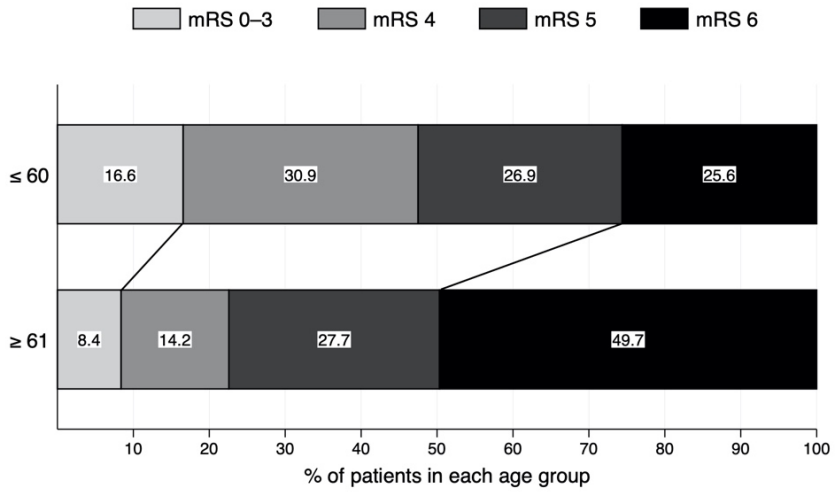

***Figure 22**. Functional outcome measured by modified Rankin scale (mRS) score at 3 months in patients who underwent decompressive hemicraniectomy (DHC), comparing age groups ≤60 and ≥61 years (n=475) of paper IV. Lines indicates modified Rankin scale score (mRS) 0-3 (good outcome) and mRS 6 (death). Not included here are the n=11 patients that were known to be alive at 3 months but hat no registered functional outcome. If they were included, the mortality was 25.2% (≤60 years) and 47.8% (≥61 years).*

4.4.3 Affected hemisphere

Right-sided involvement of vascular territory was more common than left-sided. Among all 268 patients with angiographic data, 60.4% had only right-sided and 38.4% had only left-

sided occlusions, based on examination with CT (n=260) or MRI (n=8). After restriction to the 218 patients with carotid T or MCA territory occlusions, a similar pattern remained with 62.4% right-sided versus 36.7% left-sided occlusions. Among 500 patients that were clinically evaluated for affected vascular territory, 55.0% were right-sided, 43.8% left-sided and 1.2% bilateral.

4.4.4 Missing data

198 patients (28.9% of the study population) did not contribute to calculations of mortality due to missing data. This subgroup had some baseline characteristics that indicate a better prognosis compared to the full study population, including less frequent imaging signs of acute infarction (27.0%), a higher proportion of IVT (89.9%) and EVT (48.0%) and a lower proportion of stroke unit care (67.7%). However, median age (57 years) was similar and median NIHSS was identical to the study population.

Removal of the subgroup of 143 patients (20.9% of the study population) that had no data on assessment of vascular territory resulted in negligible changes to mortality and proportions of mRS 0-3 and mRS 0-4, indicating that they did not differ in a systematic way from the rest of the population.

5 DISCUSSION

5.1 MEASUREMENT OF COED (ALL PAPERS)

Early or mild COED is difficult to distinguish from infarction [78]. Increased signal on diffusion-weighted MRI under ischaemic conditions is caused by cytotoxic oedema [78, 79]. Since early ischaemic changes on CT are caused by ionic oedema, which is the earliest phase of transvascular oedema, some degree of local swelling, as seen on CT, is part of the ischaemic process [78, 79]. In contrast to mild COED, a rating of moderate or severe COED requires more radiological signs of swelling. In particular, moderate COED requires more signs of focal swelling while severe COED also requires midline shift. Therefore, the ratings moderate and severe COED probably have a progressively higher specificity to detect transvascular oedema.

As there is no reference standard for COED, radiological or otherwise, there has not been any formal testing of the validity of the SITS COED scale or any other classification of COED. The definition of COED is imaging-based and not based on clinical findings or tissue analysis. The SITS COED scale measures COED in thirds of hemisphere and not according to vascular territories. It is however based on well-known facts about the natural course of COED. Furthermore, the work contained in this doctoral thesis has contributed to the documented use of this scale.

Potential future uses for the SITS COED scale are for evaluation of treatments and for prediction scales. When implementing this scale, it should be considered that mild COED and cerebral infarctions are parts of very similar processes, so the utility of the scale may be greatest in moderate and severe COED. This should, however, be evaluated.

5.2 PREDICTORS FOR COED (PAPER I)

The findings that baseline NIHSS, HAS and signs of infarction at baseline imaging predicted COED development confirmed earlier results on COED in IVT treated patients [84]. Because HAS and signs of early ischaemia are associated with more proximal vessel occlusions and, thus, to larger infarction volume, our results are also consistent with previous findings that regardless of IVT treatment, a major predictor for cerebral oedema is the presence of a large ischaemic core at baseline, as measured by CT or MRI [106, 105, 93, 87, 150, 165]. Impairment of level of consciousness was found to be an independent predictor of all types of cerebral oedema and may be a consequence of early oedema, predisposing for malignant cerebral oedema, but may also have other causes such as hyperglycaemia or acute delirium with severe stroke as a predisposing factor [105, 166, 167, 20].

Baseline blood glucose was an independent predictor for COED development in our study. This adds confirmation of previous observations as similar associations have been suggested

but not statistically significantly associated in earlier studies [168, 84, 107]. An explanation for this may be an impaired BBB related to high levels of blood glucose [169-173].

Functional outcome at 3 months progressively worsened with increasing COED, in particular moderate and severe COED. This is consistent with previously reported data [84]. The absolute excess mortality at 3 months, compared with patients with no COED, was between 10% and 57%. The 65% mortality at 3 months in severe COED was comparable to that of previous observational studies, as well as control groups of clinical trials of early decompressive hemicraniectomy [61, 116].

There have been some developments since this this paper was published. Ong et al. [174] published a score in 2017 to identify patients at high risk for lethal cerebral oedema in AIS; this score contained the following positive predictive factors: basal cistern effacement, high blood glucose, no tPA given or no EVT done, midline shift and no previous stroke. In a prediction score by Jo et al. [175], also published in 2017, 4 factors were independently associated with malignant cerebral oedema: higher baseline NIHSS score, early infarction on CT measured by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), worse collateral circulation and, lastly, failure of revascularization. Wu et al. in 2018 [176] published a systematic review and meta-analysis where younger age, higher NIHSS score and larger parenchymal hypoattenuation on CT were reliable early predictors for malignant cerebral oedema and revascularization reduced the risk of malignant cerebral oedema. Miao et al. [177] in 2019 published a meta-analysis where a main finding was that the risk for malignant cerebral oedema is associated with severe clinical symptoms; they concluded that this is related to larger infarction volumes. It should be noted, however, that paper I of this doctoral thesis contributed a large majority of the patients in that meta-analysis.

5.3 RECANALIZATION AS A PREDICTOR FOR COED (PAPER II)

As reported in paper II, recanalization was associated with an approximately 50% lower risk for early COED. The proportion of PH was higher in recanalized patients. Adjustment for PH resulted in slightly lower point estimates for moderate to severe COED. COED is also associated with SICH of different types. Nevertheless, the results remained consistent in three statistical models with different criteria for selection of covariates.

This study strengthens the evidence for the hypothesis that recanalization decreases the risk of COED after AIS, in particular that early (within 22-36 hours) COED is decreased in recanalized patients. Previous studies on the association between recanalization and COED were not consistent [150]. Furthermore, in animal models, reperfusion has been shown to accentuate COED [178-181]. In contrast, recent clinical studies with different lengths of radiological follow-up indicate that recanalization decreases COED [182-184]. Together with our results, with differences about patient populations and definitions of cerebral oedema taken into account, this strengthens the evidence for a decreased risk of early COED after recanalization. There is also evidence that the risk of later COED is decreased [182, 185,

184]. A clinical scoring system for malignant cerebral oedema found that non-revascularization at 24 hours was an independent predictor [175].

On a tissue level, both cerebral oedema and haemorrhage seem to result from the same process of gradually increasing BBB permeability and damage [40]. Signs of increased permeability, detected as early BBB disruption on computed tomography scan, is seen in 26.7% of patients after EVT [186]. Increased BBB permeability is associated with haemorrhagic transformation and cerebral oedema [187]. Our study showed that recanalization confers a lower risk of COED after ischaemic stroke and that this effect remains despite an increased rate of PH. It is consistent with the results of a multicentre retrospective study in which malignant MCA infarctions and mortality were reduced in patients undergoing EVT [188]. As the development of cerebral oedema in ischaemic stroke is multifactorial, persistent occlusion should be regarded as one important predictor together with other predictors that include the size of the ischaemic lesion which reflects on the NIHSS score, collateral status, and size of the occluded artery and the effect of thrombolytic drugs [53, 189, 99, 190, 41, 191].

5.4 PILOT TRIAL OF IMATINIB IN ISCHAEMIC STROKE (PAPER III)

In this phase 2, dose-finding trial, treatment with Imatinib with doses from 400 mg to 800 mg daily for 6 days in acute ischaemic stroke patients after IVT was safe and was well tolerated, at all doses. Although some patients experienced nausea or vomiting, or itching and skin reactions, when higher doses were used, tolerability was acceptable.

It is worth noticing that the effect of imatinib on prespecified outcomes seemed to increase dose dependently, so that increases were largest in the high-dose group. Differences regarding the high-dose group, versus control, even reached statistical significance in some instances, also after adjustment for EVT status. The mean NIHSS score per treatment group and time point between baseline and 90 days improved with higher dose. This could be observed not only on visual inspection of the graph but also as increasing differences between dose groups and control with the difference between the high-dose group and control, 5 points, reaching statistical significance. In a similar fashion, the mean NIHSS score at timepoints specified in advance, adjusted for EVT, was significantly improved in the high-dose group compared to the control. For the high-dose group there was a 18% absolute increase in the proportion of functional independence over the control group. This observation needs confirmation in a phase 3 trial.

There were no apparent differences between the treatment groups regarding proportions of haemorrhagic transformation. If imatinib restores the BBB, as is expected from experimental studies, some differences regarding haemorrhagic transformation between treatment groups could be expected. However, the sample size is small, and furthermore patients were divided into 3 dose groups. Also, the fact that imatinib was administered orally may have caused the effect to be too late. In post-hoc subgroup analyses, among patients receiving high-dose imatinib, there were no local or remote haemorrhages in patients that received the drug within

5 hours of stroke onset. Moreover, there were no moderate to severe CED in the high-dose group. Thus, there is some evidence indicating the conclusion that imatinib, when given early in a high dose, may decrease cerebral haemorrhage and oedema in ischemic stroke patients, consistent with the hypothesis that imatinib stabilizes the BBB.

Cerebral ischaemia is a complex process with the extent of remaining brain injury and functional deficits being dependent on the interaction of several cell types in the cerebral vasculature and brain parenchyma. As reperfusion therapy in ischaemic stroke is becoming more effective, research is needed for drugs that treat and prevent the consequences of reperfusion injury [192, 193]. Meanwhile, the term neuroprotection has been used for many years but has sometimes been interpreted narrowly to include neurons and not any other cell types in the brain. As suggested by Diez-Tejedor et al. [194], "brain protection" would perhaps be a better word to use since the aim is to globally protect the whole organ. An alternative is "brain cytoprotection" [195]. A similar point was made in 2018 in a document prepared by working groups within the European Stroke Organisation outlining future research priorities for stroke. Norrving et al. [196] argued that the concept of neuroprotection has evolved and should become wider to include systems of neurons, glial cells, pericytes, macrophages and, not least, vasculature. Other key research mentioned included vascular protection and research into inflammatory responses. Several emerging pharmacological therapies may have potential effects of brain protection in a broad sense, for example through action on different parts of the neurovascular unit [197]. A drug being investigated as potential treatment against cerebral oedema is glibenclamid, also known as glyburide, a sulphonylurea that is routinely used to treat non-insulin dependent diabetes [198]. In a randomized phase 2 trial, glibenclamid was well tolerated in patients with anterior circulation AIS but unfortunately the trial had to stop early after 86 patients due to funding reasons [199]. A phase 3 trial (CHARM) is recruiting patients [200]. Several other potential treatments against cerebral oedema in other conditions than stroke are being evaluated in mostly phase 1 and 2 trials [201, 202].

An ongoing phase 3 placebo-controlled randomized trial, I-Stroke II, is now evaluating the effect of imatinib (800 mg/day) on functional outcome in ischaemic stroke.

5.5 INTEGRATION OF FINDINGS IN PAPER I, II AND III

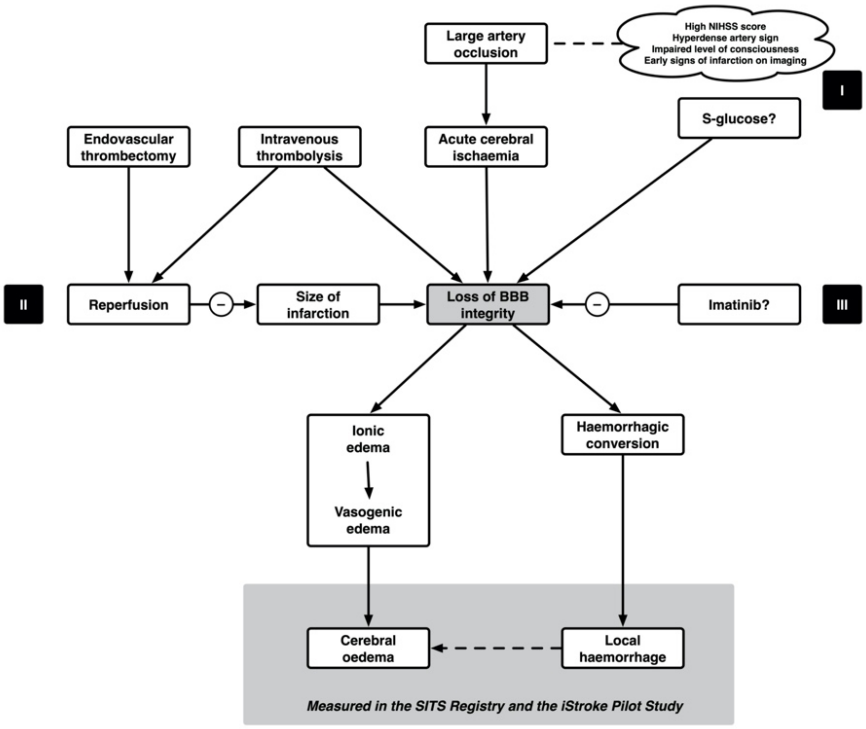

***Figure 23**. An interpretation of the results of paper I, II and III (denoted by roman numerals in black squares). Arrows with a minus ("–") sign denote a negative, or inhibiting, influence; all other arrows denote a positive influence.*

Please see figure 23 for an interpretation of results from paper I to III. According this somewhat speculative interpretation, 4 of the 5 important baseline predictors for COED presented in paper I (high NIHSS score, hyperdense artery, impaired level of consciousness and early signs of infarction) may be associated either with large artery occlusion (LAO) or extensive ischaemia of the anterior circulation in AIS. Furthermore, there is evidence from previous research that blood glucose, which was also a predictor for COED, is closely associated with, or even causative of, loss of BBB integrity. Reperfusion (paper II) decreases volume of infarction, thereby reducing damage to the tissue. Results from iStroke Pilot, a phase 2 safety study of imatinib (paper III) indicated that imatinib may reduce neurological disability in patients treated with IVT after AIS, which however remains unconfirmed while waiting for results from a further trial. Experimental evidence suggests that imatinib restores integrity of the BBB through molecular mechanisms, but this has not been shown in humans. Also depicted in the figure is the hypothesis that IVT has different effects; on one hand, the benefit of IVT using tPA in AIS is firmly evidence-based while on the other hand there is experimental evidence suggesting that tPA may contribute to damage to the BBB.

The results of damage to the BBB are twofold, as detected on neuroimaging at 22-36 hours. Transvascular (ionic and vasogenic) cerebral oedema is detected on the SITS COED scale. Haemorrhagic transformation is detected as local haemorrhage which may have a space-occupying effect as in PH type 1 and 2. For example, among the patients of paper I, the proportion of local haemorrhage with space-occupying effect, that is either PH type 1 or PH type 2, was 17.5% in patients with moderate COED and 33.0% in patients with severe COED. Local haemorrhage may contribute to COED because of this space-occupying effect, as indicated by the dotted arrow. As observed in paper II, however, adjustment for PH resulted in only a small change of the effect of recanalization on COED, indicating that most of that effect was not mediated by local haemorrhage.

5.6 DHC PATIENTS IN THE SITS REGISTRY (PAPER IV)

In this large case series of ACS patients, of which the majority (98.1%) received reperfusion therapy and all underwent DHC, it was observed that as age increased, mortality increased while the probability of a good outcome at 3 months decreased. These were statistically independent associations. Similar associations have been observed in recent observational studies of DHC patients [203-205] while other observational studies seem to disagree [206, 207]. In the present study, two thirds of all deaths occurred during the first 30 days after stroke onset. Moreover, there was a higher proportion of deaths at 3 months compared to RCTs at 6 months follow up (32.7% vs. 26%) [76]. Meanwhile, the proportion of good outcome (mRS 0-3) at 3 months was lower compared to RCTs at 6 months (13.9% vs. 20%) [76].

The differences in outcomes between this study population and randomized trials of early DHC could be attributed to a number of factors, only some of which were measured. The length of follow-up affects outcomes which could be seen as a shift between mRS categories between 6 and 12 months in randomized trials of DHC [115, 86, 121]. If the pattern in this study population was similar to those studies, there would after 6 or 12 months be more deaths, inflating the mortality, and a shift towards lower, i.e. better, mRS for the surviving patients. Later versus early DHC is associated with worse outcomes [208, 209]. However, timing of surgery was not registered. Diabetes has been associated with worse outcomes in DHC [208, 204]. Other predictive factors that have been described in DHC are infarction volume [210] and myocardial infarction [208], none of which were registered in this study. Similar to this study, a higher proportion of males compared to RCTs was observed also in other cohorts [203, 211]. This probably reflects the higher incidence of stroke among men compared to women [211].

The age distribution of this study population seems to be similar to randomized trials while outcomes still differ in subgroups of age. Patients aged ≤60 years had a mean age (49.5 years) that was comparable to the mean ages (43.2, 43.4 and 51.6 years) of the DHC treated groups in the 3 randomized trials that were pooled into an analysis with outcomes reported at 12 months [116]. Compared to that analysis, these patients from the same age stratum had slightly higher mortality (25.2% at 3 months versus 22% at 12 months) and lower proportion

of good outcome (16.6% at 3 months versus 43% at 12 months). Patients aged ≥61 years had a median age (67 years) that was roughly similar to the median age (70 years) of the treatment group of DESTINY II which reported outcomes at 6 months [121]. Compared to DESTINY II, our patients from the same age stratum had higher mortality (47.8% at 3 months versus 33% at 6 months) while the proportion of good outcome was similar (8.4% at 3 months versus 7% at 6 months). However, the proportion of mRS 0-4 was lower (22.6% versus 39%).

Involvement of right-sided vascular territory was more common than left-sided. Bias toward DHC patients having right-sided vascular involvement has been described earlier [212-214]. In addition, the finding that median NIHSS at baseline was around 4 points lower in right-sided vascular involvement versus left-sided, was repeated [134, 133].The present results indicate that in this international cohort, there was a tendency to accept DHC in infarctions of the right (usually non-dominant) hemisphere versus the left (usually dominant) hemisphere, even though right-sided lesions had lower median NIHSS than left-sided. Reasons for this may include difficulty in neurological assessment or obtaining consent in aphasic patients as well as ethical considerations regarding the patient´s future quality of life. In a multicentre survey, physicians preferred DHC on the non-dominant side [215]. However, several studies have failed to show an influence on long-term functional outcome by affected side and such considerations are not recommended in guidelines [216-218, 111, 219].

5.7 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

5.7.1 Remarks on terminology

Slightly different definitions of the widely used terms “predictor” and “outcome” can be found in the literature. The term predictor is related to exposure, determinant and, in multivariable models, independent variable [220, 131]. Terms related to outcome are endpoint, response and, in multivariable models, dependent variable [220, 131]. As the words are used in this doctoral thesis, a predictor temporally precedes and is associated with an increased probability of the outcome. A causal connection between predictor and outcome is not necessary; however, a research goal may be to infer a causal link. Examples of predictors include NIHSS score (paper I), recanalization (paper II), age (paper III) or imatinib treatment (paper IV). Some examples of outcomes are severe COED, mRS score 0-2 and being dead.

5.7.2 Validity and precision

Internal validity is the degree to which a study is free from systematic error and measures what it was intended to. Precision is the degree to which a study is free from random error [221].

Sacket [222] described a classification of 35 types of different systematic error into 6 groups. A practical classification, however, is into 3 large groups: selection bias, information bias and confounding [223, 224]. Selection bias occurs when the sample is biased so that participants have a different association between exposure and outcome than the non-participants that

were left out of the study but were theoretically eligible [224]. It can be produced at any time during a study, for example as a result from the process of selecting study participants or as a result of loss-to-follow-up [225]. Information bias is measurement error which is also called misclassification. When misclassification of a variable is related to other variables, it can cause differential misclassification in which the association is over- or underestimated [224]. Cohort studies and randomized trials, for example, can be sensitive to differential misclassification where the outcome is misclassified depending on exposure [226]. Confounding occurs when a measured or unmeasured factor is associated with both exposure and outcome while not being a part of the causal pathway from exposure to outcome [227, 228]. Confounding should be taken into account when assessing studies that aim for causal interpretations of associations. This is in contrast to studies that aim to predict an outcome or find an association that is not going to be causally interpreted, where confounding is usually less of a problem [154, 229].

Generalizability, or external validity, is a term for how well the results of a study can be applied to other populations that did not participate [221].

5.7.3 Limitations of registry studies (paper I, II and IV)

Paper I, II and IV report observational studies based on retrospective analysis of data collected from the SITS Registry. These studies have some limitations that are shared by registry studies in general, as well as some limitations that are more or less specific for the SITS Registry.

Limitations of registry studies in general

Loss to follow-up is often an issue in observational studies [230]. If the mechanisms of loss are random, the precision of the study is diminished. If dropouts are differential by exposure, so that the patients selectively drop out from one of the exposure groups, there may be bias. If the losses are differential by both exposure and outcome, there is almost certainly selection bias [231]. This may however be difficult to ascertain. There was, however, evident loss to follow-up in all 3 studies. If for example patients with successful recanalization were selectively lost from follow-up at 3 months, there would be a potential for bias when evaluating outcomes at 3 months.

There is potential for information bias in the assessment of outcomes [230]. Blinded evaluation is difficult to do. The exposure, which is known, may give rise to expectations from the medical professionals, from patients or from relatives when evaluating outcomes. This could affect clinical outcomes such as mRS or NIHSS and the result would be misclassification of outcome [226].

While the effect of random error decreases with the size of the study population, systematic error in principle does not change [226, 232]. So, as the study population grows, precision increases and confidence intervals become narrower, whereas systematic errors remain.

Confounding can occur because of measured or unmeasured factors. The researcher is in general bound by the data available [233]. This can make it difficult to statistically control for factors that are unmeasured, including medical therapy that may affect the outcome.

Limitations specific for the SITS Registry

While the organization of the SITS Registry facilitates data collection, it also contributes to the limitations of data from the SITS Registry, as has been previously noted [141, 234-236]. Data was reported by local investigators. Since there was no regular monitoring for source data verification after 2006, the researcher using the data cannot be fully certain that all data has been entered correctly and that all consecutive patients were included according to protocol. Consequently, the potential for systematic errors, such as selection bias or misclassification, has to be taken into account. However, in 2011-12, Karolinska Trial Alliance performed an independent monitoring of some selected Swedish centres and verified that data entered in the registry from these centres are accurate. Furthermore, the SITS Registry has a logical automatic validation system that prevents the entry of erroneous or impossible data in the registry, to some extent. Also, in 2002-2006, source data verification was done by monitors.

There were probably differences in capacities and technical resources that, for example, affected the assessment of neuroimaging.

Mortality data is for death of any cause, not cause specific for stroke. If a patient is missing from follow-up, the degree in activity in searching for the patient is up to the local investigator and probably varies between persons and hospitals.

The patients of the SITS Registry are a selected group compared to the general stroke population, which may limit generalizability. In the data used in papers I, II and IV, patients had received reperfusion therapy. Patients receiving reperfusion therapy have more severe deficits as exemplified among patients in Sweden during 2018. Among all patients in the Swedish Stroke Register, the median NIHSS at baseline was 3.0. In patients that received IVT, median NIHSS score was 7.0, and in EVT treated patients the median was 15.0 [5]. Moreover, since patients in the SITS Registry were selected for reperfusion therapy, they may have less concomitant disease than patients with similar stroke severity that did not receive such therapy.

5.7.4 Limitations and strengths of paper I

17.5% (8450/42187) of the study population were lost to follow-up and did not contribute to data on death and functional outcome at 3 months. There may be selection bias. However, this was not further evaluated in the paper.

Medical anti-oedema treatment was not recorded. However, no medical therapy for COED had been proven effective in controlled trials, and the rates of decompressive hemicraniectomy had been low in published studies.

The results describe COED at 22-36 hours or any extra investigation, the timing of which was not taken into account. However, extra investigations were very rare and only 3.5% of patients had their COED status changed between 22-36 hours and any extra investigation.

An analysis of impact of infarction size on the development of COED could not be done since infarction size was not measured.

The meaning of "important variable" was operationally defined by the statistical procedure in the paper so that the finally selected variables were those that remained in several models for different degrees of COED. Which variables get selected depends on implicit decisions of the researcher as well as aspects of design, for example which statistical method is chosen, cut-off points of variables and choice of significance levels. This negatively affects the generalizability of results. That being said, however, the strengths of this paper were the large sample size of data collected at many hospitals from several countries and the adjusted analysis involving several variables that is accounted for in some detail in the paper.

5.7.5 Limitations and strengths of paper II

There was approximately 18% loss to follow up for the 3 months functional outcome, which may indicate a potential selection bias.

For most of the study population, site of arterial occlusion could not be assessed through neuroimaging; it was inferred through a classification system with the aim of collecting patients with supratentorial large-vessel occlusion.

There are some issues regarding the measurement of exposure. For most patients, the recanalization was indirectly detected through HAS as a surrogate marker for vessel occlusion. Moreover, time of recanalization was not observed. However, recanalization probably tended to occur early as all patients received recanalizing treatment. Recanalization followed by re-occlusion may theoretically have occurred, although unlikely.

Since COED and PH were detected on the same neuroimaging examination, relations of temporality are not completely clear.

There may be residual confounding. However, covariates were selected on both statistical and nonstatistical grounds and furthermore a test of robustness was used.

The strengths of this study were the large sample size of data collected at many hospitals from several countries, the adjusted analysis and consistent results regardless of multivariable model.

5.7.6 Limitations and strengths of paper III

The study was planned as a safety study and the small sample size necessitates any observations on efficacy to be confirmed in a larger trial.

This was an open-label study. Patients and their relatives knew whether the patient was in the control group or received imatinib. If the patient was allocated to treatment, they may even have known to which dose group. With the exception of the final follow-up at 3 months, treatment groups were known all investigators and staff when they assessed clinical outcomes such as NIHSS scores. Thus, there was some potential for misclassification of clinical outcomes depending on treatment group, prior to the final follow-up, most likely based on people´s expectations of treatment in increasing doses improving outcomes more than control. However, regarding the direction of differences between treatment groups, the assessment of functional outcome and NIHSS score at 3 months were in agreement with results from the first 8 days. This is noteworthy since the evaluation at 3 months was done with the investigator blinded to treatment group.

The frequency of EVT was substantially higher in the high-dose group than the other groups, including control. In the high-dose group 71% underwent EVT compared to 29% in the control group (intention-to-treat population). Since EVT improves the prognosis, there is potential baseline imbalance where patients undergoing EVT, thereby having a better prognosis, were included in the high-dose group. The randomization procedure should on average distribute pre-treatment factors, such as EVT, equally over treatment groups thus achieving comparability for the follow-up [237, 238]. However, randomization can be trusted to distribute factors evenly between treatment groups only on average and imbalances may remain, especially if the sample size is small [239, 224]. Furthermore, a successively increasing proportion of thrombectomies in the population from which study participants were sampled could hypothetically affect the high-dose group which was recruited towards the end of the study period, making it difficult to fully compensate for this imbalance with randomization. However, the results were adjusted for mechanical thrombectomy and, when stratified by thrombectomy, the result was fairly robust, although the number of patients was small.

Most of the analysis regarding efficacy was done on the per protocol population instead of the intention-to-treat population, as is usually recommended in randomized trials, for example in the CONSORT statement [240]. Five patients were either moved between treatment groups or excluded. However, none of these 5 patients were taken from the high-dose group, and only 1 patient was moved to control group. Therefore, it is unlikely that this would cause an overestimation of the main finding of the per protocol analysis.

The strengths of this study were the thorough registration of clinical and adverse events, thereby fulfilling the primary objective of this phase 2 trial, and furthermore the randomization procedure, the blinded reading of neuroimaging and the blinded follow-up at 3 months. Finally, this was an example of a successful cooperation between 5 hospitals in the Stockholm region, including the study coordination that was needed in order to follow acute stroke patients during transfer between hospitals, in acute treatment and during follow-up.

5.7.7 Limitations and strengths of paper IV

There were discrepancies in the data that could be explained by misclassification. For example, while most of the study population had moderate or severe COED at 24 hours, the presence of no COED in 15.9% and mild COED in 8.1% needs explanation. Later aggravation of COED is one plausible explanation. However, patients may instead have been included without having undergone DHC, since DHC status was entered once and there were no additional procedures to check that this information was correct. Another plausible explanation is misclassification of COED.

There was loss to follow-up. Approximately 30% of DHC cases were lost to follow up in that they did not contribute to calculations of mortality due to missing data. This subgroup had some baseline characteristics that indicate a better prognosis compared to the full study population. It is likely that the results at 3 months, for the remaining patients, were biased toward higher mortality and worse functional outcome.

The lack of data relating to the DHC procedure decreases the generalizability of the study. There are no data on timing, indications, complications or other surgery related details that affect the prognosis. The lack of timing particularly complicates comparisons with randomized trials, since late DHC is associated with worse outcomes. Another consequence of the lack of data is that we have to assume that, among patients in the study population, the indication for surgery was LHI. This is, however, a reasonable assumption given that all patients had ischaemic stroke and that we excluded a group of patients with data that was consistent with posterior circulation stroke.

A strength of this study is the perspective on DHC applied in practice in 684 patients with data derived from an international database. In fact, this is one of the largest single observational study of DHC treated patients published. Furthermore, there is reason to believe that results regarding side of vascular lesions are robust and the over-representation of right-sided vascular lesions is distinct.

6 CONCLUSIONS

The most important, or strongest, baseline predictors for early COED are baseline NIHSS, hyperdense artery sign, signs of early infarction, level of consciousness, and higher blood glucose, characteristics that from previous studies are known to be associated with either a large ischemic core at baseline or BBB damage. Based on these clinical predictors, patients at risk for space-occupying COED can potentially be selected for close monitoring or treatment. Before routinely doing this, however, our findings may need to be confirmed in a prospective study with a standardized reading of image data. At the least, results can be used to create hypotheses about links between risk factors for COED, which can generate ideas for new treatments.

In patients with acute ischaemic stroke, recanalization was associated with a lower risk for COED, even after adjustment for higher rate for PH, in recanalized patients compared to non-recanalized patients at 22 to 36 hours. These results strengthen recent study results.

Treatment with imatinib, which in experimental studies of ischaemic stroke has been shown to improve blood-brain barrier integrity, is safe and tolerable in human subjects. Furthermore, results of this phase 2 safety study indicate that treatment with imatinib may reduce neurological disability in patients with acute ischaemic stroke who have received intravenous thrombolysis. Imatinib therapy is one of several emerging pharmacological therapies that may have potential effects of brain protection in a broad sense, for example through action on different parts of the neurovascular unit.

In a case series of patients with anterior circulation AIS in which a majority (98.1%) had received reperfusion therapy, and all patients underwent DHC, there was a higher proportion of death and lower proportion of good functional outcome at 3 months follow-up compared to RCTs with longer and more complete follow-up. Furthermore, outcomes worsen with increasing age. Despite caveats due to the possibility of loss to follow-up and misclassification, the study results indicate that monitoring of DHC in clinical practice, for example in treatment registries, would be very beneficial for future patients. In fact, this should probably be done. Right-sided vascular involvement was more common than left-sided which suggests that hemisphere (dominant versus non-dominant) in LHI may have an influence on treatment decision. This too requires further study and ethical discussions.

In general, this doctoral thesis added new knowledge in several aspects of cerebral oedema in acute ischaemic stroke and a potential new pharmacological therapy for acute ischaemic stroke. As paper I, II and IV reported retrospective and observational studies, results of these studies should be read with caution and further studies are required to confirm these findings. Since paper III reported a safety study, efficacy results regarding imatinib are preliminary; a phase 3 randomized controlled trial of high-dose (800 mg/day) imatinib is ongoing in Sweden.

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8 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Stroke är den vanligaste orsaken till neurologisk funktionsnedsättning hos vuxna. Cirka 15% orsakas av blödning i hjärnan. Cirka 85% orsakas däremot av att en blodpropp täpper igen en eller flera artärer (pulsådror) i hjärnan vilket kan orsaka en infarkt, alltså en hjärnskada med neurologiska symtom, exempelvis förlamning eller afasi. Detta kallas ischemisk stroke. Orsaken till det uppkommer en blodpropp kan till exempel vara förmaksflimmer (en rubbning av hjärtats rytm) eller atheroscleros (åderförkalkning) i artärerna.

Väggarna i hjärnans små blodkärl (kapillärer) består av celler som normalt är tätt sammanfogade och skapar en barriär (blod-hjärnbarriären). Om en infarkt uppstår så blir barriären mer genomsläpplig så att vätska, proteiner och eventuellt blod läcker ut till hjärnvävnaden. Ansamlingen av vätska och blod i hjärnvävnaden kallas hjärnödem. En patient som just drabbats av stroke kan på detta sätt försämras ytterligare med ökade neurologiska symtom och försämrad prognos. Denna påverkan brukar vara maximal cirka 3-5 dygn efter strokeinsjuknande men kan märkas ännu tidigare, kanske efter bara några timmar. Vid stor hjärninfarkt kan utträdet av vätska, från artärerna till hjärnvävnaden, skapa ett så högt tryck inuti skallen att patienten dör. Risken för detta är störst vid infarkter som orsakas av att mellersta hjärnartären (kalla*s arteria cerebri media*) täpps till eftersom infarkten då kan bli stor. Vid uppkomst av ödem så dör då cirka 7 av 10 patienter om ingen behandling ges.

Syftet med detta projekt var att öka kunskapen om infarktrelaterat hjärnödem, faktorer som påverkar risken att utveckla hjärnödem och dess behandling.

Faktorer som påverkar uppkomst av hjärnödem hos patienter med ischemisk stroke

Vi gjorde en undersökning bland 42 000 patienter med syfte att hitta riskfaktorer för hjärnsvullnad hos patienter som just insjuknat i ischemisk stroke. Patienterna hade registrerade i ett internationellt register som kallas SITS (Safe Implementations of Treatments in Stroke) perioden 2002-2011. Målet var att hitta de faktorer som mest påverkade risken för hjärnödem. Alla dessa patienter hade behandlats med intravenös trombolys (propplösande läkemedelsbehandling). En röntgenundersökning, datortomografi (DT) eller magnetresonanstomografi (MRT), utfördes cirka 24 timmar efter insjuknandet. Hjärnödem definierades enligt en skala i fyra steg (inget, lätt, måttligt eller uttalat) enligt utseendet på röntgen.

Vi fann att ungefär 10% av patienterna hade en måttlig eller uttalat ödem efter cirka 24 timmar. Med statistiska analyser letade vi riskfaktorer för hjärnödem bland de data som fanns registrerade för patienterna. Den viktigaste riskfaktorn var stora neurologiska symtom vid ankomst till sjukhus, konstaterat genom höga poäng enligt skalan NIHSS (National Institutes of Health Stroke Scale) som är ett standardiserat sätt att mäta neurologiska bortfall och symtom. En patient med stora neurologiska symtom hade en flerfaldigt ökad risk för måttligt eller uttalat hjärnödem efter 24 timmar. Andra faktorer som var associerade med ökad risk för

hjärnödem vid 24 timmar var om röntgenundersökning visade tecken på blodpropp i en större artär i hjärnan, om patienten hade sänkt medvetandegrad, om det fanns en synlig infarkt på DT eller om blodsocker var förhöjt. Kunskapen kan potentiellt användas för att välja patienter för extra noggrann övervakning.

Den största begräsningen i våra slutsatser är att eftersom vi inte själva kunde styra över datainsamlingen så kan det finnas andra faktorer som egentligen är viktigare eller bättre på att förutsäga hjärnödem.

Rekanalisering och risk för hjärnödem hos patienter med ischemisk stroke.

Detta var en undersökning av risken för hjärnödem hos patienter där DT eller MRT visar tecken på att den artär som gav upphov till en patients strokeinsjuknande hade öppnats upp (rekanaliserats). Detta är viktigt då rekanalisering idag är grunden vid akut behandling av ischemisk stroke. Med intravenös trombolys (propplösande läkemedelsbehandling) och trombektomi (propplösning vid ett kateterburet ingrepp i hjärnans blodkärl) försöker man lösa upp blodproppen inom några timmar efter insjuknandet. En del tidigare forskningsresultat har pekat på en ökning av risken för hjärnödem vid rekanalisering. En sådan riskökning skulle i så fall kunna förklaras med att behandlingen återställer blodflödet i skadad hjärnvävnad där även blod-hjärnbarriären är skadad. Vi undersökte risken för hjärnödem hos de 22 184 patienter i SITS-registret där den första röntgenundersökningen visade en tilltäppt artär i hjärnan. Alla patienterna fick någon behandling som syftade till rekanalisering. Röntgenundersökning 24 timmar efter insjuknandet gav information om dels rekanalisering och dels graden av hjärnödem. Hjärnödem definierades enligt en skala i fyra steg (inget, lätt, måttligt eller uttalat) enligt röntgen.

Hos patienter där hjärnartären hade rekanaliserats var risken att drabbas av måttligt eller uttalat hjärnödem nästan halverad jämfört med patienter där artären fortsatte vara tilltäppt (13.0% jämfört med 23.6%). Denna fördel kvarstod trots att fynd av blödning i hjärnan vid 24 timmar var lite vanligare hos de patienter där artären hade öppnats. Våra resultat talar alltså för att rekanalisering ger en påtaglig minskning av risken för hjärnödem.

En begränsning i våra slutsatser är att vi för majoriteten av patienterna saknade säkra data på var någonstans i hjärnan blodproppen var belägen. Detta fick härledas indirekt, med hjälp av symtomen. En annan begränsning i våra slutsatser är att våra data om öppning av artärer har en viss osäkerhet då de mestadels kom från DT- och MRT undersökningar där blodproppen avbildades utan att man gjorde kontrastundersökning.

Imatinib-behandling av patienter med ischemisk stroke

Under 2011-2016 genomfördes på fem sjukhus i Stockholm iStroke-studien där läkemedlet imatinib gavs till 60 patienter i akutfasen av akut ischemisk stroke. Djurförsök med modeller av ischemisk stroke hade tidigare visat att imatinib kan öka blod-hjärnbarriärens täthet och minska negativa konsekvenser av ischemisk stroke såsom hjärnödem och blödning. Imatinib finns sedan tidigare registrerat för andra indikationer än stroke. Huvudsyftet var att

genomföra en fas 2-prövning av imatinib vilket innebar att man för första gången gav detta läkemedel till patienter som har stroke. Studien var randomiserad, det vill säga att slumpen avgjorde vilka patienter som fick behandling respektive inte fick behandling med imatinib. Imatinib gavs som tablett under 6 dagar med början samma dag som patienten togs in på sjukhus med akut stroke. Syftet var att studera biverkningspanorama samt anpassa en acceptabel dos.

Det viktigaste resultatet av denna studie var att imatinib, givet till strokepatienter som har fått trombolysbehandling, har en god säkerhetsprofil med acceptabla biverkningar. Utöver det kan man inte dra några säkra slutsatser avseende effekten av imatinib vid ischemisk stroke. Man noterade emellertid en förbättring av de neurologiska symtomen framför allt hos de patienter som erhöll den högsta dosen imatinib (800 mg per dygn), vilket fordrar bekräftelse i en mer omfattande studie. Denna pilotstudie har nu följts upp av en större pågående studie av imatinib (iStroke del II).

Kirurgisk behandling av patienter med hjärnödem efter ischemisk stroke.

Vi redovisade 684 patienter ur SITS-registret som haft ischemisk stroke och sedan genomgått hemikraniektomi, en neurokirurgisk operation som brukar utföras vid stort hjärnödem. Vid operationen görs en hemikraniektomi vilket betyder att en del av skallbenet tas bort tillfälligt, så att hjärnan kan expandera utåt istället för inåt. Operationen är dekompressiv (tryckavlastande) eftersom den syftar till att minska trycket inuti skallen. Patienternas medianålder var 56 år, den yngsta patienten var 20 år och den äldsta var 86 år. De hade insjuknat med stora strokesymtom och nästan alla hade fått rekanaliserande behandling. Fler hade infarkt i höger hjärnhalva jämfört med vänster.

Vid röntgenundersökning 24 timmar efter insjuknandet hade 75% ett måttligt eller uttalat hjärnödem enligt en skala i fyra steg (inget, lätt, måttligt eller uttalat). Patienterna följdes upp 3 månader efter insjuknandet i stroke. Vid denna uppföljning registrerades att 13.9% hade ett utfall enligt modifierad Rankinskala mellan 0 och 3, det vill säga "måttlig funktionsnedsättning" eller bättre. Måttlig funktionsnedsättning innebär att patienten behöver viss hjälp, men klarar att gå utan hjälp av någon annan person. Andelen som hade dött någon gång mellan operationen och 3-månaderskontrollen var 32.7%.

Dessa resultat, både funktionsnivå enligt Rankinskalan och andelen döda, är sämre än vad som redovisats i de noggrant utförda kliniska prövningar av dekompressiv hemikraniektomi som tidigare publicerats. Det skulle kunna tala för att detta ingrepp, när det utförs i rutinsjukvård, har ett sämre resultat än vad som tidigare redovisats i samband med forskningsstudier som utfört randomiserade prövningar.

En begränsning i studien var att det inte fanns någon information registrerad om själva operationen eller hur lång tid som förflöt mellan strokeinsjuknande och operation. Resultatet bör alltså tolkas med försiktighet. Det är dock befogat att uppmärksamma denna patientgrupp och systematiskt följa upp de patienter som genomgår dekompressiv hemikraniektomi.

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