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TREATMENT AND LOGISTICS OF ACUTE ISCHEMIC STROKE: SAFETY AND OUTCOMES

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Treatment and logistics of acute ischemic stroke: safety and outcome
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To my wife, Henrietta and my daughter, Sonja. Eternally grateful for your love and support.

To my parents, Olga and Mark, for encouraging me to be curious and to challenge myself.

To my brother, Henrich, for not letting me off the hook too easily.

POPULAR SCIENCE SUMMARY OF THE THESIS

The “vascular” in cardiovascular disease does not only refer to blood vessels to the heart, but also the blood vessels supplying the brain. When a clot in these vessels keeps nutrients and oxygen from reaching the brain, its cells rapidly lose function, causing sudden symptoms such as paralysis or loss of speech. In medical terms, this is referred to as an ischemic stroke and it is a matter of minutes before nerve cells are irrevocably lost. Because of this, the effect of treatment aiming to restore blood flow is highly time-dependent, explaining the popular adage among stroke neurologists that “time is brain”. Yearly, around 20,000 people are hospitalized due to a stroke in Sweden, but only about 3,000 receive treatment with either an intravenous clot busting drug (intravenous thrombolysis - IVT) or mechanical removal of the clot using a catheter inserted into the blood vessel (endovascular thrombectomy - EVT).

A potentially harmful side effect of IVT is a brain hemorrhage, which occurs in 1/20 people receiving the treatment. However, the risks of treatment are less understood in two groups which are the subjects of two component studies in this thesis. Study I concerns stroke mimics: any condition that can cause symptoms that look like a stroke. Inadvertently treating a patient with a mimicking condition is unnecessary, as the patient won’t benefit from the treatment. Simultaneously, the risk of treatment is poorly understood. The findings presented in the first study show that the risk of harm with accidental treatment of a patient with a mimicking condition is low. The second study compares risk of IVT between stroke caused by a clot in the anterior (front side) and the posterior (back side) blood vessels supplying the brain. Anterior stroke has long been the focus of stroke research as the symptoms are easier to spot, and it is far more common than posterior stroke. Study II showed that the risk of brain hemorrhage after IVT is lower in posterior stroke, which is important information needed to assess the risk of treatment in each individual patient.

EVT is a very effective treatment for ischemic stroke that can only be performed by highly trained specialists at university hospitals in Sweden. Access is also limited by the size of the affected blood vessel, as it needs to be large enough to allow access with the catheter. Because “time is brain”, eligible patients would ideally be taken to a capable hospital for EVT treatment, but this is complicated by limited resources such as hospital beds, as well as transportation logistics. In 2017, the Stockholm region started having ambulance nurses test patients with suspected stroke using two simple neurological tests (weakness of the arm and leg), combined with a telephone call to a stroke neurologist at the university hospital. This system is used to identify patients that could benefit from EVT and would need to be taken to the university hospital. Previously, patients with suspected stroke were taken to the nearest hospital. Study III found that patients transported by ambulance using the new system were treated faster and had less symptoms after their stroke compared to those treated during the old system. Study IV used statistical modeling to see if the system could be improved so that more patients were taken to the right hospital immediately. Without adding information that is not already a part of clinical routine, no alternatives were better than the original.

ABSTRACT

BACKGROUND: Stroke, both ischemic and hemorrhagic, accounts for over 20000 hospital admissions in Sweden yearly. The vast majority of patients (85%), suffer from ischemic stroke, an occlusion of a cerebral artery that can be treated pharmacologically with systemic intravenous thrombolysis (IVT) or mechanically with endovascular thrombectomy (EVT). Treatment with IVT carries the risk of symptomatic intracerebral hemorrhage (SICH) in 2-5% of cases, potentially leading to severe disability or death. There remain unanswered questions regarding the safety of IVT in specific subgroups: (1) patients without ischemic stroke, but who present with stroke-like symptoms, known as stroke mimics, and (2) patients suffering from stroke in the posterior cerebral circulation (PCS). EVT is an effective treatment, but only possible for patients suffering from stroke caused by a large artery occlusion (LAO stroke) and is restricted to thrombectomy capable centers with trained neurointerventionists. The Stockholm Stroke Triage System (SSTS) was implemented in 2017 to detect and route patients with suspected LAO stroke and eligible for EVT directly to the thrombectomy center.

The first half of this thesis concerns safety and outcomes after IVT in patients with stroke mimics (study I) and PCS (study II). The second half of the thesis concerns acute stroke logistics through use of the SSTS. Study III investigated if outcomes after EVT have improved after implementation of the SSTS. Study IV described patients incorrectly routed using the system and investigated if the system could be improved using statistical modeling. Studies I-II were performed using data from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Registry (SITS-ISTR), an international database. Studies III-IV included prospectively recruited patients with suspected acute stroke transported by ambulance in the Stockholm region.

Study I included patients treated with IVT between 2003-2017 with MRI follow-up. Outcomes were parenchymal hematoma, SICH, and modified Rankin scale score and death at 3 months after treatment, with comparison between stroke mimics and ischemic stroke. Five parenchymal hemorrhages, and two SICH were identified in 429 stroke mimic patients treated with IVT. Functional symptoms, headache and seizure were the three most common mimicking conditions (>60% total). There was a higher proportion with excellent functional outcome and lower proportion of dead patients in the stroke mimic group. IVT treatment was concluded to be reasonable safe in patients with a stroke mimic diagnosis.

Study II included patients treated with IVT between 2013-2017 with available angiographic occlusion data. Outcomes were the same as in study I, with comparison between anterior and posterior circulation stroke. Adjustment of baseline differences using inverse probability treatment weighting, and a systematic review and meta-analysis were performed. Of ~5000 included patients, ~15% had PCS. Both the primary data and the meta-analysis showed fewer hemorrhagic complications in PCS. After adjustment, PCS patients had a slightly higher risk of death after treatment, with no differences in functional outcomes.

Study III included patients treated with EVT between October 2017 and October 2019 (during use of the SSTS) in the Stockholm region. Comparison was performed with historical controls treated during the two years prior. The main outcome was modified Rankin Scale scores with adjustment for baseline differences. Secondary outcomes were death, change in NIHSS 24 h post treatment, recanalization, and SICH. Time from onset to EVT was faster during SSTS by 69 minutes. Functional outcomes were better in the SSTS group with no differences in safety outcomes (hemorrhage and death).

Study IV included suspected stroke patients transported by ambulance between October 2017 and October 2018 in the Stockholm region. Three alternative triage algorithms were modelled using prehospital data and compared to the SSTS using decision curve analysis. All models included a test for hemiparesis and had similar sensitivity, specificity, and AUC. Comparison of net benefit, (correct routing of patients for EVT without increasing mistriage) showed that the SSTS was superior to the alternative models.

LIST OF SCIENTIFIC PAPERS

I. Keselman, B; Cooray, C; Vanhooren, G; Bassi, P; Consoli, D; Nichelli, P; Peeters A; Sanak, D; Zini, A; Wahlgren, N; Ahmed, N; Mazya, M V

Intravenous thrombolysis in stroke mimics: results from the SITS International Stroke Thrombolysis Register

European Journal of Neurology. 2019;26(8):1091-97

II. Keselman, B; Gdovinova, Z; Jatuzis, D; Melo, T P E; Vilionskis, A; Cavallo, R; Frol, S; Jurak, L; Koyuncu, B; Paiva Nunes, A; Petrone, A; Lees, K; Mazya, M V

Safety and Outcomes of Intravenous Thrombolysis in Posterior Versus Anterior Circulation Stroke: Results From the Safe Implementation of Treatments in Stroke Registry and Meta-Analysis

Stroke. 2020;51(3):876-882

III. Keselman, B; Berglund, A; Ahmed, N; Bottai, M; von Euler, M; Holmin, S; Laska, A.-C.; Mathé, J; Sjöstrand, C; Eriksson, E; Mazya, M V

The Stockholm Stroke Triage Project – outcomes of endovascular thrombectomy before and after triage implementation

Stroke. 2021 (online, DOI: 10.1161/STROKEAHA.121.034195)

IV. Keselman, B; Berglund, A; Ahmed, N; Grannas, D; von Euler, M; Holmin, S; Laska, A.-C.; Mathé, J; Sjöstrand, C; Eriksson, E; Mazya, M V

Analysis and modeling of mistriage in the Stockholm Stroke Triage System

Submitted manuscript

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LIST OF ABBREVIATIONS

WHO	World Health Organization
AHA	American Heart Association
ASA	American Stroke Association
ICH	Intracerebral hemorrhage
SAH	Subarachnoid hemorrhage
DALY	Disability adjusted life years
ICA	Internal carotid artery
VA	Vertebral artery
ACA	Anterior cerebral artery
MCA	Middle cerebral artery
PCom	Posterior communicating artery
Acom	Anterior communicating artery
PCA	Posterior cerebral artery
BA	Basilar artery
PICA	Posterior inferior cerebellar artery
AICA	Anterior inferior cerebellar artery
SCA	Superior cerebellar artery
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
ASCOD	Atherothrombosis; Small vessel disease; Cardiac pathology; Other causes; Dissection
AF	Atrial fibrillation
OR	Odds ratio
CHA_2DS_2-VASc	Congestive heart failure; Hypertension; Age ≥ 75; Diabetes mellitus; previous Stroke or transient ischemic attack; Vascular disease; Age 65-74; Sex
TIA	Transient ichemic attack
ABC score	Age, biomarkers, clinical history score
ESO	European Stroke Organisation
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
MAP	Mean arterial pressure
ICP	Intracranial pressure
EEG	Electroencephalography
SEP	Sensory evoked potential
ICF	International classification of functioning, disability and health
NIHSS	National Institute of Health Stroke Scale
mRS	Modified Rankin Scale
BI	Barthel index
NINDS r-tPA	National Institute of Neurological Disorders and Stroke recombinant tissue-type plasminogen activator trial
LOC	Level of consciousness
UK-TIA	United Kingdom Transient Ischemic Attack trial
IVT	Intravenous thrombolysis
EVT	Endovascular thrombectomy
SICH	Symptomatic intracranial hemorrhage
RCT	Randomized controlled trial
rt-PA	recombinant tissue plasminogen activator
FDA	Food and Drug Administration
ECASS	European Cooperative Acute Stroke Study
EMA	European Medicines Agency
SITS-MOST	Safe Implementation of Thrombolysis in Stroke Monitoring Study
NNT	Numbers needed to treat
LMWH	Low molecular weight heparin
DOAC	Direct oral anticoagulants
WAKE-UP	The MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset trial
DWI	Diffusion weighted imaging
FLAIR	Fluid-attenuated inversion recovery
EXTEND	Extending the Time for Thrombolysis in Emergency Neurological Deficits trial
EPITHET	Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial

HI	Hemorrhagic infarction
PH	Parenchymal hemorrhage
PHr	Remote parenchymal hemorrhage
IVH	Intraventricular hemorrhage
SDH	Subdural hemorrhage
LAO	Large artery occlusion
RR	Relative risk
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 trial
DAWN	Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo trial
ASPECTS	Alberta Stroke Program Early CT score
ESMINT	European Society for Minimally Invasive Neurological Therapy
CI	Confidence interval
mTICI	modified Thrombolysis in Cerebral Infarction
MeVO	Medium vessel occlusion
PCS	Posterior circulation stroke
ACS	Anterior circulation stroke
BAO	Basilar artery occlusion
IVBSS	Israeli Vertebrobasilar Stroke Scale
FND	Functional neurological disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
HaNDL	Headache associated with acute neurological deficits and lymphocytosis
FAST	Face drooping, Arm weakness, Speech difficulty and Time
AKUT	Ansikte, Kroppsdel, Uttal, Tid
PSC	Primary stroke center
TSC	Thrombectomy capable stroke center
CSC	Comprehensive stroke center
DTN	Door to needle time
DTP	Door to puncture time
MSU	Mobile stroke unit
PPV	Positive predictive value
NPV	Negative predictive value
AUC	Area under the curve
RACE	Rapid Arterial oCclusion Evaluation Scale
LAMS	Los Angeles Motor Scale
PASS	Prehospital Acute Stroke Severity Scale
ACT-FAST	Ambulance clinical triage for Acute Stroke Treatment
M-DIRECT	Madrid-Direct Referral to Endovascular Center
SITS	Safe Implementation of Treatments in Stroke
SSTS	Stockholm Stroke Triage System
SITS-ISTR	Safe Implementation of Treatments in Stroke International Stroke Registry
AIS	Acute ischemic stroke
SM	Stroke mimic
DCA	Decision curve analysis
IPTW	Inverse probability treatment weighting
ATE	Average treatment effect
AIC	Akaike information criterion
aOR	Adjusted odds ratio
IQR	Interquartile range
OCSP	Oxfordshire Community Stroke Project
POCI	Posterior circulation infarct
TACI	Total anterior circulation infarct
PACI	Partial anterior circulation infarct

1 INTRODUCTION

> *'Tis agreed by the generality of Physitians that the Brain is the seate of the Apoplexy;*
>
> *[...] they* [the patient] *generally complain of, either a vertigo, or a great oppression and paine in the head; upon which presently follow stupidness, somnolency, dazling of the eyes, a relaxation of all parts of the body, and the like: all which are so evidently deducible from the consideration of the nerves affected at their original, that twere time lost farther to prove it.*[1]

The modern concept of stroke can be traced back to the term apoplexy, mentioned already by Hippocrates (460 BC – 370 BC) in the context of sudden paralysis.[2] The Genuine Works of Hippocrates (vol.2) provide some important insights, with remarks on epidemiology: "Persons are most subject to apoplexy between the ages of forty and sixty", as well as treatment: "It is impossible to remove a strong attack of apoplexy and not easy to remove a weak attack". While readers familiar with modern medicine may find it amusing to consider what means may have been used to "remove a weak attack" at the time, it is particularly striking that this disease, known to the world for more than 2000 years, has only been treatable for a few decades.

What has been known for some time, however, is where it is located. In the passage by William Cole quoted above and written in 1688, it is made abundantly clear that the medical establishment at the time agreed on the fact that apoplexy was a disease of the brain. The text is believed to contain the first use of the word stroke as a synonym, likely derived from the meaning of the ancient Greek word apoplexia, literally translated as "to be struck down and incapacitated". Cole further mentions Swiss pathologist Johann Jakob Wepfer (1620-1695), in that the cause may be that "the brain is… denied a sufficient afflux of bloud", which Thomas Willis (1621-1675) is referenced to have disbelieved due to the many interconnections between the blood vessels supplying the brain. The importance of this work, performed more than three hundred years ago, is illustrated not least by the "circle of Willis", which is a common term for the anastomoses of the cerebral arteries, as well as Wepfer's (albeit pre-modern) understanding of apoplexy as caused by brain hemorrhage or vessel occlusion.[3]

2 LITERATURE REVIEW

2.1 STROKE – BACKGROUND AND OVERVIEW

2.1.1 Definition and epidemiology

The working definition of stroke, in use by the World Health Organization (WHO) since the 1970's, is "a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin."[4,5] This is a pragmatic definition, in that it requires no adjunct radiological examination, and therefore can be applied equally in diverse healthcare settings for the purposes of epidemiological studies. In 2013 the American Heart Association/American Stroke Association (AHA/ASA) proposed a more complex definition of stroke, with criteria for ischemic and hemorrhagic stroke, as well as silent infarction (cell death without symptoms in the form of neurological deficits). This broader definition also includes the entire central nervous system, i.e. the brain, spinal cord, and the retina.[6]

Stroke can be broadly divided into two types: ischemic or hemorrhagic (from the Greek *ískhaimos* = "stoppage of blood flow" and *haimorrhagía* = "a violent bleeding"). Ischemic stroke constitutes the majority of stroke cases, both worldwide and in Sweden at around 85%.[5,7] The remaining 15% are caused either by bleeding in the brain tissue (intracerebral hemorrhage – ICH) or in the meninges (subarachnoid hemorrhage – SAH). The subject of this thesis is ischemic stroke and cerebral infarction – which is the term for cell death caused by insufficient blood flow to the brain.

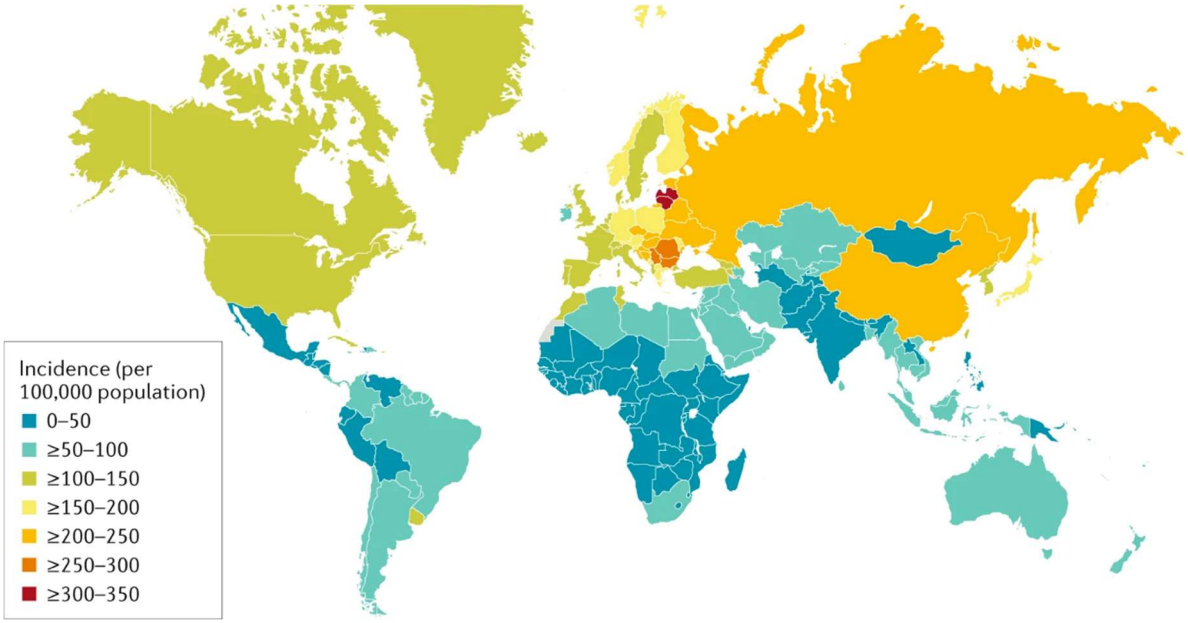

Figure 1. *The Global distribution of ischemic stroke incidence by country. Data from the Global Burden of Disease Study 2017. From Campbell and colleagues.[8] Reproduced with permission. Copyright 2019 Springer Nature.*

Globally, neurological disorders contribute to 276 million (11.6%) disability adjusted life years (DALYs), and 9.0 million (16.5%) deaths, with each DALY corresponding to one year of full health lost. Stroke is the single largest contributor in this group, accounting for nearly half of all DALYs and more than half of all deaths caused by neurological disorders.[9] The number of stroke cases in 2016 was estimated to 13.7 million worldwide, which corresponds to a decrease of 8.1% since 1990. The decrease in mortality and DALY rate during the same period was around 35%, suggesting that advances in stroke care during this time have led to more patients surviving and recovering from their strokes. However, the costs of stroke care, both in the acute treatment phase and post stroke rehabilitation remain high.[10,11] A study published in 2020, considering healthcare costs as well as social care (for patients in nursing and residential care) and productivity loss estimated a total of €60 billion in the EU in 2017.[11] In Sweden, 21,090 hospital admissions were due to stroke in 2019, with a decrease of 17% since the recorded all time high of 25,558 in 2010.[7] The healthcare costs of stroke in Sweden in 2017 were estimated to €788 million, or 1.55% of total healthcare expenditure.[11]

2.1.2 The cerebrovascular system

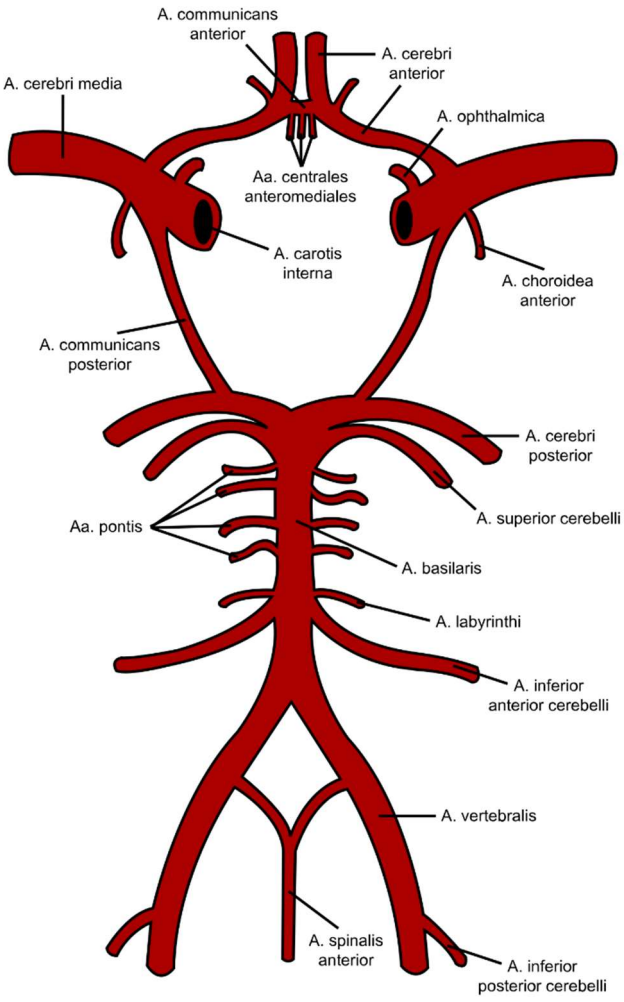

Figure 2. *Schematic representation of the circle of Willis. Names of arteries in Latin. Image in the public domain.*

The human brain accounts for 2-3% of total body mass but requires 10-20% of cardiac output as well as ~20% of available oxygen during rest.[12,13] Blood is supplied to the brain by branches of the internal carotid arteries (ICA) and vertebral arteries (VA), forming the vascular anastomosis known as the circle of Willis at the base of the brain (figure 2). The cerebral arteries are housed in the subarachnoid space, a cavity containing cerebrospinal fluid located between the pia mater and arachnoid mater. Branches of the ICA form the anterior circulation of the brain, supplying most of the cerebrum (except for the occipital lobe) as well as the thalamus, hypothalamus, pineal gland and the limbic system. The posterior circulation is derived from the VA and supplies the brain stem, cerebellum, and occipital lobe.[14] Both internal carotid arteries contribute to around 80% of cerebral blood flow, with the remaining 20% arriving via the posterior circulation.[15] The cerebral arteries form

proximal perforating arterioles supplying central structures, as well as cortical branches covering the surface of the brain. Communication between branches, called leptomeningeal or "Heubner's" anastomoses frequently occur, providing overlap between the large cerebral arteries distal to the circle of Willis.[14,16] Arterioles from these cortical branches penetrate 3-4 cm down into the white matter without further interconnections with other vessels, meaning that an occlusion here effectively denies the supplied territory with blood flow.[14,17]

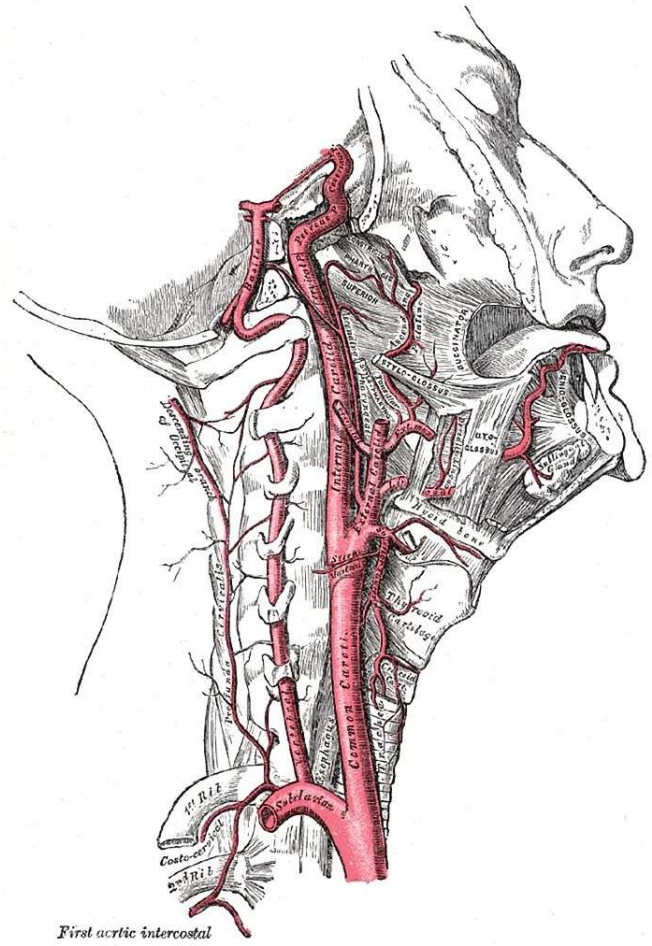

Figure 3. *Illustration of the origins of the common carotid artery and the vertebral artery as branches from the brachiocephalic trunk (right side). From Gray's Anatomy of the Human Body, 20th edition. Public domain.*

Proximally, the aortic arch branches off into the brachiocephalic trunk, which in turn branches into the right common carotid artery as well as the right subclavian artery. The left common carotid artery as well as the left subclavian are branched directly from the left side of the aortic arch. The ICA and the external carotid artery are formed from the bifurcation of the common carotid artery, with the ICA terminating in the anterior cerebral artery (ACA) and middle cerebral artery (MCA). Branches of the ICA include the ophthalmic artery, supplying the retina, the posterior communicating artery (PCom) anastomosing with the posterior cerebral artery - PCA), as well as the anterior choroidal artery. The ACA, in turn, anastomoses with the contralateral ACA through the anterior communicating artery (ACom), completing the circle of Willis.[14] Anatomical variations exist in the form of an incomplete circle of Willis (58% in a study on 150 volunteers),[18] hypoplasia of the ACA segments (or complete absence[19]), as well as varying branching patterns of the MCA.[20,21]

The VA are branches of the right and left subclavian arteries, reaching the dura mater via the transverse foramina of the cervical vertebrae. Before forming the basilar artery (BA), they branch out into the anterior spinal artery and the posterior inferior cerebellar artery (PICA). The BA supplies the brainstem, as well as the cerebellum together with the PICA via the anterior inferior cerebellar artery (AICA), superior cerebellar artery (SCA), and terminates in the PCA which supplies the thalami and occipital lobe.[14] A common anatomical variation is hypoplasia of one (35%), or more rarely both (3.4%) of the VA, and is more frequent in

patients suffering from stroke in the posterior circulation (51%).[22] Another variant is fetal origin of the PCA, meaning that supply mainly or exclusively comes from the PCom rather than the BA, present in 10-20%.[23,24] Finally, an anatomic variant of interest is the artery of Percheron – where the blood supply to both medial thalami comes from a single branch of the proximal PCA, rather than the multiple perforating branches normally present.[25,26]

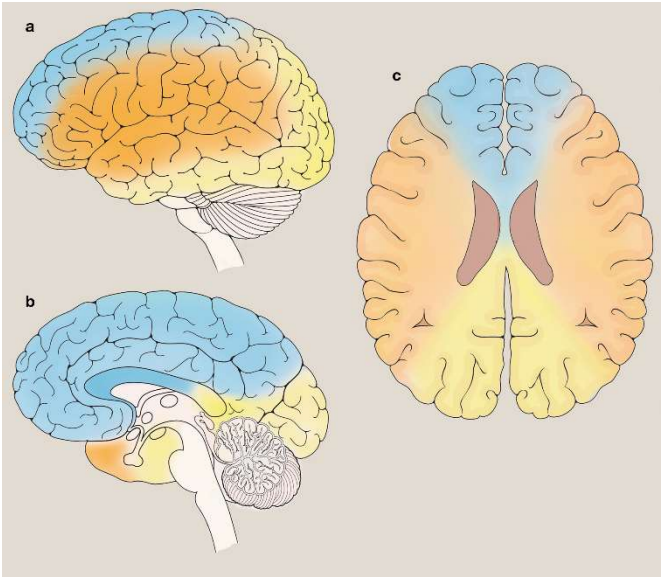

Figure 4. *Schematic distribution of cerebral vascular territories in lateral (a), sagittal (b) and axial (c) projections. Blue = ACA, orange = MCA, yellow = PCA. From Hart and colleagues.[27] Reproduced with permission. Copyright 2018, Elsevier.*

Typically, infarctions of the territory supplied by the ACA cause symptoms in the form of weakness and sensory loss in the contralateral leg, whereas a total MCA infarction causes contralateral hemiplegia, sensory loss, and hemianopia.[28,29] Occlusion of the MCA in the dominant hemisphere (usually left) additionally causes global aphasia, with hemineglect typically arising from infarction of the non-dominant hemisphere.[29,30] Occlusion of the PCA can manifest as hemisensory deficits, with bilateral thalamic infarct due to occlusion of the artery of Percheron even leading to stupor and coma. Cortical infarcts of the PCA territory typically lead to visual field defects, as well as memory impairment and aphasia.[31] Infarcts in the territory supplied by the basilar artery may present as cranial nerve deficits such as dysphagia or trigeminal sensory deficits in smaller brain stem lesions, as well as vertigo and ataxia in cerebellar infarctions. Autonomic disturbances due to medullary infarction, ipsilateral hemiparesis, as well as loss of consciousness in infarctions of the reticular activating system may also occur after basilar artery occlusion.[32] The phenotype of each individual stroke case can be quite diverse depending on individual variations in cerebrovascular anatomy, comorbidities, and stroke etiology, contributing to variations from these described textbook cases.

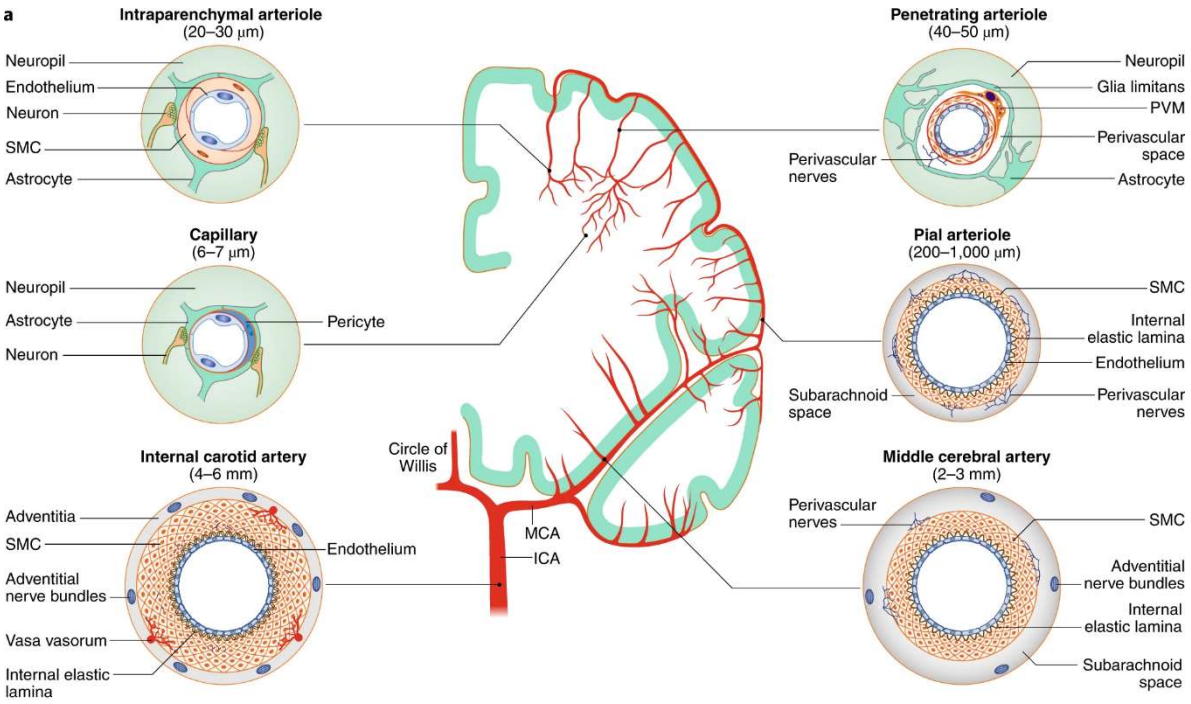

Figure 5. *Schematic visualization of the composition and diameter of the branches of the arterial cerebrovascular system. From Schaffer and Iadecola.[33] Reproduced with permission. Copyright 2021, Springer Nature.*

As cerebral vessels continue distally, branching and narrowing, the composition of the vessel walls as well as that of the surrounding brain tissue changes (figure 5). The ICA follows the histological structure of arteries elsewhere, with an innermost single layer of endothelial cells surrounded by the internal elastic lamina, followed by a large layer of smooth muscle cells and an outermost layer consisting of the adventitia and its innervation. Starting at the level of the circle of Willis, the vessels are contained in the subarachnoid space, losing some of the smooth muscle cells and the adventitia, and are innervated by perivascular plexa. After branching into penetrating arterioles, the vessels continue in the perivascular, or Virchow-Robin space, closely surrounded by glial cells. As the vessels enter the parenchyma, they are completely enveloped by astrocytes without any remaining perivascular space. Finally, the capillaries supplying the brain lose the smooth muscle cell component of the wall, consisting entirely of a single layer of brain endothelial cells.[33] These cells are connected by tight junctions, precluding the free passage of red blood cells and solutes between the blood and brain parenchyma, forming the blood brain barrier.[34] Brain capillaries are constantly perfused with blood, with the estimated cell ratio of 1:1 allowing each neuron to have its own capillary.[35]

2.1.3 Etiology, risk factors and prevention

2.1.3.1 Etiology

The causes of ischemic stroke are commonly summarized in different classification systems for use in clinical trials and clinical management, such as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) and ASCO – later updated to SSS-TOAST and ASCOD respectively. [36–39] Both systems share many similarities, with ASCOD having the benefit of an acronym and mnemonic device. A: Atherothrombosis, S: Small-vessel disease, C: Cardiac pathology, O: other causes, D: dissection.[39]

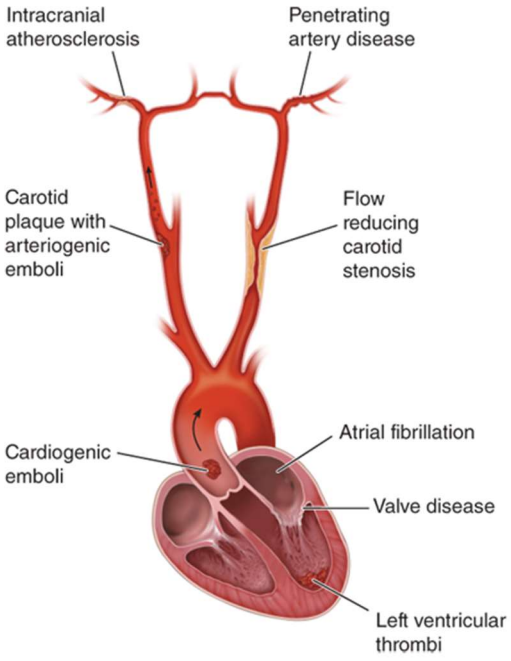

Figure 6. *Illustration of the etiologies of ischemic stroke. From Smith and colleagues: Harrison's principles of Internal Medicine. 20th Edition. Reproduced with permission. Copyright 2018, McGraw-Hill Education.*

Atherothrombosis, also termed large-artery atherosclerosis in the TOAST classification, can cause ischemic stroke by way of artery-to-artery embolization, or intracranial stenosis leading to occlusion. Endothelial dysfunction and lipid deposition with subsequent inflammation and immune cell infiltration lead to a gradual stenosis of the affected artery in the form of an atherosclerotic plaque. The fibrous cap covering the plaque undergoes thinning, increasing the risk of rupture. If the plaque ruptures, the exposed components will either migrate distally causing an embolic occlusion or activate the coagulation cascade at the rupture site – with immediate progression from stenosis to thrombotic occlusion.[40,41]

Small-vessel disease causes stroke through the occlusion of a single perforating artery either through thickening of a parent vessel due to atherosclerosis or through deposition of disorganized connective tissue in the perforating artery itself.[42] The specific term for an ischemic stroke caused by small vessel disease is lacunar infarction, named after the post-mortem findings of small holes (French *lacune* – hole) in the brain of patients that had survived an initial symptomatic stroke, performed in the 19th century.[43]

Stroke due to *cardiac pathology* is commonly attributed to atrial fibrillation (AF), which causes thrombus formation due to stagnation of blood (usually in the left atrial appendage),

with subsequent embolization to the cerebral circulation.[44] Thrombi can form in the atrium in the absence of fibrillation in cases of left atrial appendage dysfunction, which may explain some cases of embolic stroke with unknown origin.[44] Infective endocarditis may cause stroke through septic emboli, posing a challenge for clinicians in that this etiology carries a high risk of hemorrhagic transformation after thrombolysis.[45] Thrombus formation may also occur in hypokinetic regions of the heart after a myocardial infarction.[46] In cases of patent foramen ovale, emboli may travel from the venous system, across the atrial wall defect and cause embolic stroke.[47]

Other causes is a collection of relatively rare stroke etiologies, such as procoagulative states in hematological or rheumatic disorders (e.g., essential thrombocytosis, antiphospholipid syndrome or vasculitis), as well as moyamoya disease.[48–51]

Finally, *dissection* of the carotid or vertebral arteries is a rare cause of stroke in the general population, but a major contributing mechanism in patients < 50 years of age.[52] Most cases are sporadic, with trauma accounting for ~4% carotid artery dissection.[53] High levels of homocysteine in the blood as well as connective tissue disorders (e.g., Ehlers Danlos syndrome or fibromuscular dysplasia) can increase the predisposition for cervical artery dissection.[54]

2.1.3.2 Risk factors and prevention

For reasons of stroke prevention, risk factors are usually divided into modifiable (comorbidities, lifestyle factors) and non-modifiable (age, sex, and genetics). The risk of stroke increases with age, with the incidence doubling at every decade > 45 years.[55] The mean age of stroke patients in Sweden in 2019 was 75 years.[7] Due to hormonal factors such as fluctuations during and after pregnancy, as well as use of hormonal contraceptives, women have a higher risk than men at ages < 30, lower at ages 40-80, and similar at ages 80 and above.[56] There are several single gene disorders presenting with stroke, such as familial amyloid angiopathy causing rupture of cortical vessels, Fabry disease causing endothelial dysfunction, as well as Ehlers-Danlos type 4 and Marfan syndrome causing recurring arterial dissections.[57]

Among the modifiable risk factors for stroke, comorbid hypertension and diabetes mellitus, as well as smoking are shared for the etiological mechanisms of atrial fibrillation, small vessel disease and atherosclerosis.[40,42,58] In a large case-control study (INTERSTROKE) on 3,000 stroke cases (78% ischemic and 22% hemorrhagic) compared to 3,000 controls, history of hypertension had the highest odds ratio (OR) for stroke at 2.64, followed by smoking at 2.09.[59] Diabetes mellitus at 1.36 had an OR comparable to high waist-to-hip ratio (1.65) , high alcohol intake (1.51) and depression (1.35), which in turn are risk factors for AF.[58,59] In the 2019 report from the Swedish stroke registry, 64% of stroke patients had hypertension, 23% had diabetes mellitus, and 14% were smokers.[7] Interventions with the goal of stopping stroke from ever occurring (primary intervention), have been guided by the findings in INTERSTROKE that 10 modifiable risk factors account for ~90% of stroke risk, focusing

both on treating comorbidities as well as encouraging lifestyle changes and promoting healthy dietary habits.[59–61] For atrial fibrillation, the CHA_2DS_2-VASc score proposed in 2010 can be used to stratify stroke risk into low, intermediate, and high to guide clinicians in starting preventative treatment with oral anticoagulants. The acronym incorporates information on congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, previous stroke or transient ischemic attack (TIA), vascular disease, age 65-74, and sex (female).[62] Recently, a scoring system based on age, biomarkers and clinical history (ABC score) has been proposed and validated, showing better discrimination than the traditional CHA_2DS_2-VASc.[63,64]

For secondary prevention, i.e., in a patient that has already suffered a stroke, guidelines differ depending on stroke mechanism. In AF, use of the CHA_2DS_2-VASc score automatically places a patient in at least intermediate risk, with the most recent European guidelines recommending secondary prevention with non-vitamin K oral anticoagulants in non-valvular AF.[65] In cases of non-embolic, mild to moderate ischemic stroke, the European Stroke Organisation (ESO) recommends early initiation of dual antiplatelet therapy for three weeks, followed by monotherapy on the basis of four RCTs.[66–68] In the 2019 consensus statement from the ESO-Karolinska Stroke Update, further recommendations are: lowering of blood lipids with statin treatment and antiplatelet therapy in embolic stroke of unknown origin.[69] Management of diabetes mellitus and hypertension are not part of a specific strategy of secondary stroke prevention, but are covered extensively in the European Society of Cardiology guidelines on general prevention of cardiovascular disease. These guidelines state that for secondary prevention, hypertension should be treated with a two-drug combination with a target systolic blood pressure of 120-130 (<140 if aged ≥70). In diabetes mellitus type 2, treatment with SGLT2 inhibitors (gliflozins) and GLP1 receptor agonists has been shown to reduce risk of compound major cardiovascular events in patients with established atherosclerotic cardiovascular disease (such as previous stroke).[70]

2.1.4 Pathophysiology

2.1.4.1 Cerebral blood flow and the ischemic penumbra

Mean total cerebral blood flow (CBF) is ~600 ml/min (or ~50 ml/100 g/min) and decreases with increasing age.[12,13,15] The maintenance of CBF is critical in order to satisfy the high metabolic demands of the brain, an organ almost exclusively dependent on glucose metabolism while lacking extensive energy reserves.[71] The human brain consumes roughly 20% of available oxygen under normal conditions.[13] The delivery of oxygen to cerebral tissue is facilitated by the cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure (usually 60-80 mm Hg) and intracranial pressure (5-10 mm Hg): CPP = MAP – ICP. The range of the ICP is held constant at physiological conditions by regulating the intracranial volume which in turn is constituted by brain tissue, CSF, and arterial and venous blood.[72] Changes in systemic blood pressure affect the CPP, which causes compensatory changes to the CBF. When systemic blood pressure decreases, peripheral arteries relax, causing an increase in CBF and an increase of arterial blood volume which

maintains the CBF and CPP. Conversely, when blood pressure increases, peripheral cerebral arteries constrict, decreasing the CBF.[13,72] Several caveats have been introduced to the classical figure describing this relationship from the work of Lassen et al. in 1959[73], with speed being an important factor in how wide the permissible range of blood pressure change is to a constantly maintained CBF.[13]

In cases of impaired or interrupted cerebral blood flow extracranially, the anastomoses forming the circle of Willis can provide compensation in the form of the primary collateral circulation. Redistribution of blood flow between the anterior and posterior circulation can occur through the PCom, with the ACom providing interhemispheric and compensatory support in the anterior circulation. However, as stated previously, the circle of Willis is commonly incomplete.[18] Furthermore, collateral flow is dependent on blood vessel diameter, which is markedly lower in the communicating arteries (1 mm) than the anterior, posterior and middle cerebral arteries (2-3 mm).[18,74] A decompensation of the primary collateral system may lead to watershed infarction, occurring in the border zones between the large cerebral arteries due to lowered perfusion in the distal branches of the arterial system.[16,75] Secondary collateral circulation is provided by anastomoses between branches from the external carotid artery and the cerebral arteries, as well as Heubner's anastomoses, providing compensation in case of occlusion distally to the circle of Willis.[16,76] Progressive, gradual occlusion or stenosis of a cerebral artery as in moyamoya disease, can allow arteriogenesis, further increasing the vessel diameter and improving the compensatory potential of the secondary collaterals.[77,78] However, in case of sudden occlusion (e.g. clot embolism), the high vascular resistance of the anastomoses in comparison to the large cerebral arteries forming the circle of Willis, precludes full compensatory blood flow.[78] During focal ischemia, decreased blood perfusion causes dilation of resistance vessels through physiological autoregulation. As ischemia continues, lactic acid and CO2 build up stimulates further vasodilation until its maximum capacity, after which blood will flow passively with the fluctuations in systemic blood pressure.[78,79] On the capillary level, focal ischemia causes heterogenous perfusion within the ischemic tissue due to regional disturbances of microcirculation, exposing some groups of neurons to lethal levels of hypoxia despite a higher mean blood flow in the affected tissue.[78] Visualization and grading of collateral circulation has provided the pathophysiological basis for the concepts of fast and slow progressors in stroke caused by large artery occlusion.[80]

The ischemic penumbra, a concept that relates to flow thresholds for neuronal failure and remains of vital importance in the acute treatment of ischemic stroke, was introduced exactly 40 years ago (1981).[81] By using measurements of EEG and sensory evoked potentials (SEP) as proxies for neuronal function, studies performed in the 1970's demonstrated that a reduced CBF to < 15 ml/100 g/min caused impaired function in the form of a lower amplitude on the SEP and a flattening of the EEG recording.[82,83] A second threshold was found at CBF < 10 ml/100 g/min, which caused an increase of extracellular potassium (K^+), indicative of cellular membrane failure and therefore cell death.[81] Neurons affected by ischemia in the range between these thresholds would therefore be functionally silent, but still viable if the ischemia was reversed, constituting the ischemic penumbra.[81] The term penumbra, from the latin *pæne*

= “almost” and *umbra* = “shadow”, was borrowed from 17th century astronomy and describes “the half-shaded zone around the center of a complete solar eclipse”.[81] By plotting CBF against time, a schematic representation of remaining penumbra can be visualized in scenarios with varying CBF impairments at different lengths (figure 7).[84] In clinical practice, the penumbra is the target for the reperfusion therapies available in the treatment of acute ischemic stroke, as neuronal tissue that has undergone infarction can no longer be salvaged by restoring CBF.[84] Because both penumbral and infarcted neurons are functionally silent, treatment targets cannot be identified on the basis of symptomatic presentation alone. Perfusion imaging with CT or MRI can be used to identify hypoperfused neuronal tissue and differentiate it from areas that have already undergone infarction.[85]

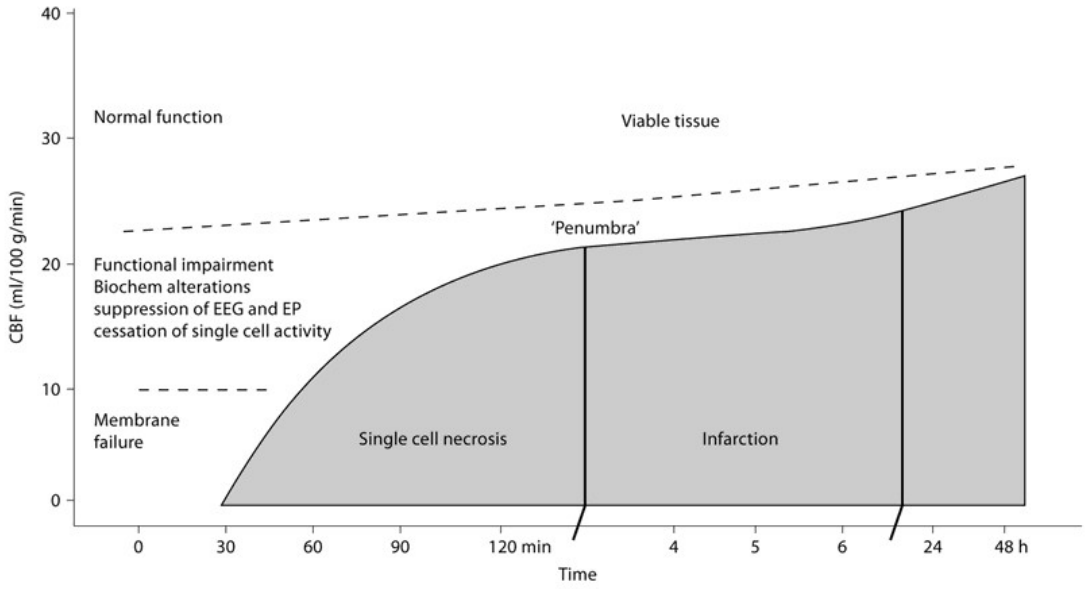

Figure 7. *A schematic representation of how penumbra decreases with increasing time and decreased CBF. From Heiss.[84] Reproduced with permission. Copyright 2011, Karger Publishers.*

2.1.4.2 Mechanisms of tissue damage

As described in figure 7, membrane failure occurs at CBF < 10 ml/100 g/min. At these levels, neurons no longer receive enough glucose and oxygen to synthesize ATP, which is required for the function of the Na^+/K^+-ATPase ion pump. This pump actively exchanges Na^+ for K^+, maintaining low levels of Na^+ and high levels of K^+ inside the cell, which are vital for the secondary transport of sugars, neurotransmitters, and amino acids across the membrane the cell requires to function.[86] CBF at these levels leads to failure of the ion pump within minutes, causing anoxic depolarization that forms the ischemic core of the infarct.[78] If the ischemia is left untreated, tissue damage progresses by means of peri-infarct cortical spreading depression. Depolarizations initiated in the infarcted neurons spread to the surrounding penumbra, which is unable to compensate the increased metabolic demands due to decompensation in the collateral circulation.[78,87] Cortical spreading depression is considered to be the pathophysiological mechanism behind the focal neurological deficits exhibited in patients with migraine aura. In these patients, without concurrent tissue damage and hypoperfusion, the phenomenon is reversible and does not lead to cell necrosis.[88]

Neuronal cell death causes the unregulated release of neurotransmitters from pre-synaptic neurons, with the excitatory amino acid glutamate being of particular importance. Clearance of glutamate in the synaptic cleft requires energy, leading to build up of toxic levels (termed excitotoxicity). Binding of glutamate to postsynaptic receptors (mGluR and NMDAR) causes influx of excess calcium inside the cell, as summarized in figure 8. The increased calcium can, in turn, induce failure of the endoplasmatic reticulum as well as mitochondria, leading to cell death in the form of apoptosis. The increase of intracellular calcium can also lead to the induction of neuronal nitric oxide synthase, with a subsequent increase in free radicals that can lead to DNA damage, intracellular structure breakdown, and induce processes leading to cell death in the form of apoptosis, autophagy, or necrosis.[8,78,89,90]

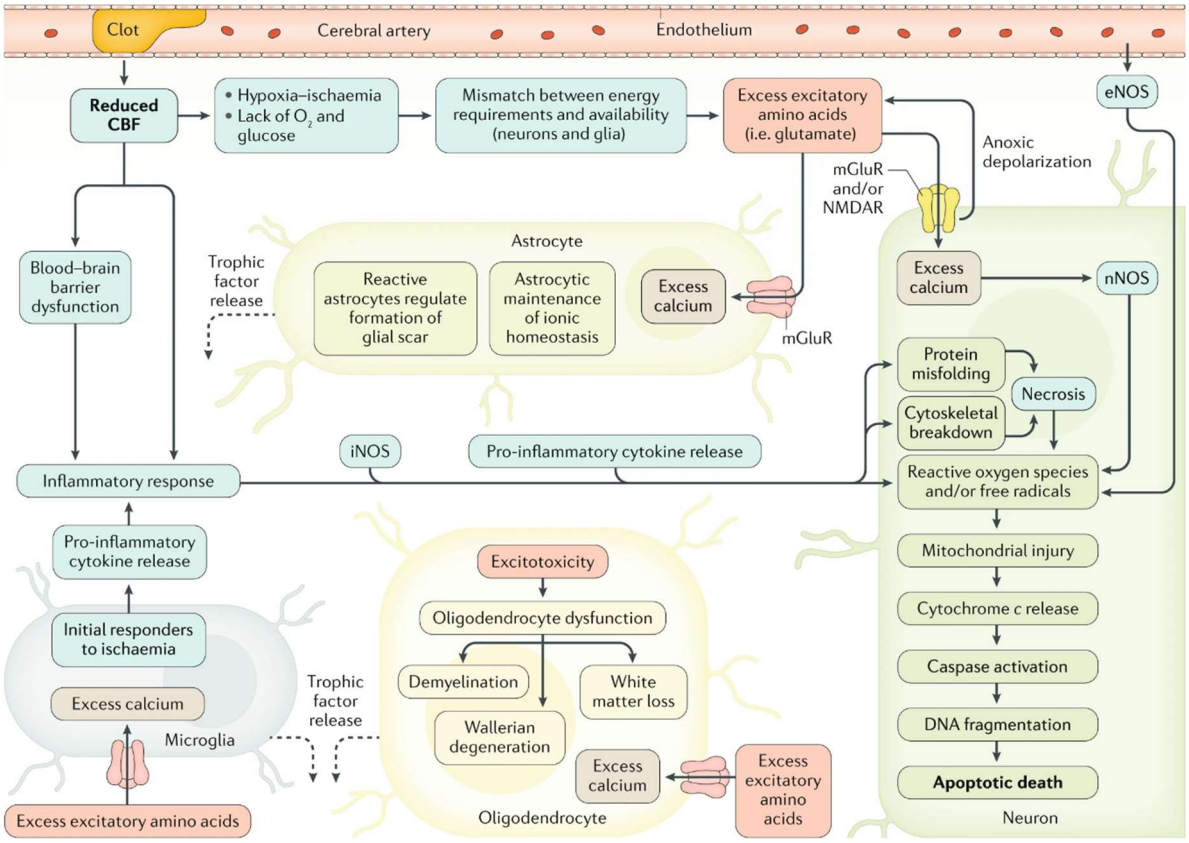

Figure 8. *Various pathways leading to neuronal tissue damage caused by ischemia. From Campbell and colleagues.[8] Reproduced with permission. Copyright 2019, Springer Nature.*

Simultaneously, occlusion of blood vessels and the subsequent hypoxia induces inflammatory signaling, formation of free oxygen radicals and the coagulation cascade, further restricting blood flow, increasing cell damage as well as recruiting immune cells to the ischemic area. This leads to breakdown of the blood brain barrier through the use of matrix metalloproteinases from macrophages, which in turn causes extravasation of blood and leukocytes into the brain parenchyma.[78,91–93] With progressive cell death, danger signals are released from affected neurons. This leads to activation and recruitment of immune cells, leading to further tissue damage and the subsequent activation of adaptive immune cells such as cytotoxic T-cells.[92] This inflammatory response is thought to be the mechanism that contributes to reperfusion injury, where the opening of an occluded artery paradoxically leads to further damage. Free radicals formed in the vessel wall during both ischemia and

reperfusion have been shown to directly affect pericytes, causing sustained contraction and inhibiting reperfusion of occluded cerebral capillaries.[94] Furthermore, reperfusion can induce the activation of glial immune cells that can cause cytotoxicity through proinflammatory signaling, as well as neuronal autophagy that can lead to cell death.[95,96]

The breakdown of the blood brain barrier in turn leads to vasogenic oedema manifesting > 24 h after the injury through leakage of osmotically active serum proteins from blood into the brain parenchyma. The dramatic clinical manifestation of this is the malignant media infarction, where damage of > 50% of the territory supplied by the MCA and subsequent vasogenic oedema can lead to transtentorial herniation compressing the midbrain, with potentially lethal consequences unless treated with decompressive craniotomy.[97] Cytotoxic oedema, which occurs when CBF falls below 30% of normal, stimulates anaerobic breakdown of glucose into lactic acid which causes swelling through osmosis. The breakdown of the sodium gradient also pulls water into the neurons after failure of the Na^+/K^+/ATPase.[78]

2.2 CLINICAL ASSESSMENT OF STROKE

As in any disease affecting the brain, stroke can manifest in a large variety of clinical phenotypes depending on the location and size of the lesion, as well as the pre-morbid characteristics of the patient. A comprehensive symptom and impairment assessment is therefore time consuming and requires competencies from different healthcare professions. This is likely one of the reasons that stroke unit care, allowing for a multidisciplinary approach, has been shown to improve the chances of patients surviving or regaining independence after a stroke.[98] In the acute setting, a full neurological examination performed by a trained physician can provide important information on possible lesion location and severity, but is by necessity highly subjective with variety in which functions are tested and how impairments are described.[99] For assessment of outcome after stroke, the international classification of functioning, disability and health (ICF), adopted by the WHO in 2001 provides a framework known as the biopsychosocial model, which is an integration of the medical and social model of disability.[100] In the medical model, disability is caused by a disease and requires intervention or treatment to be corrected, whereas in the social model, disability is caused by an unaccommodating environment that needs to be corrected.[101] In this integrated model, disability is divided into limitations on body functions and structure, activity, and participation, which in turn are influenced both by presence of a disease and contextual factors.[102] For the purposes of stroke research, several scales have been developed in order to achieve assessments that are reliable (i.e., consistent between raters and measurements) and valid (truly measure what they are intended to measure) for comparison between studies. By necessity, these scales sacrifice flexibility and are bound to omit symptoms or functional impairments that may be important for the individual patient or clinician. Symptom severity scales used in the acute phase such as the National Institute of Health Stroke Scale (NIHSS) focus on limitations in body functions and structure, while functional outcome scales such as the modified Rankin Scale (mRS) and Barthel Index (BI)

primarily concern limitations in activity and participation. The NIHSS and/or mRS were used in all four component studies of this dissertation and will be elaborated on in the following sections. The BI is the most commonly used outcome scale in rehabilitation settings and the second most common functional outcome measure in stroke trials after the mRS.[103]

2.2.1 National Institute of Health Stroke Scale

The most commonly used scale for stroke symptom severity is the NIHSS, comprised of 11 items (table 1). The NIHSS was introduced in 1989 for use in the Cincinnati/Naloxone trial and consisted of 15 items, including pupillary response, plantar reflex and change from previous examination/baseline that were removed in later versions. The scale was designed for fast bedside use, with both intra- and interreliability tested on physician and nurse examiners, as well as validity using infarction size measurements.[104] It was later modified to the current 11 items for use in the National Institute of Neurological Disorders and Stroke recombinant tissue-type plasminogen activator (NINDS r-tPA) trial.[105] During the first years of use, the scale was found to be reliable for use by neurologists, nurses and non-neurologist physicians but only after training and in a research context.[106–108] Further advantages of the NIHSS are the possibility to approximate a score from chart reviews and an association with long-term outcome after stroke.[109–111] The focus on research can make the scoring rules counterintuitive in a clinical setting. For example, a patient with severe shoulder pain and problems keeping an arm up would be scored as a motor deficit, following the "score what you see, not what you think" rule.[112] The scale has a known weight towards symptoms of left hemisphere stroke due in part to items 1.b and 1.c requiring intact language function. This has been confirmed in studies correlating CT and MRI infarct volume measurements with NIHSS score.[113,114] Furthermore, the NIHSS was specifically designed to capture supratentorial stroke symptoms, favoring areas of the brain supplied by the anterior circulation. Brain stem dysfunction such as dysphagia was not an important aspect, as patients with brain stem strokes were excluded from most clinical trials.

ITEM NAME	RESULT	SCORE
1.a Level of consciousness (LOC)	Alert	0
	Not alert, arousable	1
	Not alert, obtunded	2
	Unresponsive	3
1.b LOC questions	Answers both correctly	0
	Answers one correctly	1
	Both incorrect	2
1.c LOC commands	Obeys both correctly	0
	Obeys one correctly	1
	Both incorrect	2
2. Gaze	Normal	0
	Partial gaze palsy	1
	Forced deviation	2
3. Visual fields	No visual loss	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
4. Facial palsy	Normal	0
	Minor paralysis	1
	Partial paralysis	2
	Complete paralysis	3
5. Motor arm (a – right, b – left)	No drift	0
	Drift before 10 s	1
	Falls before 10 s	2
	No effort against gravity	3
	No movement	4
6. Motor leg (a – right, b – left)	No drift	0
	Drift before 5 s	1
	Falls before 5 s	2
	No effort against gravity	3
	No movement	4
7. Ataxia	Absent	0
	One limb	1
	Two limbs	2
8. Sensory	Normal	0
	Mild loss	1
	Severe loss	2
9. Language	Normal	0
	Mild aphasia	1
	Severe aphasia	2
	Mute or global aphasia	3
10. Dysarthria	Normal	0
	Mild	1
	Severe	2
11. Extinction/inattention	Normal	0
	Mild	1
	Severe	2

Table 1. *National Institute of Health Stroke Scale (NIHSS). Subitems with grades and scoring. Table by author.*

2.2.2 Modified Rankin Scale

The original Rankin Scale was introduced by John Rankin in 1957, in a paper describing prognosis after stroke in patients over 60. Outcome was graded I-V:

(I): No significant disability: able to carry out all usual duties

(II): Slight disability: unable to carry out some of previous activities but able to look after own affairs without assistance.

(III): Moderate disability: requiring some help but able to walk without assistance

(IV): Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance.

(V): Severe disability: bedridden, incontinent and requiring constant nursing care and attention.[115]

Changes to the Rankin Scale were made for use in the United Kingdom Transient Ischemic Attack (UK-TIA) trial in 1988, adding grade 0 for no symptoms and clarifying definitions.[116] An additional grade 6 was added later, denoting death, completing the 7 grade ordinal scale in use today.[117] Criticism has been levied against the mRS for inconsistent or imprecise wording, lack of validation and poor inter-rater reliability, leading to the development of formalized scoring, rater training as well as work on statistical analysis.[118–122] The mRS remains the most widely used functional outcome measure for stroke studies and has many advantages such as fast assessment, possibility of rating by non-physicians, as well as a wide distribution of outcomes that harmonize well with the ICF disability nomenclature.[122] The mRS has seen frequent use as a dichotomous outcome in clinical trials, usually 0-1 (excellent) or 0-2 (good). This approach has been criticized due to the loss of information inherent in converting an ordinal scale to a binary variable.[123] Recently, the shift analysis, which shows the odds of a patient improving by one point in the scale, has become more widespread as the statistical method of choice.[124–126]

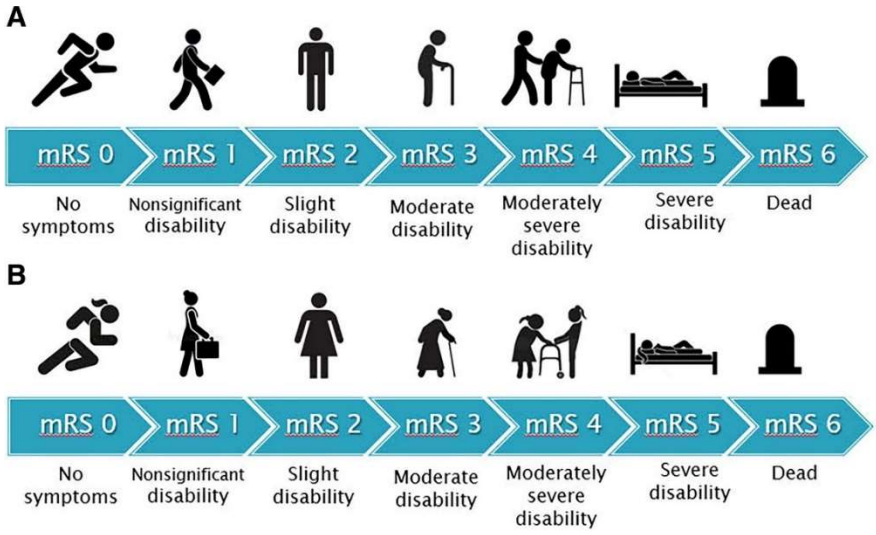

Figure 9. *Person-icons illustrating the 7 health states of the mRS. From Saver and colleagues.*[122] *Reproduced with permission. Copyright 2021, Wolters Kluwer.*

2.3 ACUTE TREATMENT OF ISCHEMIC STROKE

There are two main therapeutic avenues to achieve tissue reperfusion in acute ischemic stroke: pharmacological treatment administered intravenously to lyse the thrombus (intravenous thrombolysis – IVT) using alteplase or tenecteplase, and endovascular treatment using stent retriever thrombectomy or contact aspiration (EVT) to mechanically remove the thrombus. A common feature of all stroke treatment is the importance of timely intervention, summarized in the adage "time is brain".[127] An important risk of IVT is symptomatic intracranial hemorrhage (SICH), which occurs in 2-5% of treated patients.[128,129] As a rough approximation of the natural course of ischemic stroke, one can regard the outcomes in control groups of various earlier randomized controlled trials (RCTs), with a review from 2014 reporting 58.9 % dead or dependent (mRS 3-6) at 3 months after randomization.[130]

2.3.1 Intravenous thrombolysis

Initial studies of IVT performed using streptokinase and urokinase in the 1960s and 1970s, failed to demonstrate any beneficial effect with a simultaneous increase in the risk of intracerebral hemorrhage in the treated patients.[131,132] Initial pilot studies of recombinant tissue plasminogen activator (rt-PA) alteplase performed in 1992 established a first dosage (<0.95 mg/kg) and time window (< 180 minutes), that would be the foundation for the first randomized controlled trial (RCT).[105,133,134] This trial, abbreviated NINDS (National Institute of Neurological Disorders and Stroke rt-PA study group), demonstrated lower mRS scores compared to placebo at three months follow up, when treatment was performed within three hours from symptom onset, making alteplase the first (and only) Food and Drug Administration (FDA) approved therapy for acute ischemic stroke in 1996.[105] The time-dependent effect of alteplase was later demonstrated in a pooled analysis of several RCTs, including the European Cooperative Acute Stroke Study (ECASS) I and II, with a greater proportion of patients achieving favorable outcomes with faster treatment times.[135–137] In 2002, approval from the European Medicines Agency (EMA, previously EMEA), was contingent on an observational registry study to be performed demonstrating safety and a follow up RCT testing an extended time window. The Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST), based on the Safe Implementation of Treatments in Stroke registry (described later), concluded the safety of alteplase using real world data and was published in 2007.[138] One year later, results from ECASS III trial demonstrated effectiveness of alteplase in the extended 3-4,5 hour time window, with confirmation in an observational study from SITS published in the same year.[139,140] The efficacy of alteplase depending on time from onset to treatment can be summarized using the concept of numbers needed to treat (NNT). NNT answers the question of how many patients need to be treated in order for one more patient to achieve a positive outcome (or avoid a negative outcome). The corresponding values are 9 for mRS 0-1 and 3 for at least a 1 point improvement in mRS within 0-3 hours; 13 for mRS 0-1 and 7 for a 1 point improvement in mRS within 3-4.5 hours.[105,139]

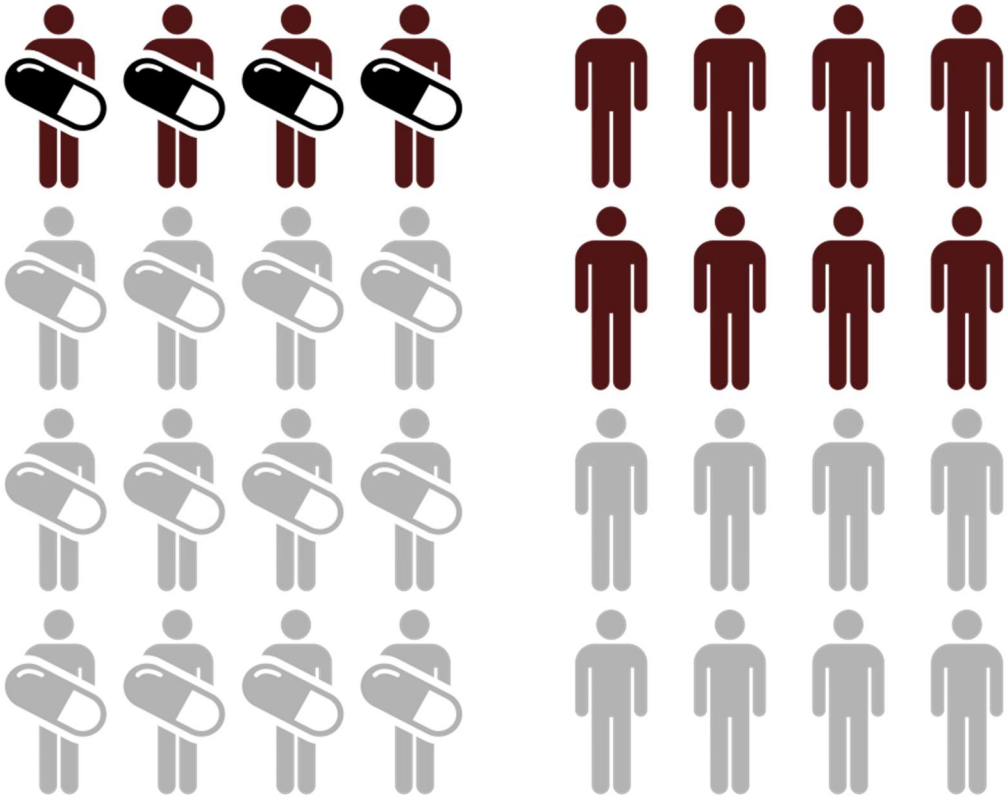

Figure 10. *Illustration of NNT = 4. The treated group (left) has a lower risk of negative outcome (dark red). In order to avoid one instance of negative outcome, four patients need to be treated. From Wikipedia, illustration by Psarka.*[141] *CC-BY-SA 4.0*

With increasing evidence and experience, guidelines have recommended use of IVT in various subgroups in whom the label has contraindicated treatment, mirroring the inclusion criteria of the pivotal IVT trials. According to the ESO and ASA guidelines, IVT, dosed at 0.9 mg/kg (maximum 90 mg) over 60 minutes with 10% given as a 1-minute bolus, is recommended in patients ≥ 18 years of age within 0-4.5 hours of symptom onset. There are no longer contraindications for age > 80, mild symptoms (as long as they are disabling), very severe symptoms (NIHSS > 25), Low Molecular Weight Heparin (LMWH) in prophylactic dose, high blood glucose (>22.2 mmol/L) and patients on warfarin with INR ≤ 1.7.[142,143] Among the remaining contraindications and important limitations are current use of warfarin with INR > 1.7 or direct oral anticoagulants (DOAC).

Recent trials have opened the possibility of IVT treatment beyond the 4.5-hour time limit. The MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (WAKE-UP) trial, a placebo-controlled RCT, randomized patients presenting outside the standard time-window for IVT by MRI, demonstrating an ischemic lesion on diffusion weighted imaging (DWI) without a corresponding hyperintensity on fluid-attenuated inversion recovery (FLAIR). Patients treated with IVT had a significantly higher proportion of favorable outcome per the mRS. There was however a trend towards higher rate of mortality and SICH in this group.[144]

A meta-analysis was performed using individual patient data from three trials: Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND - stopped due to results from WAKE-UP), European Cooperative Acute Stroke Study 4 (ECASS-4 ExTEND - stopped due to results from the DAWN and DEFUSE-trials) and Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). These trials used CT- or MRI-perfusion mismatch to guide treatment and the meta-analysis similarly demonstrated better functional outcomes in the IVT group, albeit with a trend towards higher mortality and significantly higher rate of SICH.[126] These advanced imaging modalities offer an opportunity for more detailed patient selection than in the NINDS and ECASS III trials, that used non-contrast CT in order to exclude patients with intracranial hemorrhage or a large infarction.[105,139] The current ESO guidelines recommend IVT 4.5 to 9 hours from symptom onset (or midpoint of sleep in wake up stroke), but only in patients where EVT is not planned and in centers with access to the imaging modalities used in the trials.[143]

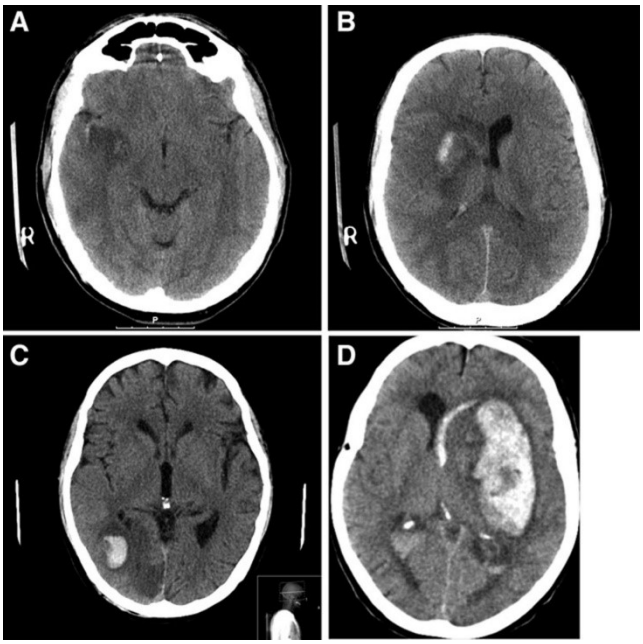

Figure 11. *CT scans showing bleeding complications after IVT. A: Hemorrhagic infarction (HI) type 1. B: HI type 2. C: Parenchymal hematoma (PH) type 1. D: PH type 2. From von Kummer and colleagues.[147] Reproduced with permission. Copyright 2015, Wolters Kluwer.*

Important risks with IVT are hemorrhagic complications early after treatment. In its mildest form, infarcted brain tissue may undergo petechial hemorrhagic transformation. In more severe forms, hematomas, with or without mass effect, may arise within or outside infarcted brain parenchyma.[145,146] The Heidelberg bleeding classification has provided terminology for hemorrhagic complications after reperfusion therapy, visualized in figure 11 and described in table 2.[147] A symptomatic intracranial hemorrhage (SICH) should ideally be classified according to the likelihood the bleeding to have caused neurological deterioration, with an HI1 unlikely to cause symptoms due to its small size.[147]

The frequency of SICH after IVT occurs in 2-5 % of treated patients, depending on definition. [128,129] SICH according to the National Institute of Neurological Disorders and Stroke (NINDS) is the most inclusive, defined as an intracerebral hematoma regardless of size and a simultaneous increase in NIHSS of at least 1 point or leading to death.[105] The European Cooperative Acute Stroke Study (ECASS II) definition requires 4 points worsening of NIHSS[137], whereas the Safe Implementation of Treatments in Stroke Monitoring Study (SITS-MOST) definition requires the demonstration of a large hematoma with significant mass effect, as well as 4 points worsening of NIHSS.[138] SICH regardless of definition is

associated with poor 3-month outcome and increase risk of death in patients treated with IVT.[148] Meanwhile, it is important to note that the more radiologically liberal definitions, NINDS and ECASS II, may erroneously label as SICH patients with a few petechia within extensive infarcts (HI1), who may have deteriorated for other, non-hemorrhagic reasons. Several risk scores have been designed to assess the risk of SICH after IVT, commonly using NIHSS, age, systolic blood pressure, and pre-treatment glucose levels in their calculations.[129,149]

CLASS		ABBREVIATION	DESCRIPTION
Hemorrhagic transformation of infarcted brain tissue (class 1)	1a	HI1	Scattered small petechiae, no mass effect
	1b	HI2	Confluent petechiae, no mass effect
	1c	PH1	Hematoma within infarcted tissue (< 30%), no substantive mass effect
Intracerebral hemorrhage within and beyond infarcted brain tissue (class 2)	2	PH2	Hematoma occupying ≥ 30% of infarcted tissue with mass effect
Intracerebral hemorrhage outside the infarcted brain tissue or intracranial/extracerebral hemorrhage (class 3)	3a	PHr	Parenchymal hematoma remote from infarcted brain tissue
	3b	IVH	Intraventricular hemorrhage
	3c	SAH	Subarachnoid hemorrhage
	3d	SDH	Subdural hemorrhage

Table 2. *The Heidelberg bleeding classification, from von Kummer and colleagues.[147] HI: Hemorrhagic transformation. PH: parenchymal hematoma. Reproduced with permission. Copyright 2015, Wolters Kluwer.*

Tenecteplase, compared to alteplase, has a longer half-life allowing for bolus injection of the entire dose and is more fibrin-specific, making it a theoretically attractive alternative in medical therapy of ischemic stroke.[150] The NOR-TEST trial showed similar outcomes and safety when comparing tenecteplase with alteplase and could not demonstrate superiority.[151]

This was followed by EXTEND IA TNK, a smaller trial (n=202), comparing alteplase vs tenecteplase in patients eligible for EVT. The trial demonstrated higher rates of recanalization at first angiographic assessment with significance both in superiority and non-inferiority vs alteplase.[152] A study pooling patients with complete vessel occlusion from two RCTs comparing alteplase and tenecteplase has similarly shown higher rates of recanalization as well as higher odds of mRS improvement.[153] In light of these findings, the 2021 ESO guidelines now recommend tenecteplase over alteplase within 4.5 hours of treatment onset in patients eligible for EVT.[143]

2.3.2 Endovascular thrombectomy

An occlusion of a proximal artery supplying the brain, or large artery occlusion (LAO), can cause a subtype of ischemic stroke with potentially severe consequences for the untreated patient but which may be accessible for a particularly effective recanalization treatment – EVT. Even with IVT treatment, only 25% reach functional independence at 3 months and the 3-month mortality is 20%. It is estimated that around 40% of acute ischemic stroke is caused by large artery occlusion, but accounts for > 60% of unfavorable outcome after stroke (mRS 3-6).[154]

	mRS 0-2	Death	SICH
IVT (RR)	1.18	1.05	3.54*
EVT (RR)	1.50	0.85	1.05**

Table 3. *Summary of treatment effect for intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) on functional independence (mRS 0-2), death and symptomatic intracranial hemorrhage (SICH) expressed as relative risk (RR) *: Within 7-10 days **: Within 90 days. Data adapted from Cochrane meta-analyses on IVT and EVT.*[130,155]

Initial small randomized trials of endovascular therapy for stroke were performed in 1998, testing intra-arterial thrombolysis using pro-urokinase for MCA occlusion stroke with promising results for recanalization and better outcomes compared to placebo or IV heparin only when started within 6 hours.[156,157] This was followed by a similar study on 16 patients with posterior circulation stroke (BA or VA occlusion) in 2005, with a higher proportion of patients with good outcome when treated within 24 hours.[158] In 2013, a disheartening year for EVT, two large RCTs failed to show superiority over IVT alone using different techniques (e.g. aspiration, stent retriever, intra-arterial thrombolysis). However, as CT angiography was not part of routine practice in many participating hospitals, presence of a large artery occlusion prior to attempted EVT was not ascertained.[159,160] This issue was addressed in five RCTs with results published in 2015 and summarized in a meta-analysis, showing that EVT treatment in combination with medical therapy compared to IVT alone doubled the proportion of patients with functional independence (mRS 0-2), with a statistically non-

significant trend towards lower mortality at 15%.[161–166] In these trials, almost all patients had an occlusion of the intracranial ICA, M1, or M2 (98%) and those with posterior circulation stroke were excluded entirely.[166] The latest breakthrough came in 2018, when results were published from two RCTs: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) and Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN). These trials used automated software to measure infarct volume (RAPID, iSchemaView Inc.), showing that EVT can be effective in selected patients with an occlusion in the anterior circulation up to 24 hours after symptom onset.[167,168] Radiological screening for early infarct signs in several of the studies was performed using the Alberta Stroke Program Early CT score (ASPECTS).[161,163–165,168] Originally introduced in 2000 for use in guiding treatment with IVT, ASPECTS has a maximum score of 10 (for no early ischemic signs) and subtracts one point for each affected part of the MCA territory.[169]

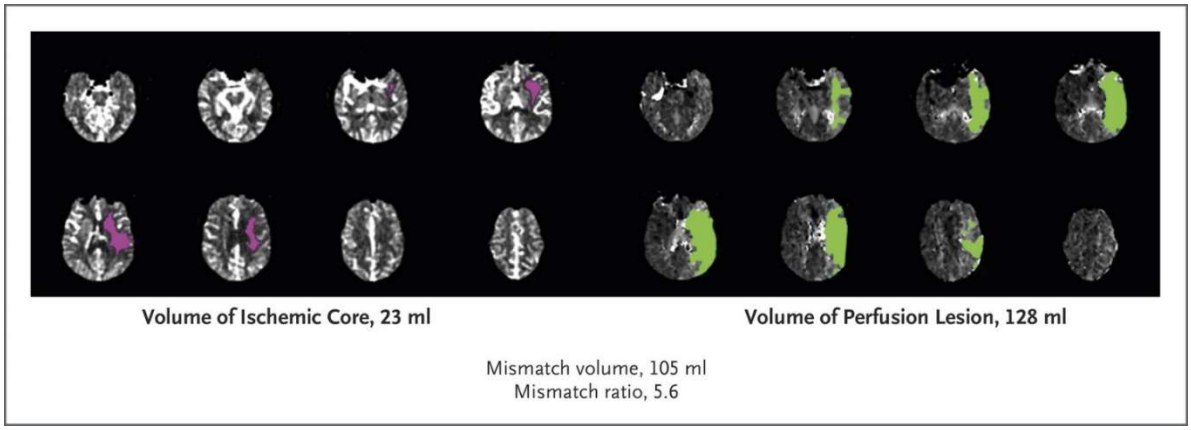

Figure 12. *Example of patient in the DEFUSE 3 trial with mismatch between ischemic core and perfusion lesion, representing the ischemic penumbra. From Albers and colleagues. Reproduced with permission. Copyright 2018, Massachusetts Medical Society.*

Evidence summarized in the ESO – ESMINT (European Society for Minimally Invasive Neurological Therapy) guidelines published in 2019 shows clear superiority of EVT using stent retriever techniques in combination with medical therapy, compared to medical therapy alone within 6 hours of symptom onset and up to 24 hours after onset in patients meeting the inclusion criteria for the DAWN and DEFUSE 3 trials. In the early time window, a patient with LAO stroke and an ASPECTS of ≥ 6 can be eligible for EVT, without the need for perfusion imaging. There is no contraindication with concurrent use of IVT or oral anticoagulants.[170] Furthermore, a Cochrane review of 19 studies and a total of 3,793 patients providing risk ratios (RR, 95% CI), showed an increased chance of mRS 0-2 at 3 months follow up (1.50, 1.37-1.63) and a lower risk of death (0.85, 0.75-0.97).[155] Reperfusion effect after thrombectomy is graded using the modified Thrombolysis in Cerebral Infarction (mTICI) score. The mTICI scale grades reperfusion from 0 (no perfusion), 1 (minimal perfusion), 2 (partial perfusion), to 3 (complete reperfusion). Commonly, the mTICI scale is dichotomized 0-2a (2a: < 50% reperfusion) vs 2b-3 (2b: > 50% reperfusion), with the latter constituting successful reperfusion. A subcategory of 2c (near complete reperfusion with

slow flow or distal emboli) has been shown to be better associated with good functional outcome, but has not replaced the 2b-3 dichotomization.[171,172]

The definition of "large artery" varies somewhat, but usually includes the intracranial portion of the ICA, the M1 segment of the MCA and the BA.[154] As the concept of the large artery occlusion has evolved together with EVT use, later studies have included more vessels such as the intracranial VA, the P1 segments of the PCA, the A1 segment of the ACA and the M2.[173–176] The term medium vessel occlusion (MeVO) has been suggested for the M2/M3, A2/A3 and P2/P3 segments.[177] Occlusions in these sites may present as primary occlusions as well as after fragmentation of a proximal large artery thrombus and are commonly treated using EVT with promising results on safety and outcomes, albeit without current guideline support.[178]

As yet, there is insufficient evidence to say if EVT is effective in posterior circulation stroke.[155] Results were published in 2020 from an RCT performed in China, but the trial was terminated prematurely due to poor recruitment and high crossover.[179] However, the treatment is used routinely in many thrombectomy centers and observational data suggests efficacy without raising safety concerns.[180–183] In all previous trials of EVT, IVT was offered to all eligible patients as this was the only approved therapy for acute ischemic stroke. Recently, this combination has been the subject of several ongoing RCTs, investigating whether patients eligible for EVT should undergo IVT at all.[184–186] However, available evidence from smaller RCTs as well as a large observational study do not support foregoing IVT in patients that are planned for EVT treatment.[187–189]

2.4 POSTERIOR CIRCULATION STROKE

Posterior circulation stroke (PCS) is a subtype of acute ischemic stroke caused by occlusion in the vertebral arteries or their branches (i.e., the vertebrobasilar system). Presenting symptoms of distal PCS may be subtle, as a cortical infarction in areas supplied by the PCA (the terminal branch of the vertebrobasilar system) can cause e.g., achromatopsia (loss of color differentiation); prosopagnosia (inability to recognize faces); or Anton's, syndrome (cortical blindness with denial of blindness and confabulations); in addition to the "classic" anopsia caused by occipital lobe infarction. These may not be the most common clinical syndromes of PCS, but serve as an illustration of deficits that may be easily overlooked in an initial neurological examination performed in the emergency department. In cases of proximal PCS, symptoms range from cranial nerve dysfunction (e.g., dysphagia, diplopia, hearing loss) to coma, or locked-in-syndrome (quadriplegia, facial and tongue paralysis with spared consciousness due to pontine infarction). Brain stem infarctions can cause a relatively large number of deficits despite a small infarct volume due to the dense organization of cranial nerve nuclei. Meanwhile, stroke syndromes of the cerebellum are characterized by vertigo, ataxia and nystagmus.[190]

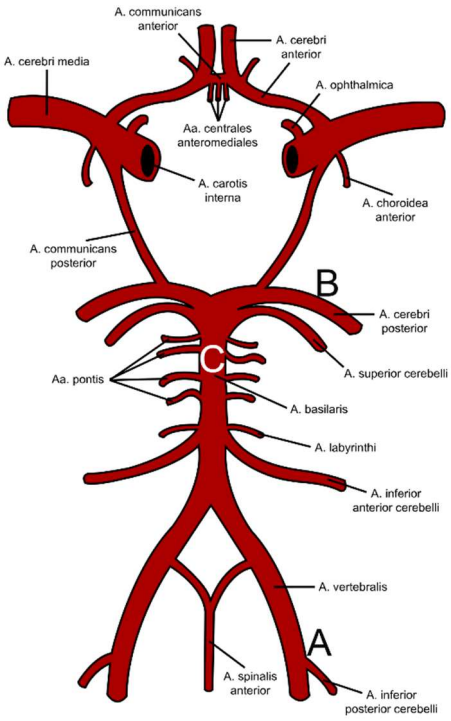

Figure 13a. *Schematic representation of the circle of Willis. Names of arteries in Latin. Image in the public domain, adapted to show sites of occlusion causing infarct changes shown in figure 13b.*

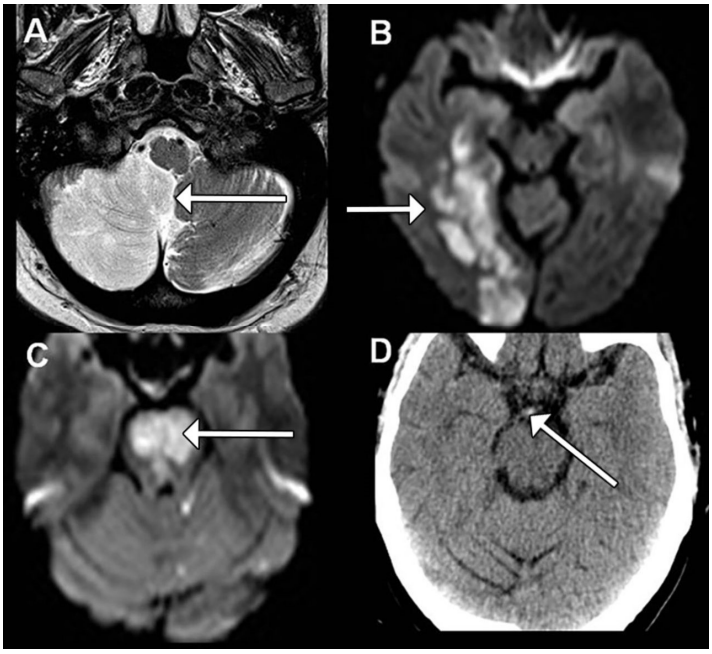

Figure 13b. *Imaging findings of infarction caused by occlusion in figure 13a. A: T2 weighted MRI showing a lesion of the right cerebellar hemisphere caused by an occlusion of the PICA. B: Diffusion weighted MRI showing an infarction caused by occlusion of the right PCA. C: Diffusion weighted MRI showing an infarction caused by occlusion of the basilar artery. D (not shown in figure 13a): non-contrast CT showing dense vessel sign, indicate of an occlusion of the basilar artery. From Merwick and Werring.*[191] *Reproduced with permission. Copyright 2014, BMJ Publishing Group Limited.*

PCS was under-represented in the initial clinical trials of IVT in acute ischemic stroke. The proportion of patients with PCS in the 1995 NINDS trial was 5%, and the patient group was excluded in the ECASS-I and II trials.[105,136,137] The same pattern was seen in the trials of EVT, where patients with PCS were excluded altogether.[166–168] Results from treatment of PCS have therefore been limited to observational studies and the proportion of IVT treated patients with PCS varies between 5-16%.[192–195] Several studies (total n=3231) have shown lower risk of SICH after IVT in PCS compared to anterior circulation stroke (ACS).[193–196] However, other studies (total n=879), have found no such difference in safety.[192,197,198] These heterogenous results may be explained by the relatively small sample sizes in the latter studies, making them insufficiently powered to detect any difference. Furthermore, only the largest study showing less risk of SICH post IVT could demonstrate a difference in functional outcome in favor of patients with PCS.[194]

As noted previously, the NIHSS was designed with stroke trials in mind and is explicitly focused on symptoms occurring in anterior circulation stroke.[112] Therefore, it does not grade potentially disabling symptoms such as balance disturbance, dysphagia and vertigo, which may be the reason why stroke severity per the NIHSS does not correlate with infarct size in

PCS.[199] This is likely why several studies have shown a markedly lower NIHSS among patients with PCS.[200–203] However, in the subpopulation of patients with severe stroke (NIHSS ≥ 25) the proportion of PCS rises steeply to 36%.[204] These are likely patients with basilar artery occlusion (BAO), which can present with tetraplegia, coma or in a locked-in state and are known to have a poor prognosis despite treatment with IVT.[205] An alternative to the NIHSS exists in the form of the Israeli Vertebrobasilar Stroke Scale (IVBSS), with including assessment of diplopia, dysphagia and gait. This is a stroke scale designed in order to quantify symptoms from PCS, which has been studied and validated, but is not used in routine clinical practice.[206]

2.5 STROKE MIMICS

There are several conditions that can cause symptoms that mimic a focal neurological deficit with sudden onset and can be mistaken for a stroke. These stroke mimics lack clear definitions and subcategorizations, as differences in clinician training and experience will produce a variation in how similar to stroke a presentation needs to be to qualify as a stroke mimic. Differential diagnosis is further complicated by stroke chameleons, ischemic stroke with atypical presentations that are often mistaken for other disorders.[207]

The management of acute stroke patients in most primary stroke centers (without EVT capability) mirrors that of the initial RCTs for alteplase in which imaging with non-contrast CT was used to exclude patients with hemorrhage or a large established infarction.[105,139] In practice, this means that the decision to administer IVT is based on clinical presentation and negative radiological findings, risking treatment of patients with a mimicking condition. Initial imaging of patients with suspected stroke using CT is generally preferred to MRI because of lower costs, easier use and faster acquisition time.[208] However, multiple studies have found that MRI using DWI (see also section 2.3.1) is better at diagnosing ischemic and hemorrhagic stroke than CT.[209–211]

The proportion of patients with suspected stroke ultimately diagnosed with a mimicking condition varies highly between clinical settings and the diagnostic criteria used. In a 2013 review, including 8839 patients, almost half of those with suspected stroke in the ambulance setting were found to have a stroke mimic. The proportion declined to 26% in the emergency department and further to 8% in a specialized stroke unit – highlighting the complexity involved in recognition and correct diagnosis of stroke symptoms, as well as the importance of training and experience.[207] The 20 most common causes of mimicking symptoms found in this meta-analysis are listed below. The figure also illustrates that risk factors for mimicking conditions, by necessity, must be presented per diagnostic category as they vary widely between groups.

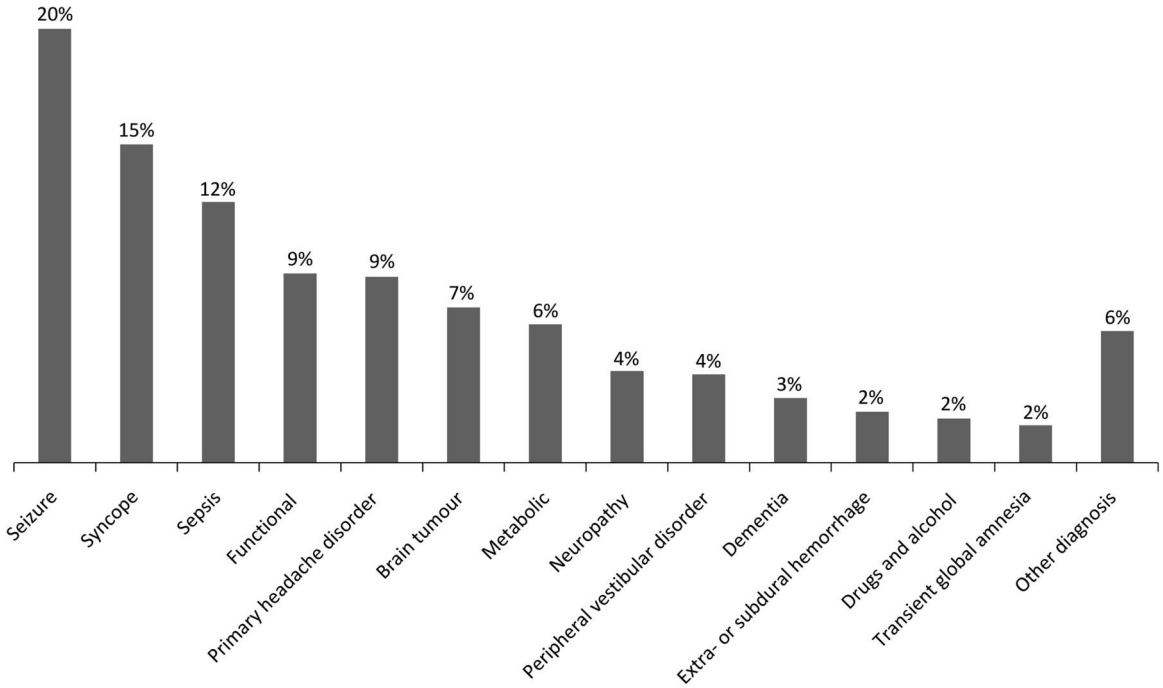

Figure 14. *Proportion of stroke mimic categories in various clinical settings, identified in a systematic review. From Fernandes and colleagues.[207] Reproduced with permission. Copyright 2013, BMJ Publishing Group Limited.*

Reported proportions of stroke mimic patients treated with IVT vary with setting and definitions, with a large multi-center study finding 2%[212], and several single-center studies as high as 7-17%.[213–216] However, with continued efforts to decrease time from patient arrival to treatment with IVT, there are concerns that the proportion of patients with stroke mimics given IVT may rise, incurring unnecessary costs and potentially risking hemorrhagic complications.[217]

The risk of SICH after IVT treatment of stroke mimics has been shown to be low. A multi-center European study found one case of SICH per the ECASS II and one case of SICH per the NINDS definition. Both patients recovered from the symptoms caused by the hemorrhage.[212] Current ASA guidelines refer to these data, stating that initiating IVT is preferred over delaying treatment and that the risk of SICH in SM is "quite low".[218] A meta-analysis of nine studies using the SICH definition "imaging evidence of intracerebral hemorrhage with an NIHSS increase of ≥4 points", found 2/392 (0.5%) such cases, compared to 417/8085 (5.2%) in the ischemic stroke group.[214]

The three most common diagnostic groups receiving IVT despite a discharge diagnosis other than stroke are: ***epileptic seizure*** (i.e. Todd's paralysis), ***functional*** (psychogenic/conversion disorder) and ***primary headache disorders*** (most commonly migraine, but including other benign conditions with headache being the main symptom).[212,219] Other important causes include recrudescence, where symptoms from a previous stroke are unmasked due to infection, toxicity or metabolic dysfunction, as well as peripheral vertigo caused by inner ear dysfunction, acute MS and neoplasia.[220]

2.5.1 Epileptic seizures

Todd's paralysis (alternatively postictal paresis) was first described by R.B. Todd in 1849 and is a focal, transitory, neurological deficit appearing after an epileptic seizure that can mimic stroke.[221] The paresis is one of the clinical manifestations comprising the postictal syndrome, which is a state that immediately follows seizure termination. Neurophysiologically and radiologically, the postictal state is characterized by suppressive patterns on EEG examination and hyperintensities that generally do not follow known vascular territories on diffusion weighted MRI.[222,223] Symptoms of postictal syndrome follow the areas of the brain affected by the seizure. After a tonic-clonic seizure (with either generalized or focal onset), the patient gradually returns to consciousness with a period of impaired orientation and memory.[223] However, after a seizure with lateralized motor or speech phenomena the postictal syndrome may cause paresis or aphasia, lasting up to 36 hours.[224] A study of 328 patients undergoing evaluation for epileptic surgery via video-EEG showed postictal paresis in 13.4 % of patients. In these highly selected patients, the majority of cases were preceded by evident motor phenomena, but 10% showed no motor seizures whatsoever. In this study, the symptoms were always unilateral and contralateral to the seizure focus. The median duration of postictal paresis was 173 s, but could be longer (range 11 seconds - 22 minutes) after tonic-clonic seizures.[225]

The mechanism causing postictal syndrome is unknown, but neuronal exhaustion and active inhibition have historically been postulated as explanations.[226,227] More recently, hypoperfusion and hypoxia due to vasoconstriction secondary to the epileptic seizure has been proposed, which may explain the phenomenon of so-called "heraldic" seizures precipitating an ischemic stroke.[228–230] Further complicating diagnosis is the finding that ischemic stroke can precipitate seizures in the acute phase, with rare cases occurring within 24 hours of the infarction.[231] The ASA guidelines state that treatment with IVT is reasonable in patients with seizures at symptom onset "if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon."[142]

2.5.2 Functional disorders

Functional neurological disorder (FND) is an official term in the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and has evolved from the more problematic "hysterical conversion" and conversion disorder used previously.[232,233] The condition was erroneously thought to be exclusively female (from the Greek *hystera* = "uterus") or requiring a precipitating psychological trauma that was mentally converted into physical symptoms.[234] The change in nomenclature no longer implies a cause, which reflects the uncertainty surrounding the mechanisms underlying the symptoms. Predisposing factors can be psychological trauma and stress, previous injury to the affected limb or a previous stroke.[235] Physiological arousal caused by a panic attack and dissociative processes may be the precipitating cause.[235] A psychological component of FND is likely, as symptoms are often internally inconsistent, attention dependent, and phenotypes often conform to prevalent false ideas about how neurological symptoms manifest.[236,237] Functional neuroimaging has

shown a difference between FND and voluntary (feigned) weakness, providing neurobiological support for FND as a disease entity in its own right.[237] FND is common in the context of suspected ischemic stroke. In a study published in 2015, with a total of 1106 patients admitted to a stroke unit in London, 163 were medical mimics and 98 were functional (8.9%). Patients with FND were younger and more commonly female with fewer cardiovascular risk factors than in the true stroke and medical mimic groups. Common comorbidities in the functional group were asthma, migraine, depression, and back pain.[238] However, differences at the group level are not a reliable aid in the diagnosis of the individual patient in an acute setting.[239] The diagnosis of FND is not one of exclusion, but should be based on positive signs such as deficit inconsistency, Hoover's sign, give-way weakness and non-anatomical focal disturbance.[236] To the author's knowledge, there have been no reported bleeding complications after IVT treatment of an FND stroke mimic.

2.5.3 Headache

Between 3 and 20% of stroke mimics belong to the primary headache disorders group.[214,240] A large subcategory is migraine with aura, affecting roughly 4% of the world's population with a female predominance of 3:1.[241,242] The aura phenomenon, in which a patient experiences focal neurological symptoms prior to the headache, can cause focal neurological deficits such as paralysis, aphasia or scotoma, suggestive of an ischemic stroke. The mechanism is thought to be caused by cortical spreading depression with subsequent changes in cerebral blood flow that are reversible in contrast to the phenomenon seen in ischemic stroke (see also section 2.1.4.2.).[243] The typical clinical course of a migraine aura provides important diagnostic information, as the progression from one affected area to the next is for an ischemic lesion.[207] A typical migraine aura subsides with time, but can in rare cases precede a migrainous infarction, typically affecting the posterior circulation.[244] A Swedish twin registry study has shown a 27% increased risk of stroke in patients suffering from migraine with aura.[245] Rare headache disorders that may be harder to diagnose as stroke mimics are familial hemiplegic migraine, and headache associated with acute neurological deficits and lymphocytosis (HaNDL). A family history, if possible, will provide insight on the former, as familial hemiplegic migraine is autosomal dominant with a high penetrance.[207] HaNDL typically occurs in young patients with few risk factors for cerebrovascular disease and shows no abnormalities on brain imaging. The symptoms spontaneously resolve, but may recur several times during a three month period.[207,246] Importantly, headache may obscure a stroke chameleon, as more than one quarter of patients with acute stroke (ischemic and hemorrhagic) present with headache.[247]

2.6 PREHOSPITAL STROKE TRIAGE

With the advent of the first treatment for ischemic stroke came the necessity to organize a system of care that could rapidly identify and transport patients to a specialized stroke center for diagnosis and treatment: prehospital stroke triage. Historically, important subjects of stroke triage have been the early recognition of stroke symptoms and reliable stroke mimic screening. Since 2015 and the proven effectiveness of EVT, a major issue has been the

differentiation of patients that would benefit from the more advanced care available at hospitals providing EVT or if the nearest stroke center would suffice.

The time-dependent effect of stroke treatment means that there is a large focus on reducing time from symptom onset to arrival at the hospital. Limited recognition and awareness of stroke symptoms in the general public is a known reason for prehospital delay shown in several studies.[248,249] Internationally, the acronym FAST (**F**ace drooping, **A**rm weakness, **S**peech difficulty and **T**ime to call 911/999) has been promoted by the American Stroke Association as well as the National Health Service in the UK.[250,251] In Sweden, the acronym AKUT (**A**nsikte, **K**roppsdel, **U**ttal, **T**id) has been used in public awareness campaigns to spread knowledge about the initial symptoms of ischemic stroke, as well as a tool for emergency medical personnel for use in recognition of stroke symptoms.[252,253] Importantly, the AKUT test does not focus specifically on arm weakness, but allows for weakness of the leg as well (Swedish *kroppsdel* = "limb").

Following recognition, the patient must be transported to a hospital capable of providing acute stroke treatment. Due to economic and geographic factors, access to different levels of stroke care varies greatly within and across countries. In a recent survey study of 44 European countries, 2/44 did not have any hospitals capable of IVT treatment and 4/44 could not provide EVT at all.[254] In the US, 1/6 stroke patients lack access to EVT even with transfer.[255] When treatment is available, it is more commonly IVT than EVT, with around 30% of European stroke units having EVT capability.[254] The US based Joint Commission has provided terminology to describe the different degrees of stroke treatment capabilities in four levels; acute stroke ready hospital providing acute treatment with IVT, primary stroke center (PSC) with the addition of a dedicated stroke unit and access to an ICU, thrombectomy capable stroke center (TSC) with an angio suite and neurointerventionists able to perform EVT and finally the comprehensive stroke center (CSC) capable of handling the most advanced stroke cases.[256]

Following this distribution of treatment options, the ambulance destination must be chosen with care, considering that the nearest stroke center may be a PSC and that bypassing it to take a patient directly to a TSC or CSC may take significantly longer. Several observational studies have shown that in patients treated with EVT, secondary transport between hospitals (e.g., PSC to TSC) is associated with worse outcome than in those with a correct primary destination.[257–260] Meanwhile, in patients with distal occlusions where IVT is the only treatment option, bypassing a PSC may even be detrimental as time from onset to treatment is unnecessarily prolonged. The triage paradigms have been termed drip and ship (for initial PSC evaluation, IVT if eligible and subsequent transport) or mothership (for taking all patients to a TSC or equivalent).[261,262] An alternative, and in use in the projects described in this thesis, is the term PSC bypass.[263] By using known quality metrics such as time transport times, time from hospital arrival to IVT initiation (door to needle time – DTN), and door to EVT initiation (door to puncture time – DTP), mathematical models have been computed

describing optimal triage strategies under different geographical and logistical circumstances.[264,265]

A different strategy for stroke triage has been the use of mobile stroke units (MSU), which are ambulances equipped with a CT scanner. Initially, the objective of the MSU was to differentiate ischemic from hemorrhagic stroke on site in order to provide swift treatment with IVT when eligible, with initial studies showing markedly lowered onset to treatment time with the use of an MSU.[266–268] With the addition of CT angiography and telemedicine, the MSU could also be used for PSC/TSC triage.[269] An RCT comparing triage using an MSU with a prehospital symptom scale (see next section) has shown a 100% accuracy for triage destination.[270] However, the cost-effectiveness and effect on patient outcomes remains to be investigated and is the subject of ongoing randomized trials.[271,272]

2.6.1 Symptom-based triage scales

By using a short assessment of a limited number of stroke symptoms, prehospital scales can be used to guide ambulances by testing for high likelihood of LAO stroke or EVT eligibility. Both triage endpoints have their respective benefits and drawbacks, as some patients with LAO stroke may have contraindications for treatment, while a screening tool for EVT eligibility may fall short as guidelines and indications are updated with new evidence. Several scales are in use internationally, with examples in Aarhus, Barcelona, Madrid and Melbourne.[258,273,274] As this is a question of predictive performance, the utility of the scales is generally compared using sensitivity, specificity, positive and negative predictive value (PPV and NPV), as well as accuracy and area under the curve (AUC). Many scales have been derived from the NIHSS, using the high interrater reliability of the subitems for arm and leg paresis, gaze, visual field and LOC commands.[104,108,275] In addition, there is considerable overlap with the predictive performance for stroke caused by large artery occlusion, with high sensitivity and specificity for arm and/or leg paresis, facial weakness, gaze and LOC.[276,277]

A quick summary of the different diagnostic metrics with LAO stroke as an example:

- *Sensitivity:* What is the probability that a patient with LAO stroke will test positive?
- *Specificity*: What is the probability that a patient without LAO stroke will test negative?
- *Positive predictive value:* What is the probability that a patient with a positive test result has LAO stroke?
- *Negative predictive value:* What is the probability that a patient with a negative test result does not have LAO stroke?
- *Accuracy:* What is the proportion of correct test results (positive or negative) among all tests performed?
- *AUC:* What is the probability that a randomly selected patient with LAO stroke will score higher on the test than a random patient without LAO stroke?

These metrics have different implications in practical use and cannot be compared simply by finding the test with the highest score. A test with high sensitivity generally has lower specificity (and vice versa), which in the context of LAO stroke suspicion would mean a trade-off between unnecessary transport of patients to a TSC that do not require thrombectomy (low specificity) or a large number of secondary transports from the PSC due to low sensitivity. The predictive values (negative and positive) are highly influenced by disease prevalence, with rarer conditions lowering the PPV and increasing the NPV. Accuracy, as a compound measure of both PPV and NPV is therefore less volatile. The benefits and drawbacks of AUC will be discussed later under the methods section of the thesis.

SCALE NAME	WEAKNESS			CORTICAL SYMPTOMS
	Face	Arm	Leg	
RACE	x	x	x	x
LAMS	x	x		
C-STAT		x		x
G-FAST	x	x	x	x
PASS		x		x
CPSS	x	x		x
CG-FAST	x	x		x
FAST-plus	x	x	x	x
GACE	x			x

Table 4. *Summary of common characteristics in the nine prehospital triage scales described in two recent reviews.[173,175] RACE: Rapid Arterial oCclusion Evalution Scale. LAMS: Los Angeles Motor Scale. C-STAT: Cincinnati Stroke Triage Assessment Tool. G-FAST: Gaze Face Arm Speech Test. PASS: Prehospital Acute Stroke Severity. CPSS: Cincinnati Prehospital Stroke Scale. CG-FAST: Conveniently Grasped Field Assessment Stroke Triage. FAST-plus: Face-Arm-Speech-Time plus severe arm or leg motor deficit. GACE: Gaze facial Asymmetry, level of Consciousness, Extinction/inattention.*

Prehospital scales are generally built as a short series of tests or as decision trees. Starting with LAO scales, the Rapid Arterial oCclusion Evaluation Scale (RACE) tests for facial palsy, head/gaze deviation and hemiparesis with instructions to continue either with aphasia (right side) or neglect (left side), depending on which side is affected.[273] Meanwhile, the Los

Angeles Motor Scale (LAMS) tests for facial droop, arm drift and grip strength without any cortical symptoms and the Prehospital Acute Stroke Severity Scale (PASS) evaluates LOC, gaze palsy and arm weakness.[278] Two recent studies performed on large cohorts of suspected stroke patients in the Netherlands have externally validated a total of nine LAO scales, providing head-to-head comparisons.[173,175] Depending on the definition of large artery, and if the posterior circulation is included, sensitivities range from 0.50 – 0.67 and specificities 0.80 – 0.89, with high marks for the Rapid Arterial Occlusion Evaluation Scale (RACE) and Los Angeles Motor Scale (LAMS).[173,175] PPV was higher in the study by Duvekot and colleagues, (0.30-0.40 vs 0.21-0.32), likely because of a lower proportion of mimics (25% vs 38%). NPV was high in both studies at around 0.95, likely influenced by the relatively low LAO stroke prevalence of ~10%.[173,175] A full list of the included scales and some common features are summarized in the table below.

Examples of scales for EVT eligibility are the Ambulance clinical triage for Acute Stroke Treatment (ACT-FAST) in Melbourne and Madrid-Direct Referral to Endovascular Center (M-DIRECT scales).[174,274] ACT-FAST is a stepwise test, starting with unilateral arm drift and continuing to speech disturbance (right side) or gaze deviation/neglect (left side). Finally, eligibility is ascertained if the patient has no pre-existing deficits, onset is < 6 hours and a stroke mimic screen is performed for seizures, low blood glucose and information on active brain malignancy. In a prospective study validating the score, ACT-FAST had a specificity and PPV of 1.00, but the deficits were assessed in the hospital emergency department and the proportion of LAO stroke patients was greater due to the inclusion of those undergoing secondary transfer.[274] M-DIRECT tests for severe weakness of the upper or lower limb (NIHSS scores 3-4), as well as gaze deviation and aphasia or neglect. This is combined with negative scores for high blood pressure and age > 85 (exception for patients with excellent baseline status).[174]

Regarding patient outcomes after use of triage scales, observational studies have shown associations with better functional outcome in triaged patients, indicating a positive effect of stroke triage in Rhode Island and Aarhus.[258,279] Jayaraman and colleagues reported on the use of LAMS ≥ 4 as assessed on patients presenting within 24 h of symptom onset and could demonstrate a difference between 68% vs 42% with mRS 0-2 at follow up.[279] Several RCTs are ongoing or awaiting publication of results, most notably the RACECAT trial comparing outcomes in patients transported either to the nearest PSC or bypassing to a CSC using the cut-off of ≥ 5 points in RACE. [280]

3 RESEARCH AIMS

There are two main topics within acute ischemic stroke investigated in this thesis:

(1) Safety and outcomes of treatment with intravenous thrombolysis in specific subgroups

(2) Triage logistics of patients with suspicion of stroke caused by large artery occlusion.

Using data from an international stroke registry, studies I and II aimed to present large scale observational data regarding bleeding complications in the acute phase and functional outcomes at 3-month follow-up.

Study I: Given the paucity of published cases of stroke mimic patients with cerebral hemorrhagic complications after thrombolysis, we sought to investigate the occurrence of parenchymal hematoma and symptomatic intracranial hemorrhage in patients with stroke mimics registered in the Safe Implementation of Treatments in Stroke (SITS) International Stroke Thrombolysis Registry. The aim of this study was to compare safety and outcomes in two groups of patients treated with intravenous thrombolysis: stroke mimic vs acute ischemic stroke. Our hypothesis was that IVT treatment in patients with stroke is safe regarding acute and 3-month functional outcomes.

Study II: There are conflicting data regarding the risk of symptomatic intracranial hemorrhage in patients treated with intravenous thrombolysis suffering from posterior circulation stroke, with some studies showing a lower and others a higher risk than in patients with a stroke in the anterior circulation. Due to the limited statistical power in previous comparisons of hemorrhagic complications, our study was designed to combine data from the SITS registry with a systematic review and meta-analysis in order to generate as precise an estimate of hemorrhagic risk as possible. The aim of this study was to compare safety and outcomes in patients treated with thrombolysis between those with a posterior circulation stroke and those with a stroke in the anterior circulation. Our hypothesis was that treatment with intravenous thrombolysis is safer in posterior than in anterior circulation stroke, with better functional outcomes and a lower risk of death at 3-months follow-up.

Studies III and IV were based on data gathered in the Stockholm region, following implementation of the Stockholm Stroke Triage System (SSTS).

Study III: After implementation of the new triage system, time from stroke onset to treatment initiation with endovascular thrombectomy was lowered by 69 minutes. The aim of this study was to evaluate the functional outcomes in patients treated with endovascular thrombectomy during the first two years of the SSTS compared to the two years before implementation. Our hypothesis was that the faster treatment time meant that patients treated during the new system would have improved functional outcomes compared to historical controls.

Study IV: This study was a pre-planned analysis of the SSTS, designed to characterize incorrectly triaged patients based on clinical parameters available in the prehospital setting, as well as occlusion data and final diagnosis. The aim of this study was to describe and compare patients that were correctly and incorrectly triaged using the triage system and to establish whether alternative triage algorithms, with higher predictive performance for recognition of patients undergoing thrombectomy or suffering from an acute ischemic stroke caused by a large artery occlusion and LAO stroke could be designed with available prehospital data.

4 MATERIALS AND METHODS

	POPULATION	INTERVENTION/ EXPOSURE	COMPARISONS	OUTCOME
Study I	SITS database, IVT treatment	IVT treatment in stroke mimics	Stroke mimic vs acute ischemic stroke	Bleeding complications, death, functional outcome
Study II	SITS database + systematic review, IVT treatment	IVT treatment in posterior circulation stroke	Posterior circulation stroke vs anterior circulation stroke	Bleeding complications, death, functional outcome
Study III	Treated with EVT in Stockholm region	EVT treatment during SSTS	Patients before and after SSTS was implemented	Functional and safety outcomes
Study IV	Suspected stroke in Stockholm region	Triage using SSTS	SSTS vs alternative triage models	Improvement in triage accuracy

***Table 5**. Summary of the study design in the four component studies of the thesis.*

4.1 THE SAFE IMPLEMENTATION OF TREATMENTS IN STROKE INTERNATIONAL STROKE REGISTRY (SITS-ISTR)

SITS is a non-profit, research-driven, independent, international collaboration that was started in 1996 by participants in the European-Australian randomized stroke thrombolysis studies (ECASS). Initially, the registry only included patients treated with alteplase. Following approval by the FDA, the EMEA requested that all patients treated with IVT be registered in SITS for a period of three years, which became a condition for approval of the treatment in the EU. These data were analyzed in the SITS Stroke-Monitoring Study (SITS-MOST) in 2006 and published in 2007, confirming safety and efficacy of IVT in routine clinical use. In the following years, additional registries have been added to SITS such as the Endovascular Thrombectomy Registry, the Atrial Fibrillation Registry, and the Intracerebral Hemorrhage Registry. Additionally, SITS collaborates with ESO and WSO-Angels with a quality registry. SITS is overseen centrally by an international coordinating office, which monitors the data

monthly to identify errors or inconsistencies. Regionally, oversight is performed by an international regional coordinator, nationally by a national coordinator, and finally a local coordinator ensuring consecutive registration of all stroke patients at each participating hospital. The global network forming SITS is represented across five continents and in 80 countries. A scientific committee consisting of senior stroke researchers provides scientific guidance for studies performed by SITS members using the database. Any scientific project based on SITS global data must be approved by the scientific committee. The SITS registry consists of data gathered during the normal course of treatment and follow-up at each center. Data is registered through an online tool protected by 2-way authentication, with individual data pseudoanonymized to a treatment file number generated by the registration system. SITS contains data on patient demographics, comorbidities, clinical parameters assessed at the hospital, summarized radiological findings, information on treatment, and outcomes up to three months from hospital admission. Methods and assessments of clinical parameters, imaging, and outcomes are performed according to clinical routine at participating centers.

4.1.1 Study I

All patients treated with IVT recorded in the SITS-ISTR between February 2003 and September 2017, were considered. Patients were divided into two groups by discharge diagnosis, with ischemic stroke and non-stroke forming the acute ischemic stroke (AIS) and the stroke mimic (SM) groups respectively. The inclusion criterion was imaging with MRI at 22-36 hours after treatment, in order to provide higher diagnostic certainty compared to CT.[209–211] Patients that had undergone EVT were excluded, as this treatment requires evidence of a large artery occlusion and by definition cannot be performed in those with a mimicking condition. The SM group was subclassified into 14 distinct diagnostic categories, based on descriptions available in the database. The choice of categories was based on previous studies on prevalence of stroke mimics in various settings.[207,212,214,238,240] In ambiguous cases, or if information was limited (e.g., entries containing only “stroke mimic”), further information was acquired by email contact with local coordinators at individual participating centers.

4.1.2 Study II

All patients treated with IVT recorded in the SITS International Stroke Thrombolysis Register (SITS-ISTR) between February 2013 and September 2017, were considered. Patients with available occlusion data on CT or MR angiography were included in the study and divided into two groups: those with a stroke in the anterior circulation (ACS) and those with stroke in the posterior circulation (PCS). As this was a study of IVT safety, patients who had undergone any endovascular intervention were excluded. Cases with occlusions in both vascular territories were excluded, as they could not be designated as either anterior or posterior circulation stroke. Patients with an occlusion in the ICA, MCA, or ACA formed the ACS group, whereas those with occlusion in the VA, BA, or PCA formed the PCS group (options for entering AICA, PICA or SCA are not available in the SITS registry).

In both study I and II, collected data on demographics, baseline characteristics, comorbidities, medication history, stroke severity per the NIHSS, time logistics, imaging data (on admission and follow-up), as well as death and functional outcome per the mRS at three months follow-up were used.

4.2 THE STOCKHOLM STROKE TRIAGE SYSTEM

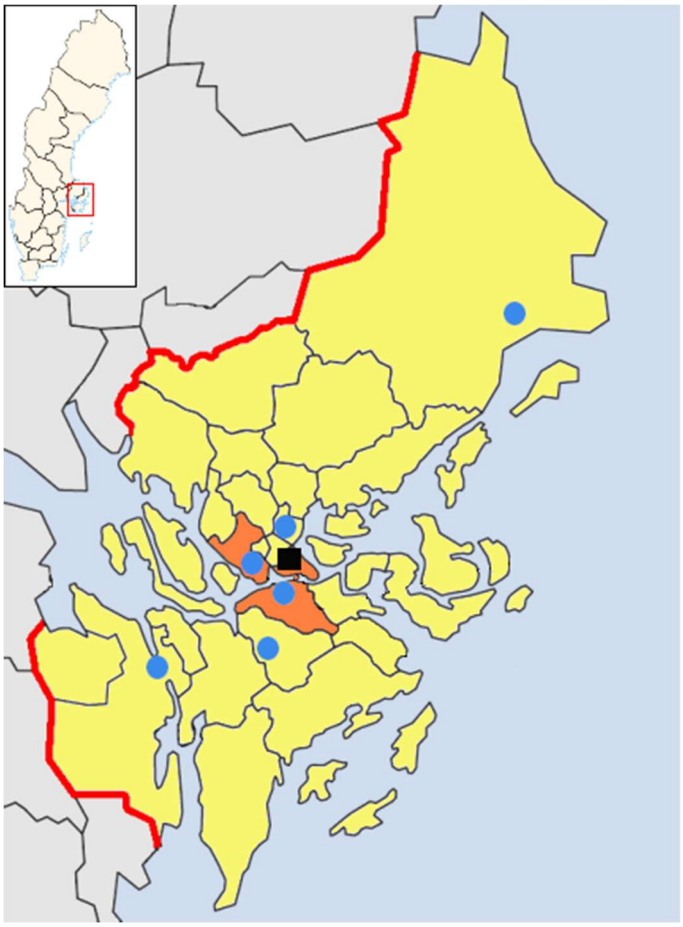

Figure 15. *The geographical distribution of stroke centers in the Stockholm region. Blue circle = primary stroke center. Black square = comprehensive stroke center. Orange = Stockholm municipality. Yellow = municipalities in metropolitan Stockholm. Adapted from Wikipedia, originally by users TimSE and Nordelch. CC-BY-SA 2.5,2.0,1.0*

Stroke care in the Stockholm region (see figure 15), with a population of 2.4 million across 6519 km^2, is provided by one CSC (black square) and six PSCs (blue circles). Previously, all patients with suspected ischemic stroke and symptom onset within six hours were transported by priority level 1 (immediate call) ambulance to the nearest stroke center, regardless of symptom severity. For patients with critical vital signs or impaired consciousness, priority 1 transport was used regardless of time from symptom onset.[281] Patients would receive treatment with IVT if deemed eligible after non-contrast head CT, followed by CT angiography. In case of large artery occlusion demonstrated at a PSC, the regional stroke consultant at the CSC would be contacted for a discussion on EVT eligibility. Patients without significant comorbidities or pre-stroke disability (mRS < 3) were accepted for secondary transport unless a large infarction was demonstrated on the non-contrast CT. If the CSC was the first hospital, the patient would undergo non-contrast head CT, CT angiography, and CT perfusion to determine eligibility for IVT and/or EVT on site. Patients were eligible for treatment regardless of age or stroke territory (anterior or posterior circulation. As illustrated in figure 15, the nearest stroke center for a majority of patients is one of the PSCs, which explains why ~75% of patients treated with EVT underwent secondary transport.[282]

In October 2017, this was changed to a prehospital triage system called the Stockholm Stroke Triage System (SSTS), which is currently in use. The SSTS uses a combination of symptom assessment for hemiparesis and tele-consultation in order to guide ambulances to the nearest

PSC or bypass them for direct transport to the CSC. The goal of the SSTS is to correctly identify patients eligible for EVT, with successful triage defined by initiation of EVT. All patients transported using the SSTS have been prospectively registered in a database, with information on patient demographics, clinical and imaging parameters, time logistics, as well as functional and safety outcomes. In detail, the Stockholm Stroke Triage System (SSTS) uses the following three steps (see also figure 16):

1. The ambulance nurse assesses the patient for suspicion of stroke, using the AKUT-test (or other clinical symptoms at the discretion of EMS personnel)
2. If the ambulance nurse has reason to suspect acute stroke in a patient, the patient is assessed for hemiparesis using the NIHSS items for ipsilateral arm and leg (subitems 5 and 6): the A2L2 test. If the NIHSS score is ≥ 2 for both the arm and the leg, the patient is termed A2L2-positive.
3.
    a. If the A2L2 test is positive, the ambulance nurse contacts the regional stroke consultant by phone for EVT eligibility and direction to CSC or nearest PSC.
    b. If the A2L2 test is negative (or not assessable – e.g. unconscious patient, bilateral paresis, seizures), the ambulance nurse contacts a stroke physician at the nearest PSC for pre-notification.

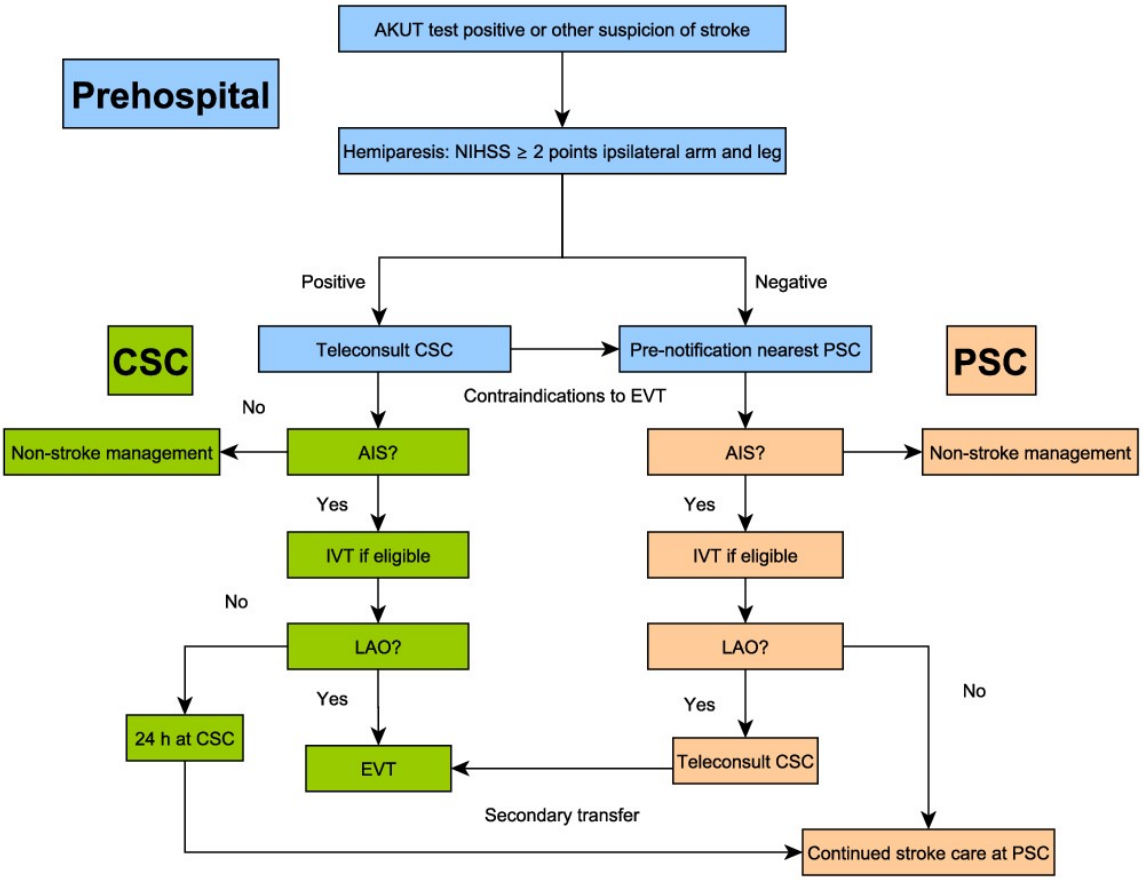

Figure 16. *Flowchart describing the Stockholm Stroke Triage System. AKUT: Arm, Kroppsdel, Uttal, Tid, Swedish version of the FAST-test. CSC: comprehensive stroke center. PSC: Primary stroke center. EVT: endovascular thrombectomy. AIS: Acute ischemic stroke. IVT: Intravenous thrombolysis. LAO: Large artery occlusion. Image by author.*

The regional stroke consultant may decline patients for direct CSC transport based on low suspicion of stroke, low pre-stroke functional status or life expectancy, or need for emergency resuscitation at the nearest PSC due to vital sign irregularities. In all declined cases, the stroke consultant at the CSC notifies the nearest PSC, explaining why the patient was ineligible for PSC bypass. Hemiparesis was chosen due to the ease of the test, as well as high inter-rater reliability and predictive values for LAO stroke.[104,276,277] In order to lower the strain on the bed capacity of the CSC, the Stockholm region was divided into catchment areas for each stroke center with the goal of repatriation of patients to a PSC after 24 hours at the CSC. Similarly, there was a focus on high specificity in order to avoid unnecessary transport of patients to the CSC. During the first year after implementation, median onset to arterial puncture (OTP) time for EVT was reduced from 206 minutes to 137 minutes. The triage system's accuracy for detecting patients with LAO stroke was 87% and for treatment with EVT, 91%.[263]

4.2.1 Study III

All patients subjected to arterial puncture with the intention of EVT and symptom onset in the Stockholm region were included and divided into two groups. The patients forming the SSTS group were prospectively registered during the first two years of the SSTS (October 10, 2017 – October 9, 2019). Historical controls consisted of patients treated with EVT during the two years immediately preceding SSTS (October 10, 2015 – October 9, 2017), forming the pre-SSTS group. Patients with in-hospital stroke, transported by helicopter, private means or with an initial suspicion of a different condition than stroke (e.g., myocardial infarction, sepsis, major trauma) were excluded, as they would not have qualified for use of the SSTS. Occlusion sites considered for treatment were ICA, MCA segments M1 and M2, ACA, BA, PCA and intracranial VA, based on CT angiography findings. There was no change in guidelines on imaging, treatment indications and EVT methods, as well as stroke unit and rehabilitation practices during the study period (2015-2019). ASPECTS score was calculated from the latest scan performed before arterial puncture. Occlusion site data was extracted from digital subtraction angiography reports. The source of clinical assessments, imaging data, treatments, time logistics, and outcomes was the region-wide common electronic health record system. Data extraction was performed by study authors B Keselman and M Mazya, with any disagreement resolved by consensus.

4.2.2 Study IV

All patients transported by priority 1 ambulance for suspected stroke in the Stockholm region during the first year of SSTS were included, with the same exclusion criteria as in study 3. Patients were divided based on triage status for two separate endpoints: presence of LAO stroke or arterial puncture with the intention of EVT. Triage status was divided into four groups: correct triage to PSC, correct triage to CSC, overtriage and undertriage (to CSC), with the following definitions:

- *Overtriage* (EVT): patient routed directly to CSC but not treated with EVT.
- *Overtriage* (LAO stroke): patient routed directly to CSC but not diagnosed with LAO stroke.
- *Undertriage* (EVT): patient routed to PSC undergoing secondary transport to CSC for EVT.
- *Undertriage* (LAO stroke): patient routed to PSC and diagnosed with LAO stroke.

Data was collected on patient demographics (age, sex), AKUT-test subitems, known onset time, wake-up stroke, time logistics, as well as NIHSS subitems, arterial occlusion data and diagnosis at discharge. Diagnosis was divided into the four categories LAO stroke, non-LAO ischemic stroke, intracerebral hemorrhage, and stroke mimic. LAO stroke was defined as acute ischemic stroke in combination with CT angiography evidence of occlusion or subocclusion in arteries accessible by stent retriever EVT in routine practice at the CSC (see 4.2.1). A decision to abstain from CTA could be made due to contraindications to intravenous contrast or EVT (e.g., renal failure, contrast allergy, or severe pre-stroke comorbidities). Patients with acute ischemic stroke and unknown occlusion status were classified as non-LAO ischemic stroke in the analyses.

4.3 SYSTEMATIC REVIEW AND META-ANALYSIS

In addition to data from the SITS-ISTR, study II consisted of a systematic review and meta-analysis. A literature search was performed, with the last iteration on November 27, 2018, for studies reporting on any of the hemorrhagic and functional outcomes described under section 4.4.1 with comparisons of IVT treatment between ACS and PCS. Studies on human subjects, written in English, Russian, French, German or Swedish and published between 2007 and 2018 were included. Three search blocks were constructed, using MESH-terms and other synonyms pertaining to stroke territory comparison (ACS vs PCS), treatment with IVT, and outcome (hemorrhage, functional outcome) for use in the MEDLINE and EMBASE databases. Two independent reviewers, B Keselman and M Mazya, examined all studies found in the database search and performed data extraction as well as assessment of methodological quality of studies deemed relevant for the review. Any disagreement regarding selection of relevant studies, results of the quality assessment or outcome data was resolved by consensus.

4.4 OUTCOMES

4.4.1 Study I-II

The main outcome was any intracerebral parenchymal hematoma (PH). PH was defined radiologically as any non-petechial bleeding in the brain parenchyma acquired via imaging at any timepoint during the acute in-hospital stay.

Secondary outcomes were SICH, as well as mRS and death at three months. We used SICH per the SITS-MOST, ECASS II and NINDS definitions. For functional outcome, mRS was dichotomized into 0-1 vs 2-6, 0-2 vs 3-6, as well as the full range of 0-6.

For the meta-analysis in study 2, SICH was chosen as the main outcome due to its clinical significance as well as clear definitions in each of the component studies. If a study reported more than one SICH definition, the one with the highest proportion was used in order to facilitate comparison between studies. A dichotomized mRS 0-2 vs 3-6 at three months was used for functional outcome and extracted from all studies with available data.

4.4.2 Study III

The main outcome was shift in the full range of the mRS (0-6) at three months (see statistical analysis).

Secondary outcomes were dichotomized mRS (0-1 vs 2-6; 0-2 vs 3-6), absolute NIHSS values and change from baseline at 24 hours after treatment, arterial reperfusion and SICH. Arterial reperfusion was defined as dichotomized Thrombolysis in Cerebral Infarction (TICI) score of 0-2a vs 2b-3. SICH was defined as a ≥ 4 increase in NIHSS within 24 hours after treatment, in conjunction with a parenchymal hematoma (PH), remote PH (PHr), subarachnoid hemorrhage or intraventricular hemorrhage determined to be the cause of the neurological deterioration. In cases of unavailability, for example due to general anesthesia, SICH was classified if the required increase in NIHSS occurred within 7 days after treatment.

4.4.3 Study IV

The main outcome was net benefit per a decision curve analysis (DCA) performed on the alternative triage models for initiation of EVT treatment (see statistical analysis).

Secondary outcomes were sensitivity, specificity and AUC for both triage endpoints, as well as net benefit for the LAO stroke triage endpoint.

EVT initiation was chosen as the main outcome to reflect the purpose of the SSTS, which is the identification and triage of patients eligible for EVT rather than all patients with LAO stroke.

4.5 STATISTICAL ANALYSIS

Descriptive statistics for univariate comparisons between groups were performed in all component studies. For continuous variables, median and interquartile range values were calculated. For categorical variables, we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases. The Mann-Whitney U-test was used for calculations of significance of difference between medians. The Pearson χ^2 was used for calculations of significance of difference between proportions. In cases of low cell count, Fisher's exact method was used instead. Two-tailed p-values of < 0.05 were considered statistically significant. Analyses were performed in Stata 15.1 (College Station, TX: StataCorp LLC), R 4.1.0 (https://www.R-project.org/) and Meta-Essentials in Microsoft Excel for Office 365 MSO (16.0.11629.20238). Results from studies 1-3 were reported in accordance with the STROBE guidelines for observational studies.[283]

Results from study 4 were reported in accordance with the STARD guidelines for studies on diagnostic accuracy.[284]

4.5.1 Study I

Due to the MRI requirement, a risk of bias was identified in that patients with deteriorating clinical status would be more likely to undergo faster CT imaging. This would have been more likely in patients with severe ischemic stroke and high risk of SICH, where time might not suffice for an MRI in case of sudden neurological worsening. Therefore, a sensitivity analysis was performed, comparing patients with a diagnosis of ischemic stroke treated with IVT and examined using CT with the original stroke mimic group.

4.5.2 Study II

For the original data in study II, adjusted comparisons were performed using inverse probability treatment weighting (IPTW) in order to provide a more precise estimate of the effect that affected vascular territory has on outcomes after IVT treatment. Adjustment was performed in order to compensate for the baseline imbalances between the two groups (ACS and PCS), which in an observational study could not be considered due to chance as opposed to an RCT. Characteristics which were identified as important for outcomes were age, sex, NIHSS score, systolic blood pressure, blood glucose, atrial fibrillation and treating center. IPTW was performed in two steps, beginning by estimating the probability (or propensity score) of a patient belonging to the ACS group given their distribution of the seven characteristics listed above. Following this, outcomes in each patient are weighted according to the inverse probability of belonging to the ACS group and an average proportion of the binary outcome (e.g., PH, SICH, mRS 0-1) is computed. The difference of the weighted averages, also known as the average treatment effect (ATE) is the estimate of the effect that vascular territory has on the outcomes of interest. ATE is presented as risk differences between the two groups, together with a 95% confidence interval, with negative values denoting lower risk of the outcome in the PCS group compared to ACS. A test of the overlap assumption, i.e., that patients in both groups share some of the seven characteristics (allowing for comparison using IPTW), was tested using an overlap plot. Balance between groups was evaluated using absolute standardized differences, calculated before and after IPTW.

A risk of bias was identified in published data showing that a minority of patients with minor stroke registered in the SITS-ISTR had arterial imaging at baseline.[285] Therefore, a sensitivity analysis was performed, instead using a clinico-radiological diagnosis of ACS or PCS, as provided by the treating physicians. The SITS-ISTR provided this option as a binary variable before registration of detailed occlusion data was made available. Cases with available occlusion location data were included in the larger material used for the sensitivity analysis.

For the meta-analysis, a risk ratio (RR) with a 95% confidence interval was calculated using the numbers of events in PCS and ACS patients. The random effects method for pooling the overall RR for the component studies was used, with the assumption that the treatment effect might vary between studies due to design. Inconsistency (I^2) was calculated according to the

method proposed by Higgins and colleagues, defining the levels for low (25%), moderate (50%), and high (75%) heterogeneiety.[286] Statistical significance for heterogeneity was considered at $p < 0.1$. Publication bias was assessed visually using a funnel plot and Egger's test for asymmetry.[287]

4.5.3 Study III

In analogy with the methodological limitations in observational studies described under section 4.5.2, multivariate adjustment for baseline imbalances was used to compare mRS outcomes between the SSTS and pre-SSTS groups after EVT treatment. Variables were selected for the multivariate models based on a combination of statistically significant baseline differences and clinical significance for the outcome. Initially, an ordinal logistic regression (or shift analysis) was performed, which provides an odds ratio for a 1-point improvement across the entire mRS scale. However, shift analysis requires proportionality of odds, i.e., uniform odds between all scale levels, which was tested using the Brant test.[288] A significant result on this test showed that the proportionality assumption was violated. Following this and in analogy with the method described by Lees and colleagues, comparisons of all possible dichotomizations of the mRS scale were performed in order to ascertain if there was evidence of inversion of odds.[289] These analyses were performed using binomial logistic regression with adjustment for baseline differences in NIHSS and age. Comparisons of dichotomized mRS 0-1 and 0-2, as well as death at three months were also performed using binomial logistic regression. In order to provide further support for the associations found in this observational study, E-values were calculated using the method described by VanderWeele and Ding.[290] The E-value provides a value for how strongly an unmeasured confounder would need to be associated with the outcome in order for the calculated difference to no longer reach statistical significance.

4.5.4 Study IV

Analysis was performed in two steps: modeling of alternate triage algorithms and comparison of these models to the full SSTS, as well as the A2L2 test alone for both of the triage endpoints: initiation of treatment with EVT and diagnosis of LAO stroke. Modeling was performed using logistic regression, with three different strategies for variable inclusion:

1. Univariate comparison and clinical relevance
2. Stepwise regression using the Akaike Information Criterion (AIC). Starting with the A2L2-test, variables were iteratively added with as long as predictive value was increased, as assessed by a lower AIC value.
3. All variables available in the prehospital setting.

Variables that were possible to assess by the ambulance, and therefore available for inclusion were A2L2 status, age, sex, wake-up stroke, onset-to-ambulance time (or time from last known well), known exact onset time, and AKUT-test subitems facial weakness, and speech problems. AKUT-test subitems for arm and leg (denoting any weakness of the limbs) were

not considered due to high correlation with the A2L2-test. Patients with incomplete data were excluded from the modeling calculations and comparisons.

Decision curve analysis (DCA) was chosen as the main method for model comparison. DCA, introduced and described by Vickers and colleagues, can be used to evaluate the net benefit of prediction tools and diagnostic tests across a range of patient/clinician preferences for accepting risk of undertreatment (undertriage) and overtreatment (overtriage).[291] In the case of the SSTS, benefit can be expressed as the number of patients treated with EVT correctly transported directly to the CSC. Undertreatment = undertriage, i.e. patients requiring secondary transport from the PSC, whereas overtreatment = overtriage, i.e. patients not treated with EVT transported directly to the CSC. The impact of overtreatment is derived from the probability threshold, which is the diagnostic certainty at which it would be acceptable to treat the patient. This can alternatively be expressed as the answer to the question: "How many patients would need to be transported directly to the CSC in order to treat one patient with EVT?" Net benefit is calculated by subtracting the false positive rate multiplied by the threshold probability, from the true positive rate. In the graphical output of the DCA, standardized net benefit is plotted on the Y-axis, against a range of clinically relevant threshold probabilities on the X-axis. Included models are plotted against the default treatment strategies of taking all, or none of the patients to the CSC.

Only patients with complete prehospital data were included in the modeling. Additionally, sensitivity, specificity, and AUC were calculated for all models, as well as the A2L2-test, and the full SSTS triage algorithm (A2L2-test + teleconsultation). A risk of bias was identified in that patients without CT angiography imaging may have had LAO stroke, which would skew the results for that triage endpoint. Therefore, a sensitivity analysis for LAO stroke was performed, excluding patients with unknown occlusion status.

4.6 ETHICAL CONSIDERATIONS

For studies I-II, ethical approval was obtained from the Stockholm Regional Ethics Committee as part of the SITS-MOST (Safe Implementation of Thrombolysis in Stroke Monitoring Study) II (Dnr 2015/767-31). The gathering of SITS data is performed according to the laws and regulation in each participating country, with each center owning its own data. The stated purpose of SITS is to *"assure excellence in acute stroke treatment and secondary prevention of stroke, as well as to facilitate clinical trials."* Special care is taken in order for all participants (locally, nationally and regionally) to benefit from the data they contribute to SITS, both as a quality registry and for research purposes. The SITS annual report from 2019 shows that many of the top contributors are countries in eastern Europe. These countries form a regional network called SITS-EAST and data gathered there is specifically used for local quality improvement and SITS publications have shown an increasing number of patients being treated with thrombolysis or thrombectomy in recent years. SITS-MENA and SIECV-SITS are the counterparts in Middle East/North Africa and South America respectively.[292]

For studies III-IV, ethical approval was obtained from the Stockholm Regional Research Ethics Committee (Dnr 2017/374). The purpose of gathering this data is to scientifically evaluate the new triage system and its benefits for patients suffering a stroke in the Stockholm region. In parallel with the studies described in this thesis, data from the SSTS database has been used to evaluate diagnostic precision and treatment time logistics of the SSTS, differences in how men and women are triaged, with planned studies on patient experiences of triage.

Under Swedish law, collection of data for SITS as well SSTS is regulated under 7 kap. Patientdatalagen (2008:355), concerning national and regional quality registries. This means that explicit consent from individual patients is not required for their personal data to be used in research and gathering and analysis of data. However, patients are informed of this and that they have the right to have all personal data removed from the registry. A few (4 of 2909) patients have already withdrawn their consent, making it clear that the system works and that patients are aware of their rights as research subjects. Their data was immediately removed from all study datasets.

5 RESULTS

5.1 STUDY I

Of 10,436 eligible patients treated with IVT at 560 centers in 43 countries, 429 (4.3%) had a stroke mimic diagnosis. The three most common mimic categories were functional (30.8%), migraine (17.5%) and seizure (14.2%), adding up to 62.5% of all cases (see table 6). In the baseline comparison, patients with a mimicking condition had fewer risk factors for stroke, as well as for bleeding complications after IVT. Onset to treatment time was longer for patients with stroke mimics, compared to those with ischemic stroke, but not the door to needle time (time from hospital arrival to administration of IVT).

Stroke mimic patients had fewer hemorrhagic complications compared to those with ischemic stroke according to all definitions (table 7). However, the difference in SICH per SITS-MOST did not reach statistical significance at p=0.28. Similarly, the stroke mimic patients had significantly better functional outcome according to dichotomizations of the mRS (0-1 and 0-2), as well as a lower proportion dead at three months after treatment. There was no clinically relevant difference demonstrated in the sensitivity analysis comparing stroke mimic patients with ischemic stroke patients that had undergone CT imaging rather than MRI (n=85,664).

MIMIC CATEGORY	n (%)
Functional	132 (30.8)
Migraine	75 (17.5)
Seizure	61 (14.2)
Mimic	59 (13.8)
Other	22 (5.1)
CNS infection	20 (4.7)
Metabolic disorder	17 (4.0)
Brain tumor	15 (3.5)
Demyelinating disease	7 (1.6)
Circulatory compromise	6 (1.4)
Peripheral vestibulopathy	6 (1.4)
Peripheral nerve palsy	4 (0.9)
Spinal cord compression	3 (0.7)
Delirium	2 (0.5)

Table 6. *Categories of mimicking conditions. Mimic: no further information available. Other: an identifiable but rare disease not falling into any of the categories.*

Outcome	MIMIC (%)	ISCHEMIC STROKE (%)	P-VALUE
PH	5/429 (1.2)	508/9993 (5.1)	< 0.001
SICH (SITS-MOST)	0/429 (0.0)	52/10001 (0.5)	0.28 †
SICH (ECASS II)	1/427 (0.2)	212/9918 (2.1)	0.007
SICH (NINDS)	2/427 (0.5)	383/9939 (3.9)	< 0.001
mRS 0-1 3m	276/328 (84.1)	5004/8668 (57.7)	< 0.001
mRS 0-2 3m	303/328 (92.4)	6020/8668 (69.4)	< 0.001
Death 3m	9/342 (2.6)	456/8518 (5.4)	0.028

Table 7. *Outcomes. PH: parenchymal hematoma. SICH: Symptomatic intracranial hemorrhage. SITS-MOST: Safe implementation of thrombolysis in stroke Monitoring study. ECASS II: Second European Co-operative Acute Stroke Study. NINDS: Neurological Disorders and Stroke definition. mRS 0-1 3m: modified Rankin Scale score 0-1 at 3 months. mRS 0-2 3m: modified Rankin Scale score 0-2 at 3 months. Death 3m: Death at 3 months. †: Analyzed using Fisher's exact test.*

5.2 STUDY II

Of 5146 patients treated with IVT at 560 centers in 33 countries, 753 (14.6%) had PCS and 4393 (85.4%) ACS. There were several statistically significant baseline differences in known risk factors for SICH. PCS patients were younger and had lower NIHSS scores (lower risk), but were also more commonly male and had higher levels of systolic blood pressure and blood glucose (higher risk). Pre-stroke comorbidities and pharmacological treatments were similarly distributed in the two groups. Occlusion sites in the PCS group were evenly distributed among BA (33%), VA (32%) and PCA (35%) sites.

Unadjusted comparisons were in favor of the PCS regarding bleeding outcomes according to all definitions, as well as functional outcomes (table 8). Fewer patients in the PCS group were dead at 3-month follow-up, but this difference was not statistically significant. However, after IPTW analysis with adjustment for baseline differences in seven variables (age, sex, atrial fibrillation, NIHSS, systolic blood pressure, blood glucose and center) significant differences remained only for PH and SICH per SITS-MOST. The ATE was -4.6% and -1.5% respectively, denoting that the risk for these outcomes was lower in patients with PCS compared to ACS. For death, the difference was statistically significant in favor of ACS, with an ATE of 6.6%. The sensitivity analysis, including patients with a clinico-radiological vascular territory diagnosis (n=29,704) confirmed lower rates of bleeding complications in PCS, in addition to a statistically significant difference in proportion of dead patients at three months after treatment.

Outcome	PCS (%)	ACS (%)	P-VALUE	ATE	95% CI
PH	22/677 (3.2)	321/4057 (7.9)	< 0.001	-4.6%	-6.3%, -2.9%
SICH (SITS-MOST)	4/680 (0.6)	79/4072 (1.9)	0.013	-1.5%	-2.2%, -0.8%
SICH (ECASS II)	12/673 (1.8)	213/3942 (5.4)	< 0.001	-1.9%	-5.4%, 1.6%
SICH (NINDS)	21/674 (3.1)	310/3956 (7.8)	< 0.001	-2.7%	-6.4%, 1.1%
mRS 0-1 3m	230/509 (45.2)	1103/2939 (37.5)	0.001	-1.9%	-6.8%, 3.0%
mRS 0-2 3m	312/509 (61.3)	1452/2939 (49.4)	< 0.001	2.1%	-3.4%, 7.1%
Death 3m	97/525 (18.5)	620/3027 (20.5)	0.29	6.6%	1.1%, 12.8%

Table 8. *Outcomes. PCS: Posterior circulation stroke; ACS: Anterior circulation stroke; ATE: Average treatment effect; CI: Confidence interval; PH: Parenchymal hematoma. SICH: Symptomatic intracranial hemorrhage. SITS-MOST: Safe implementation of thrombolysis in stroke Monitoring study. ECASS II: Second European Co-operative Acute Stroke Study. NINDS: Neurological Disorders and Stroke definition. mRS 0-1 3m: modified Rankin Scale score 0-1 at 3 months. mRS 0-2 3m: modified Rankin Scale score 0-2 at 3 months. Death 3m: Death at 3 months.*

The systematic review yielded 634 unique records, of which 13 fulfilled inclusion criteria and were included in the meta-analysis. There were 10,313 patients treated with IVT for acute ischemic stroke included in the meta-analysis, of which 1224 (11.9%) had PCS. Additionally, seven studies had data on functional outcome three months after treatment as proportion of

patients with mRS 0-2. The risk of SICH after IVT was lower in patients with PCS compared to ACS (RR = 0.49, 95% CI: 0.32-0.75), see figure 17. For mRS 0-2, patients with PCS had an RR of 1.19 (95% CI: 1.06-1.33), indicating better functional outcome after treatment compared to patients with ACS.

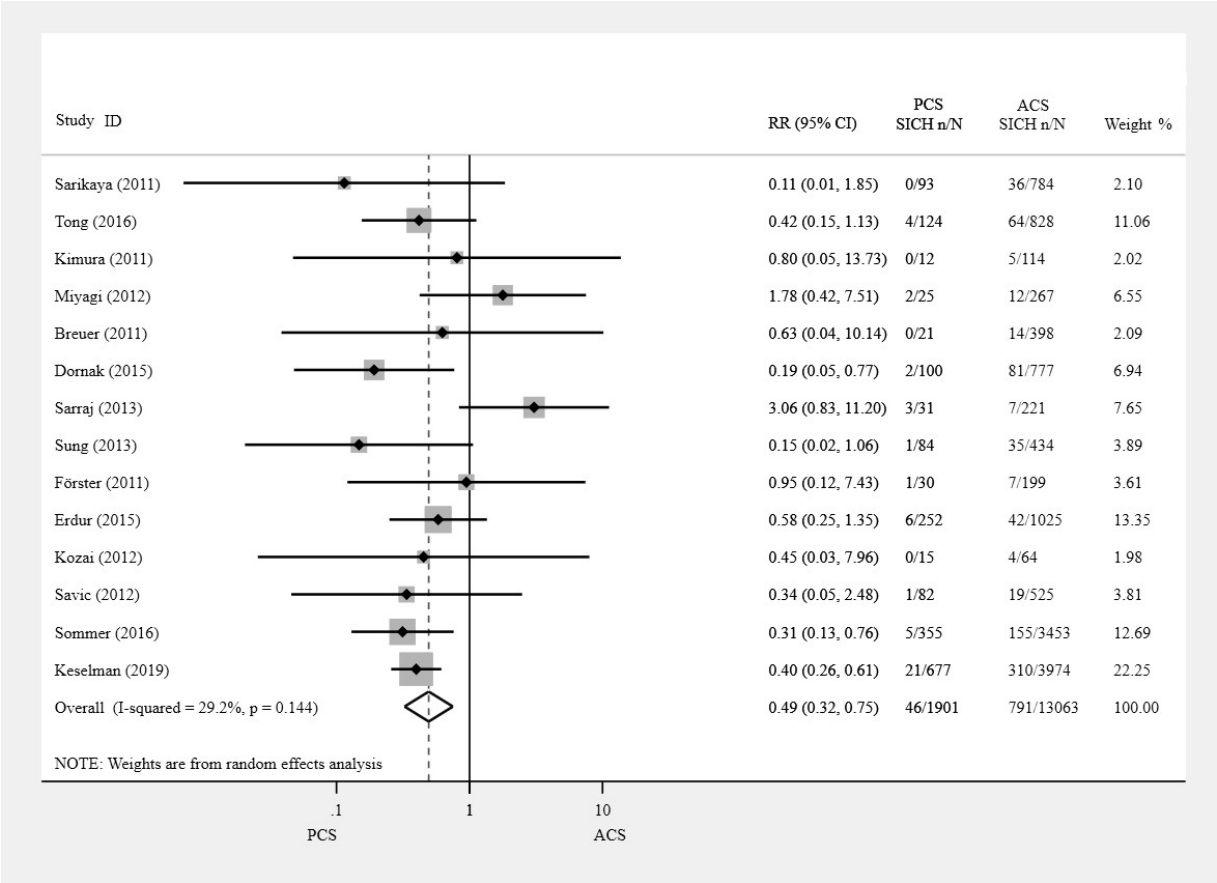

Figure 17. *Forrest plot of risk ratios (RR) for symptomatic intracranial hemorrhage (SICH) between patients with posterior circulation stroke (PCS) and anterior circulation stroke (ACS) treated with IV thrombolysis. CI: Confidence interval. Keselman (2019): original results from the SITS data analysis are included in the meta-analysis*

5.3 STUDY III

Of 640 patients who underwent arterial puncture for EVT at the Stockholm region CSC during the study period (October 10, 2015 – October 9, 2019), 431 were included in the study. Of these, 244 were treated during use of the SSTS and the remaining 187 formed the pre-SSTS group. A majority of SSTS patients (70.5% vs 27.8% pre-SSTS) were transported directly to the CSC, with a median onset-to-puncture time of 136 minutes (205 minutes pre-SSTS). The SSTS patients had higher median age (74 vs 71) and baseline stroke severity (17 vs 15). Apart from a higher proportion of smokers in the pre-SSTS group, risk factors and comorbidities and pre-stroke functional status was similar in the two groups.

Unadjusted distribution of the full mRS (0-6) at three months (figure 18) showed better functional outcomes in the SSTS group, with the largest difference in mRS scores 0-1. Adjustment was performed for the baseline differences in age and NIHSS using logistic regression. Ordinal logistic regression (shift analysis) yielded an adjusted odds ratio (aOR) of 1.7 (95% CI 1.2-2.3), meaning better odds for a 1-point improvement in the mRS in the SSTS

group. Following a statistically significant Brant test (see section 4.5.3) binomial logistic regression analyses for all dichotomizations of the mRS scale were performed, showing no inversion of odds (i.e., higher odds of better functional outcome in the pre-SSTS group).

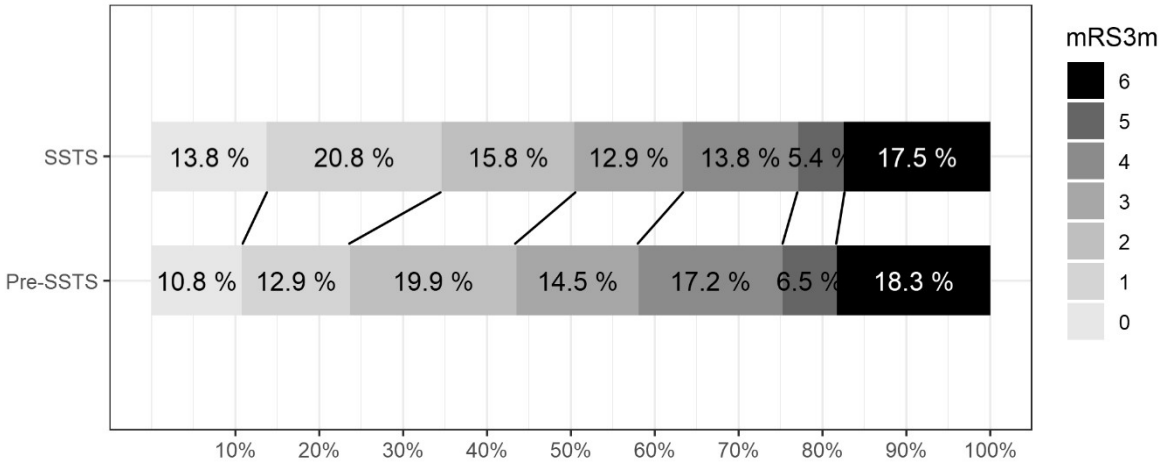

Figure 18. *Functional outcomes three months after treatment. mRS: modified Rankin Scale. SSTS: Stockholm Stroke Triage System*

Secondary analyses using binomial logistic regression for dichotomized mRS (0-1 and 0-2) demonstrated higher odds of better functional outcome and no significant difference in death (see table 9). Further outcomes are presented in table 8, with the SSTS group showing a larger improvement in NIHSS assessed 24 hours after treatment without statistically significant differences in rates of recanalization or SICH.

OUTCOME	SSTS (%) or median (IQR)	PRE-SSTS (%) or median (IQR)	P-VALUE	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
ΔNIHSS 24 h after treatment	6 (1-12)	4 (0-10)	0.005		
NIHSS 24 h after treatment	8 (2-16)	10 (4-17)	0.064		
Recanalization (TICI 2b-3)	201 (82.4%)	145 (77.5%)	0.21		
SICH	3 (1.2%)	5 (2.7%)	0.30*		
mRS 0-1 3 m	83/240 (34.6%)	44/186 (23.7%)	0.014	1.7 (1.1-2.6)	2.3 (1.4-3.6)
mRS 0-2 3 m	121/240 (50.4%)	81/186 (43.5%)	0.16	1.3 (0.9-1.9)	2.1 (1.3-3.3)
Death 3 m	42/241 (17.4%)	34 (18.2%)	0.84	0.9 (0.6-1.6)	0.7 (0.4-1.3)

Table 9. *Unadjusted and adjusted outcomes after EVT treatment. SSTS: Stockholm Stroke Triage System. OR: Odds ratio. ΔNIHSS: Change in NIHSS score. TICI: Thrombolysis in cerebral infarction. SICH: Symptomatic intracranial hemorrhage. mRS: modified Rankin Scale.*

5.4 STUDY IV

All results are presented on the main outcome: EVT initiation. There were 2905 patients with symptom onset in the Stockholm region, transported by ambulance for suspected stroke included in the study. There were a total of 1929 patients (66.4%) with a final diagnosis of stroke, with the remaining classified as stroke mimics. The majority (n=1592) had an ischemic stroke, of which 316 (10.9% of the cohort) had LAO stroke. See the flowchart in figure 19 for the distribution of the four triage categories (overtriage, correct to CSC, undertriage and correct to PSC).

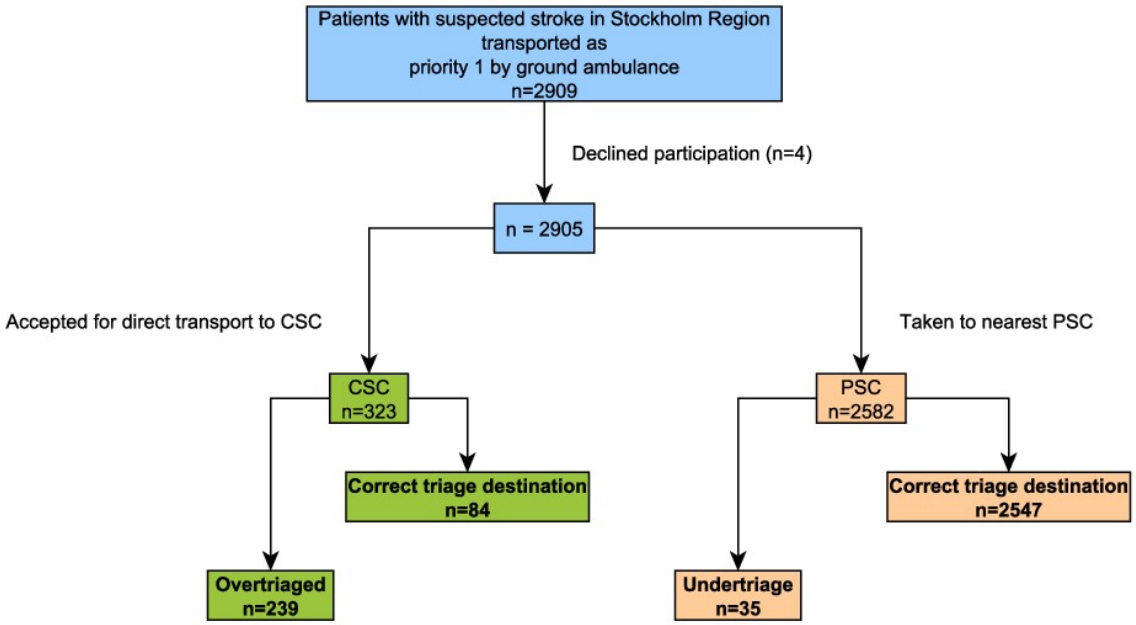

Figure 19. *Flowchart describing distribution of included patients according to triage category. CSC: Comprehensive stroke center. PSC: Primary stroke center.*

Of the 2582 patients that were transported to the PSC, 34 (1.4%) required secondary transport to the CSC for EVT (undertriage). The undertriaged patients had the lowest median age (67 vs 72-76.5 in the other groups). Stroke severity was lower in this group compared to those correctly triaged to the CSC (median NIHSS 10 vs 18), with only four patients assessed as having a positive A2L2 test. More than half of undertriaged patients had an unknown time of stroke onset, higher than in those taken to the CSC (correct and overtriage at 28.6% and 31.4% respectively). Of the 323 patients that were transported to the CSC 239 (74.0%) were not treated with EVT (overtriage). The proportion of patients with a mimicking condition was lower in this group compared to those correctly triaged to the PSC (23.0% vs 43.9%).

There were 2753 patients with complete entries for all required prehospital variables (94.8%), which were included in the statistical modeling and decision curve analysis. Three triage models were computed using the method described in section 4.5.4. All models included the A2L2 test due to its high predictive performance (see table 10).

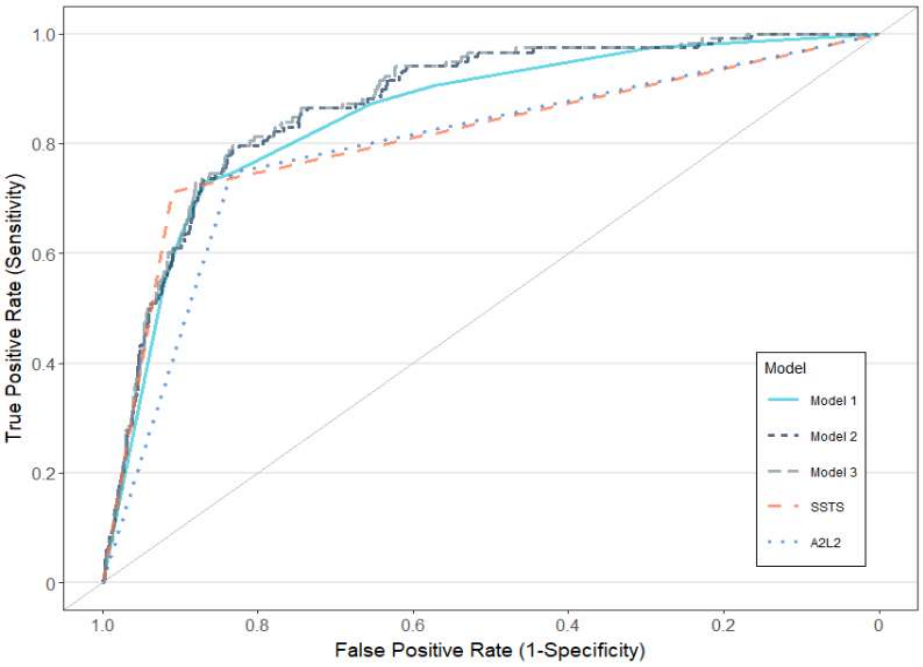

Figure 20. *Prediction metrics for models 1-3 in comparison to the A2L2 test alone as well as the SSTS are shown graphically as ROC-curves.*

	AUC (95% CI)	SPECIFICITY	SENSITIVITY
Model 1	0.85 (0.82 - 0.88)	0.91	0.56
Model 2	0.87 (0.85 - 0.90)	0.90	0.62
Model 3	0.87 (0.84 - 0.90)	0.90	0.63
A2L2 test	0.79 (0.75 - 0.83)	0.83	0.75
SSTS	0.81 (0.77 - 0.85)	0.91	0.71

Table 10. *Comparison of models 1-3 at a high specificity cutoff of 0.90. AUC: area under the curve.*

Model 1*:* A2L2 test + facial weakness, and speech problems (AKUT-test subitems).

Model 2: A2L2 test + facial weakness, speech problems, and age.

Model 3: A2L2 test + age, sex, wake-up stroke, onset-to-ambulance time, known exact onset time, facial weakness, and speech problems.

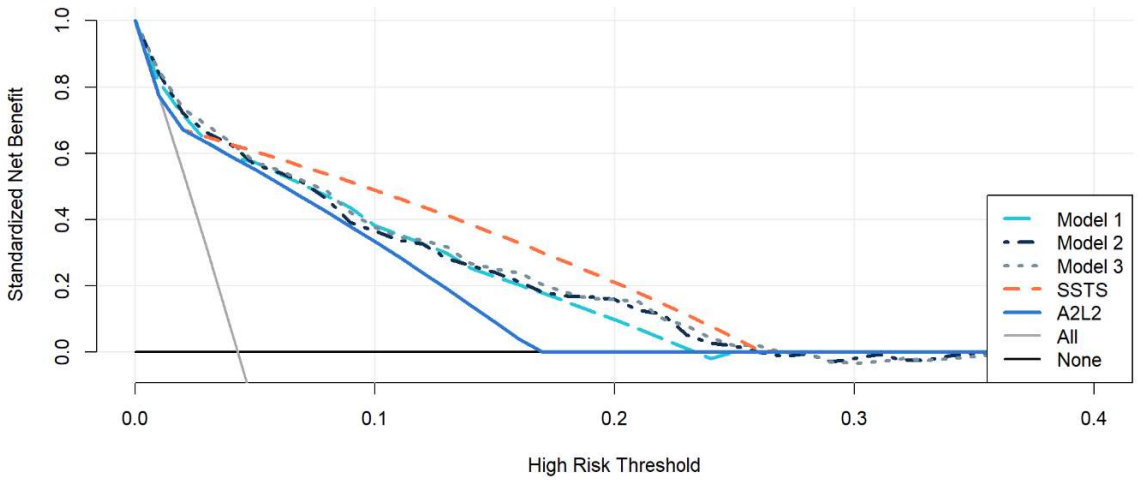

Figure 21. *Decision curve analysis with comparison of models 1-3 with the SSTS and A2L2 test. All: treatment strategy of taking all patients to the CSC. None: treatment strategy of taking of no patient to the CSC.*

Decision curve analysis showed a higher net benefit for the SSTS at risk thresholds 0.05 – 0.25 (see figure 21). A risk threshold of 0.05 translated into patient numbers corresponds to the triage system accepting 19 overtriaged in order to correctly triage one patient to the CSC for EVT treatment. At the 0.25, the limit is three overtriaged for one patient to be correctly triaged to the CSC. At risk thresholds close to 0, taking all patients to the CSC yields the highest net benefit, whereas at levels > 0.25, taking no patients to the CSC is the most beneficial. Secondary outcomes for the LAO stroke triage endpoint showed that the SSTS was inferior to all three models, as well as the A2L2 test alone.

6 DISCUSSION

The two aims of this thesis were to investigate safety outcomes of treatment with intravenous thrombolysis (study I-II), and transportation logistics of patients with suspicion of stroke caused by large artery occlusion (study III-IV). This chapter will discuss the findings of each study in sequence.

6.1 STUDY I – SAFETY OF IVT IN STROKE MIMICS

In this large, multi-center study using prospectively collected observational data, treatment with intravenous thrombolysis of patients with a condition mimicking acute ischemic stroke was shown to be reasonably safe. Hemorrhagic complications were far less common in the mimic group, with only five instances of parenchymal hematoma, and two symptomatic intracranial hemorrhages according to the NINDS definition (of which one fulfilled the ECASS II criteria as well). No SICH per SITS-MOST, the most severe form, was recorded in the mimic group. In the 3-month follow-up, > 80% patients with a mimicking condition had an mRS of 0-1, compared to < 60% in the group with ischemic stroke. In this cohort, representing conditions with such a high suspicion of acute ischemic stroke that IVT was administered and follow-up with MRI was performed, the three most common conditions were functional symptoms, headache, and seizure.

The proportion of patients with a stroke mimic in this study was 4.1%, similar to a meta-analysis performed by Tsivgoulis and colleagues in 2015 at 4.4%, but higher than the 1.8% reported by Zinkstok and colleagues.[212,214] Comparison of stroke mimic frequency is a complicated matter, primarily due to contextual issues. Medical dispatch services, serving as the first node in acute stroke management rely on a symptom description presented over the phone. These descriptions are commonly vague and varied, leading to a specificity for stroke alert initiation as low as 21%.[293–295] Diagnostic accuracy is improved for ambulance personnel, but the proportion remains high at ~40%.[207,296] Patients with a mimicking condition receiving IVT would then represent the most complex cases, as managing physicians have more time, experience, and access to adjunct diagnostic tests capable of identifying common stroke mimics. Six single-center studies reporting on mimics treated with IVT have shown a wide range of proportions, 3.7% – 14.5%, despite an imaging requirement for MRI, albeit with varying definitions.[213–216,297,298] Meanwhile, Zinkstok and colleagues collected data at highly experienced academic stroke centers and used strict mimic criteria, but had no imaging requirements.[212] Our cohort consisted of patients with a stroke mimic diagnosis established as part of clinical routine at 560 centers participating in the SITS-ISTR, which has a high variation in patient volumes and IVT treatment across hospitals.[299] The cohort in study I may therefore be considered to be representative of the patients treated with IVT and subsequently diagnosed as stroke mimics.

The complication rate among patients with acute ischemic stroke and MRI follow-up in our cohort was low. In comparison with previous studies using SITS data, this group had lower baseline NIHSS, age and fewer comorbidities than in unselected patients treated with IVT.

This would explain the low rates of hemorrhagic complications and high proportion of patients with good functional outcome after treatment, as these are known risk factors for SICH.[129,138] In the sensitivity analysis, the new comparator group of patients with ischemic stroke and CT follow-up suffered more complications, which further underscored the lower risk associated with IVT treatment of patients with stroke mimics.

Study I had several limitations, the foremost being that only an association between treatment and outcome can be demonstrated in an observational registry study. Due to the few occurrences of PH and SICH in the mimic group, a logistic regression analysis with adjustment for the many baseline differences between the groups could not be performed. Detailed data regarding diagnostic work-up, such as imaging protocols and adjunct methods for differential diagnosis were not available and may have been different across the participating hospitals, as clinical routine varies across countries and regions. This could be one reason for the relatively large proportion of patients with an unspecified mimicking condition, of which two patients had a SICH. Attempts were made to clarify diagnosis by direct contact with the centers, but the lack of information remained. This is especially problematic in the cases suffering complications. The certainty of a non-stroke diagnosis is likely to have increased due to the MRI requirement, which remains the superior imaging modality in differential diagnosis of acute stroke symptoms compared to CT.[300] However, this inclusion criterion may have excluded any stroke mimic patients with a massive SICH and rapid deterioration, where an MRI follow-up would not have been performed. This limitation, which may be a necessary trade-off between specificity and generalizability, is common for all studies of stroke mimics using MRI. Furthermore, there was a lack of 3-month outcome data in 14% of cases. However, the outcome results presented in the study were consistent with previous publications.[212,214,301]

6.2 STUDY II – SAFETY OF IVT IN POSTERIOR CIRCULATION STROKE

This large observational study reported on a ~50% lower risk of hemorrhagic complications after IVT treatment of patients with PCS, compared to ACS. These results were consistent between the original data analyzed from SITS and the meta-analysis of 13 studies, with a relative risk of 0.49 for SICH in this group.

In the baseline comparison, there were several important differences between the PCS and ACS groups. Median NIHSS was markedly lower in the PCS group (7 vs 13), which is unsurprising considering that the scale is designed for detection of supratentorial stroke in anterior circulation vascular territory.[112] Furthermore, patients with PCS had higher systolic blood pressure, higher levels of blood glucose and a longer time delay from symptom onset to treatment initiation. Meanwhile, patients with ACS were older, more commonly female and had a higher proportion with atrial fibrillation, which is consistent with previous comparisons between ACS and PCS.[302] Importantly, these characteristics are known risk factors for SICH, with atrial fibrillation and hyperglycemia having an association with hemorrhagic transformation after ischemic stroke as well.[129,303,304]

In the unadjusted comparison between groups, PCS had a markedly lower risk of hemorrhagic complications, contributing to 6.4% of PH despite constituting 15% of the study cohort. After adjustment for the baseline differences described above using IPTW, risk was lower for PH and the most severe SICH (SITS-MOST), but no longer statistically significant for the NINDS and ECASS II definitions. The reason for this may have been that the requirement for neurological deterioration included in SICH definitions is measured in an NIHSS increase of 1 or 4 points. Aggravation of cerebellar or brain stem symptoms, such as diplopia or dysphagia, may have been caused by a hemorrhagic complication but would have remained unscored in the NIHSS, precluding a SICH classification. The choice of PH as main outcome may therefore have been a better reflection of hemorrhagic risk in PCS patients. Furthermore, NIHSS score has shown a weaker correlation with outcome and infarct volume in PCS than in ACS.[305] The low number of SICH outcomes in the PCS group in our cohort was similar to previous studies, and the reason for abstaining from adjustment using logistic regression.[194–197,200,306] This issue was instead addressed using IPTW to adjust for baseline differences in known risk factors for SICH.

Sex was included in the IPTW adjustment due to the known association between male sex and a higher risk of death at three months after IVT treatment.[303] The over-representation of male patients in the PCS group (48.3 vs 36.9%) could have offset the lower NIHSS in the group, potentially masking the difference in death at three months which was revealed after IPTW. A reason for this difference may have been the large proportion of patients with an occlusion of the basilar artery (~1/3), which is known to have a poor prognosis even with treatment.[205]

The unadjusted comparison of dichotomized mRS was in favor of PCS both in the original data and the meta-analysis. However, the RR of 1.2 for mRS 0-2 found in the seven studies reporting on functional outcome should be interpreted with caution. After adjustment, this study found no statistically significant difference, and of the seven component studies reporting on functional outcome and included in the meta-analysis, only two used a matched outcome analysis.[194,200] Of these, only Tong and colleagues found a statistically significant difference in favor of PCS.[194] Outside of the systematic review, the IST-3 trial reported on the efficacy of IVT in ischemic stroke grouped using the Oxfordshire Community Stroke Project (OCSP) classification.[307,308] Patients were classified as POCI (posterior circulation infarct) and TACI/PACI (total/partial anterior circulation infarct), with no difference in functional outcomes between the two groups. However, there were only 246 patients with POCI included in the trial, and the OCSP classification is strictly clinical without adjunct imaging. The question of whether the lower risk of hemorrhage after IVT translates into better functional outcomes for the PCS group therefore remains unanswered.

There were several limitations in this study, apart from those inherent in the observational design. The requirement for available occlusion data on CTA/MRA could have biased patient selection, as those without a proven occlusion would be excluded. This was addressed in a sensitivity analysis, including cases classified as ACS or PCS at the discretion of the

participating center (n=29,704). The sensitivity analysis showed no clinically relevant differences in outcomes compared to the main analysis. Infarct volume data was not available in the SITS database, which would have been a better parameter than the NIHSS for use in IPTW adjustment. There was a lack of 3-month outcome data in ~30% of patients, indicating that these differences need to be interpreted with caution. In the systematic review and meta-analysis, a limitation was the difference in definitions of SICH across studies. In order to maintain consistency in data extraction and comparison between studies, if more than one definition was used in a study, the one with the highest proportion was extracted. An additional limitation was the lack of matching procedures or other measures of bias reduction in six of the component studies.

6.3 STUDY III – EVT OUTCOMES AFTER SSTS IMPLEMENTATION

This prospective, observational study showed that treatment with EVT during the two first years of SSTS use was associated with better 3-month functional outcomes compared to historical controls. The reduced need for secondary transport from PSC to CSC (60 – 30%), as well as a decrease in time from onset to arterial puncture (69 minutes) confirmed the findings in a previous study on the SSTS.

Patients in the SSTS group had a somewhat higher median age and NIHSS at baseline, which are known risk factors for SICH and poor outcome after treatment with EVT.[304,309] Despite these differences, the study did not find more patients with SICH or dead at 3-months follow-up in the SSTS group. The reason for this may have been the large reduction in onset to puncture time following implementation of the SSTS, which could be an explanation for the lower ASPECTS in the pre-SSTS group.[309] Despite longer treatment delay and lower ASPECTS, both known risk factors for SICH after EVT, these variables were not included in the multivariate adjustment. The hypothesis was that these differences between groups were an effect of the improved transportation logistics during the SSTS and were therefore a subject of the study rather than confounders. Ordinal logistic regression with adjustment for age and NIHSS showed an aOR in favor of the SSTS group of 1.7, which needs to be interpreted with caution due to violation of the proportionality of odds demonstrated by the Brant test. This was addressed by performing binomial logistic regression for all dichotomizations of the mRS, which were always in favor of the SSTS group, showing no inversion of odds. For mRS 0-1, the aOR was 2.3 and the corresponding NNT was 9 with use of the SSTS. The proportion of mRS 0-1 was 34.6% in the SSTS group, which can be compared to the 26.9% reported in the HERMES collaboration meta-analysis of the five pivotal RCTs proving the efficacy of EVT.[166] Patients with pre-stroke disability, excluded in the randomized trials, constituted 17% of our cohort and the median age of 68 was lower than in the SSTS at 74 and pre-SSTS groups at 71. The main difference that may explain the difference in outcomes is that the median onset to puncture time was 103 minutes faster in the SSTS group compared to the pooled HERMES patients (136 vs 239).

Supporting the association between better outcomes and PSC bypass is a study performed in Rhode Island and Massachusetts using matched-pairs analysis. In this study, the proportion of

mRS 0-1 in the group taken directly to the CSC was 31%, compared to 23% in the group requiring secondary transfer from a PSC.[279] Two randomized trials, RACECAT and TRIAGE, using prehospital symptom scales for bypass decision are still unpublished, with recruitment ongoing for TRIAGE.[280,310] Results from RACECAT, which was performed in Barcelona, were presented at the ESO/WSO conference in 2020 and indicated no difference in outcomes. However, functional outcome was assessed in all patients (including those not undergoing EVT treatment), meaning that an effect may have been obscured by a large number of patients without intervention in both comparator groups.

Study III had several limitations that need to be addressed. Multivariate adjustment was performed to mitigate bias inherent in the observational design, using historical controls for comparison. However, this would not have eliminated other sources of bias. Meanwhile, the e-value indicated that an unmeasured confounder would require an association of ≥ 2.4 beyond the two variables included in the regression model, in order for the difference to no longer reach statistical significance. This was a study of EVT treatment, with outcomes after IVT beyond the scope of the study. However, a previous study on first-year data of the SSTS showed no change in time from stroke onset to IVT initiation making a change in outcomes before and after SSTS implementation unlikely.[263] A related limitation is the potential for recanalization of a large artery occlusion using only IVT. A patient treated at a PSC before SSTS implementation would not have undergone arterial puncture at the CSC if repeated CTA showed restored blood flow. These patients, which may have achieved good functional outcome with IVT treatment alone, were not included in the analysis. However, the most common occlusion sites in both groups were ICA-T and M1, with low recanalization rates after IVT only.[311] It is therefore unlikely that these rare cases would have significantly changed the results of the study. As part of the SSTS implementation, EMS personnel were educated on hemiparesis assessment which may have led to a gradual improvement in stroke recognition and influenced triage accuracy. In the results from the first year of the SSTS, there was no indication of this, but rather an immediate reduction in time from onset to puncture that was sustained during the entire study period.[263] The common electronic health record, used by six of the seven stroke hospitals as well as most primary care and rehab facilities in the Stockholm region was an important part of the teleconsultation. Access to information on pre-stroke comorbidity, functional status, and medication available in this record was not part of the change in stroke triage and may limit the generalizability of this study. Furthermore, the possibility to repatriate patients to a PSC after 24 h observation at the CSC was important to balance the strain on bed capacity. A specialist stroke physician was available for teleconsultation 08:00 – 16:00, which may not be possible elsewhere. The question of associated costs was beyond the scope of the study and not formally calculated. However, there was no change in staffing, equipment, or work hours, with training conducted as part of routine professional development. There was a marginal increase in ambulance patient load which did not require additional prehospital resources. Outcome data was missing in five patients, one pre-SSTS and four SSTS, but it is unlikely to have influenced the results.

6.4 STUDY IV – STATISTICAL TRIAGE MODELING

This study, a pre-planned analysis of data from a prospective observational study of prehospital stroke triage, could not show that alternative models using prehospital variables improved the predictive performance of the SSTS regarding the identification of patients eligible for EVT.

The smallest triage category were the 35 patients that required secondary transport for EVT. These patients were younger (< 70) and had a lower median NIHSS at baseline compared to those correctly triaged to the CSC as well as the 244 patients treated with EVT in study III (18 and 17 respectively). This relatively low NIHSS was surprising, considering that > 70% had a proximal anterior circulation LAO and it is therefore likely that these patients were well compensated with collaterals, reducing the initial symptom severity. The remaining 30% in this group had an M2 occlusion or PCS, which were less likely to produce the hemiparesis required for a positive A2L2 test. Importantly, a detailed review of the four A2L2 positive patients indicated that only one was actively referred to a PSC on suspicion of stroke mimic, whereas the remaining three were taken to the nearest PSC in violation of the SSTS protocol. Overtriaged and correctly triaged patients to the CSC had several baseline similarities regarding symptom severity, which may be explained by the large proportion of ICH (~30%) that can produce neurological deficits similar those of an LAO stroke. At the prehospital level, these patients would have required an immediate CT scan using a mobile stroke unit to be distinguishable from ischemic stroke.

The triage algorithm with the highest net benefit, as assessed by decision curve analysis, was the SSTS in comparison to the three alternative models or the A2L2 test alone. This result illustrates the difficulty in comparing triage stroke scales, as the sensitivity, specificity, and AUC were comparable for all five. Specifically, in models with a binary predictor such as the SSTS, the AUC is known to be harder to interpret.[312] An alternative would have been to use PPV or NPV, but these metrics are highly influenced by prevalence (see also section 2.6.1). In a patient population with 20% LAO stroke, even a screening tool with very high sensitivity and specificity would at best produce a PPV of around 51%.[313] In a similar analogy, if no patients were taken to the CSC, the NPV of the SSTS for EVT initiation would have been 0.96. Additionally, AUC has an equal weight on sensitivity and specificity, which may be impractical in healthcare systems with limitations in CSC bed capacity and ambulance resources. Indeed, this was the rationale when designing the SSTS, with a focus on high specificity. An important part of the teleconsultation is the ability of the stroke neurologist to identify contraindications for EVT, such as low pre-stroke functional status or severe comorbidity, allowing for patients to be routed to the nearest PSC, even when the probability of LAO stroke is high. This also explains the lower net benefit for the LAO stroke triage endpoint, as the objective of the SSTS is to find eligible patients for EVT and not all patients with LAO stroke. The sensitivity (0.41) and specificity (0.93) for LAO stroke were comparable to other prehospital symptom scales, with ranges 0.50 – 0.67 and 0.82 – 0.93 respectively, tested in other patient populations with varying proportions of large artery occlusion.[173,175] In terms of EVT eligibility, the M-DIRECT score was evaluated in a study

comparing direct transfer to TSC with triage to either TSC or PSC using the scale. This observational study showed a sensitivity of 0.79, specificity of 0.82 and a PPV of 0.53 (compared to 0.26 in the SSTS). However, their cohort had a lower proportion of mimics (22% vs 44%) and higher proportion of LAO stroke (32% vs 11%) compared to the SSTS data, as well as previous studies.[173,174,207,314]

Several limitations of this study need to be addressed. The specific geographical and organizational circumstances, discussed in detail in the limitations of study III, may affect the generalizability of this study. However, there is reason to believe that the cohort is representative of unselected patients with suspected acute ischemic stroke. In comparison with the study performed by Duvekot and colleagues, proportions of stroke mimics, ICH and LAO stroke were quite similar.[173] There was a lack of information on NIHSS in 388 patients, a majority with stroke mimics, precluding the addition of this variable in the statistical modeling. However, EMS personnel do not perform a full NIHSS assessment, and the managing physician at the receiving stroke center would likely abstain in case of an apparent stroke mimic. Including NIHSS scores would therefore preferentially exclude patients with a mimicking condition, leading to selection bias. Furthermore, inclusion of a full NIHSS examination in a prehospital symptom scale would be unfeasible for logistical reasons. Some AKUT-test subitems were missing in 153 patients, forming 5.2% of the study cohort that could not be included in the analysis. However, there was no reason to suspect systematic bias in the patterns of missing data for these patients. As this was a retrospective analysis, the study was performed on variables available per clinical routine, precluding inclusion of other variables of interest.

7 CONCLUSIONS AND FUTURE RESEARCH

Study I, with data from a large, multi-center patient cohort, presented observational data showing that IVT treatment in patients with a mimicking condition appears to be safe. This question does not lend itself well to investigation with a randomized controlled trial, as the patient group has no conceivable benefit from the treatment. The lack of a reasonable pathophysiological mechanism for intracranial hemorrhage in most stroke mimics provides further support to the assumption that a patient with an intact central nervous system and blood brain barrier is unlikely to suffer a brain hemorrhage after IVT. Training in diagnostic evaluation of patients with focal neurological deficits remains highly important in order to minimize the risk of inadvertent IVT treatment of a mimicking condition. However, the results in study I lend further support to the AHA/ASA guidelines that IVT should not be withheld for fear of treating a mimicking condition, especially if the main differential diagnosis is a functional neurological deficit. Patients with stroke mimics still provide ample questions for research, however. Notably the mechanisms behind postictal paresis, as well as functional deficits remain largely unknown. Regarding differential diagnosis, stroke mimic screening scales are developed and validated to avoid the situation of inadvertent IVT altogether. Mobile stroke units can also be used for the identification of mimics, but large-scale implementation is hindered by unanswered questions regarding cost-efficiency.

Study II, based on the same large SITS dataset as study I, could show that IVT treatment in patients with posterior circulation stroke carries a relatively low risk of bleeding. The results emphasize that the risk of cerebral hemorrhage is roughly half of anterior circulation stroke. The study is strengthened by a meta-analysis, but limited by the fact that the NIHSS is a poor surrogate for infarct size in the posterior circulation. Meanwhile, the grim prognosis of the subset of PCS caused by basilar artery occlusion warrants special care in this patient group. Unfortunately, the exclusion of PCS in the initial IVT RCTs in combination with the widespread use of the NIHSS for stroke trials has led to knowledge gaps regarding efficacy of reperfusion treatment in this group. With more observational data suggesting treatment benefit with EVT, an RCT providing only best medical treatment for a control group with PCS might be considered unethical. Problems with visualizing infarct lesions in areas supplied by the posterior circulation with CT imaging may be overcome with faster and more readily available MRI protocols for acute stroke.

The Stockholm Stroke Triage System, a symptom based prehospital algorithm using grading of hemiparesis and teleconsultation for detection of EVT eligible patients was implemented in 2017. Study III has provided good reasons to believe that the system has led to better outcomes in patients treated with IVT, in addition to the previous findings of high diagnostic accuracy and faster treatment times. The pathophysiology of stroke, summarized as “time is brain”, makes it reasonable to assume that patients treated faster after onset will have better outcomes than those that must wait for an ambulance to transport them between hospitals. Under the organizational and geographical circumstances present in the Stockholm region, the SSTS appears to be an effective way to organize prehospital transport logistics with

observable benefit for patients. However, use of the SSTS directs some patients to the wrong hospital as their initial destination. Study IV found no systematic problems in the SSTS that could be improved with statistical modeling using available data, even when disregarding potential increases in cost and additional time used for assessment. Stroke triage is a large and expanding field, with several strategies for optimal patient transportation. Results from the TRIAGE trial, which randomizes patients with a PASS ≥ 2 for transport to the nearest PSC or directly to the CSC, will be important in this ongoing discussion. However, the trial will only include patients with stroke onset within 4.5 hours, limiting the utility for patients eligible for the extended IVT treatment window of up to 9 hours. Importantly, if randomized trials on combinations of IVT + EVT or EVT alone show that EVT is better, this may drastically change future directions for stroke triage research.

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